Statement

From Assoc. Prof. Dr. Mladena Nikolaeva Radeva, MD, PhD
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Internal member of the Scientific Jury,
appointed by Order of the Rector of MU-Varna No. R-109-405/20.11.2024

Regarding

Dissertation of Dr. Vladislava Nikolaeva Yotsova for the award of the educational and scientific degree "Doctor" in the scientific specialty "Ophthalmology," code 03.01.36

Dissertation Topic:

"Contemporary Diagnostic Possibilities for Fuchs Endothelial Corneal Dystrophy"

Brief Biographical Information:

Dr. Vladislava Yotsova was born in 1988. She completed her secondary education in 2007 at the Foreign Language High School "Exarch Joseph" in Razgrad, with intensive German language studies. From 2007 to 2013, she studied Medicine at the Medical University of Pleven. In 2014, she began her residency at the University Specialized Hospital for Active Treatment of Eye Diseases (USBOBAL) in Varna. In December 2018, she obtained her specialization in Ophthalmology after successfully passing the examination at the Military Medical Academy in Sofia. In 2020, following a competitive exam, Dr. Yotsova was enrolled as a full-time PhD student in the scientific specialty "Ophthalmology" at the Department of Ophthalmology and Visual Sciences, Medical University – Varna, under the supervision of Prof. Dr. Christina Nikolova Grupcheva, MD,. Since 2020, she has been an assistant professor in the "Medical Optics" program at the Medical College.

Relevance of the Problem and Literature Review:

Fuchs endothelial corneal dystrophy (FECD) is a significant ophthalmological issue due to its high prevalence (4-7% of the population) and its leading role as a cause of corneal transplantation (36% in the USA). Primarily affecting individuals over 40-50 years, particularly women, FECD leads to progressive loss of endothelial cells, impairing corneal transparency and causing blurred vision, pain, and permanent visual acuity loss in advanced stages. The incompletely elucidated pathogenesis, linked to genetic mutations and oxidative stress, underscores the need for further research. Modern diagnostic methods, such as specular and confocal microscopy, and advanced therapeutic approaches, including refined surgical techniques, highlight the relevance of the topic and the importance of developing effective strategies for diagnosis, treatment, and management of FECD to improve patients' quality of life.

Structure of the Scientific Work:

The dissertation spans 179 standard pages and is illustrated with 43 figures and 34 tables. It includes the following sections: Table of Contents – 3 pages; List of Abbreviations – 2 pages; List of Figures – 3 pages; List of Tables – 3 pages; Abstract in Bulgarian – 3 pages; Abstract in English – 2 pages; Introduction – 3 pages; Literature Review – 45 pages; Aim and Objectives – 1 page; Materials and Methods – 18 pages; Results – 50 pages; Discussion – 22 pages; Summary – 2 pages; Conclusions – 1 page; Contributions – 1 page; Publications and Scientific Communications Related to the Dissertation – 1 page; Appendices – 2 pages; References – 16 pages; Acknowledgments – 1 page. The bibliography comprises 217 sources, including 2 in Cyrillic and 215 in Latin script. The research was conducted at the University Specialized Hospital for Active Treatment of Eye Diseases – Varna.

Aim:

To analyze and evaluate topographic and microstructural corneal parameters in patients with varying degrees of Fuchs endothelial corneal dystrophy using Pentacam Scheimpflug tomography and specular microscopy.

Objectives:

1. To perform specular microscopy and Pentacam Scheimpflug tomography on the corneas of patients with Fuchs endothelial corneal dystrophy.
2. To analyze the obtained results through qualitative and quantitative topographic and microstructural analysis.
3. To assess the diagnostic value of corneal parameters generated by Pentacam Scheimpflug tomography and specular microscopy in patients with Fuchs dystrophy.
4. To analyze and summarize the advantages of combining these two techniques in the contemporary diagnosis of patients with Fuchs corneal dystrophy.
5. To evaluate the visual quality of patients with FECD using a questionnaire assessing anterior segment discomfort.

Materials and Methods:

This study, approved by the Ethics Committee of MU-Varna (protocol No. 130/20.04.2023), was conducted at USBOBAL – Varna between May 2023 and December 2024, involving 89 individuals (58 women, 31 men) divided into two groups: a control group (42 individuals, 84 eyes) without FECD and an FECD group (47 individuals, 94 eyes). Patients were stratified by gender and age (10-year intervals). Strict inclusion and exclusion criteria ensured group homogeneity. Clinical methods included medical history, ophthalmological examination (visual acuity, intraocular pressure, biomicroscopy, ophthalmoscopy), specular microscopy (Nidek CEM-530) for endothelial cell analysis (cell density, polymegethism, hexagonality, corneal thickness), and corneal tomography (Pentacam HR) for densitometry and topographic features (loss of parallel isopachs, displacement of the thinnest corneal point). Statistical analysis was performed using SPSS v19, employing descriptive analysis, T-tests, and ANOVA with a significance level of $\alpha=0.05$. All procedures complied with ethical standards (Helsinki Declaration), with participants providing informed consent. The study provides valuable data for FECD diagnosis and monitoring, focusing on endothelial morphology and corneal transparency.

Original Research, Results, and Discussion:

The study included 89 individuals (58 women, 31 men), divided into an FECD group (47 individuals, 94 eyes) and a control group (42 individuals, 84 eyes). The mean age of women with FECD was 70.71 ± 9.428 years, and of men, 75.44 ± 6.928 years. Specular microscopy (Nidek CEM-530) revealed a statistically significant reduction in endothelial cell count (NUM) in women with FECD in the 60–69 ($p<0.001$), 70–79 ($p<0.001$), and 80–89 ($p<0.001$) age groups, and in men in the 70–79 ($p<0.001$) and 80–89 ($p<0.001$) age groups. An increase in the standard deviation of cell area (SD) was observed in women in the 60–69 ($p=0.010$) and 70–79 ($p=0.002$) groups, and in men in the 70–79 ($p=0.001$) and 80–89 ($p=0.006$) groups. The coefficient of variation (CV) was significantly elevated in women in the 70–79 ($p=0.005$) and 80–89 ($p=0.031$) groups, and in men in the 70–79 ($p=0.002$) and 80–89 ($p<0.001$) groups. The percentage of hexagonal cells (HEX) was reduced in women in the 70–79 ($p=0.010$) and 80–89 ($p<0.001$) groups, and in men in the 70–79 ($p=0.045$) and 80–89 ($p<0.001$) groups. Central corneal thickness (CCT) was significantly increased in women in the 50–59 group ($p=0.010$) and in men in the 60–69 group ($p=0.001$). Comparison between women with FECD in the 50–59 and 80–89 groups showed reductions in NUM ($p=0.002$), cell density (CD) ($p=0.033$), and HEX ($p=0.001$), and an increase in maximum cell count (Max) ($p=0.031$). In men, comparison between the 60–69 and 80–89 groups showed reductions in NUM ($p=0.008$), CD ($p=0.039$), and HEX ($p=0.006$), and increases in mean cell area (AVG) ($p=0.034$), Max ($p=0.023$), and minimum cell count (Min) ($p=0.027$). Gender differences in the 60–69 group showed higher CD in women ($p=0.012$) but lower AVG ($p=0.001$), SD ($p=0.016$), Min ($p=0.001$), and CCT ($p=0.011$); in the 70–79 group, CV was lower in women ($p<0.001$); in the 80–89 group, men had lower CD ($p=0.006$) but higher AVG ($p=0.012$), Max ($p<0.001$), Min ($p<0.001$), and CCT ($p=0.022$).

Pentacam Scheimpflug tomography showed that in women in the 50–59 group, corneal densitometry for the 0–12 mm zone was 20.138 ± 2.2659 in FECD versus 16.900 ± 0.7071 in controls ($p=0.005$), with increased backscatter in the 6–10 and 10–12 mm zones ($p<0.007$). In the 60–69 group, no significant difference was found ($p=0.903$), but increased backscatter was observed in the posterior 0–2 mm zone ($p<0.001$). In the 70–79 group, no significant difference was noted ($p=0.684$), but differences were seen in the posterior 0–2 ($p=0.047$) and 10–12 mm zones ($p<0.001$). In the 80–89 group, densitometry was 24.057 ± 4.2583 in FECD versus 22.660

± 4.8454 in controls (p=0.241), with increased backscatter in the 0–2 and 2–6 mm zones (p<0.017). Comparison between women in the 50–59 and 80–89 groups showed increased backscatter in the 0–2, 2–6, and 6–10 mm zones (p<0.012). In men in the 60–69 group, densitometry was 18.750 ± 0.7895 in FECD versus 22.890 ± 2.5826 in controls (p=0.002), with increased backscatter in the 6–10 and 10–12 mm zones (p<0.041). In the 70–79 group, no significant difference was found (p=0.247), but the 0–2 and 2–6 mm zones showed increased backscatter (p<0.040). In the 80–89 group, densitometry was 26.700 ± 4.5233 in FECD versus 30.450 ± 6.0973 in controls (p=0.098), with increased backscatter in the 6–10 and 10–12 mm zones (p<0.028). Comparison between men in the 60–69 and 80–89 groups showed increased backscatter in all zones (p<0.029). Densitograms demonstrated progression from a "high-backed chair" pattern to a "hammock" pattern with advancing age, more pronounced in men.

The thinnest corneal point was most commonly located in the inferior temporal quadrant. In women with FECD in the 50–59 and 60–69 groups, significant displacement along the Y-axis was observed (p=0.011 and p=0.014). No significant displacement was noted in men. Loss of regular isopachs increased with age: in women, isopachs were regular in 100% in the 50–59 group, 44.5% in the 70–79 group, and 31.25% in the 80–89 group; in men, 50% showed loss in the 70–79 group, and 100% in the 80–89 group. CCT, measured by Pentacam (e.g., 552.875 ± 25.159 μm in women aged 50–59) and specular microscopy (562.75 ± 21.191 μm), showed higher values with the latter, with significant differences in women aged 60–69 (p=0.046) and men aged 70–79 (p=0.020).

Visual quality was impaired in 57.14% of women in the 50–59 and 60–69 groups and 100% in the 70–79 and 80–89 groups, with complaints including blurred vision, glare, photophobia, and foreign body sensation. In men, 100% across all groups reported impaired vision. Family history was noted in 7 women and 2 men. Awareness of FECD was higher in women (11 vs. 3 men). Comorbidities, primarily hypertension and non-insulin-dependent diabetes, were common (90.3% in women, 75% in men).

Discussion:

This study analyzed endothelial cell parameters using specular microscopy (Nidek CEM-530) and corneal changes using Pentacam Scheimpflug tomography in 47 FECD patients (31 women, 16 men) and 42 healthy controls, stratified by gender and age (50–89 years for women,

60–89 for men). Specular microscopy, a gold standard for endothelial assessment before keratoplasty, demonstrated significant reductions in endothelial cell count (NUM) in women aged 60–69 ($p<0.001$), 70–79 ($p<0.001$), and 80–89 ($p<0.001$), and in men aged 70–79 ($p<0.001$) and 80–89 ($p<0.001$). Cell density (CD) was lower in women (2162.21 ± 672.782 cells/mm²) compared to controls, with increased coefficient of variation (CV) (34.60 ± 6.264%) and reduced hexagonal cell percentage (HEX) (62.14 ± 7.477%) in the 70–79 and 80–89 groups ($p<0.031$). In men aged 80–89, all parameters (CD, CV, HEX, mean cell area – AVG) were significantly altered ($p<0.007$), except CCT. Comparisons between women in the 50–59 and 80–89 groups showed reductions in NUM ($p=0.002$), CD ($p=0.033$), and HEX ($p=0.001$), while in men between the 60–69 and 80–89 groups, reductions in NUM ($p=0.008$), CD ($p=0.039$), and HEX ($p=0.006$) were observed. Pentacam tomography revealed increased light backscatter, particularly in the anterior layer, escalating with age and more pronounced in men with FECD. Densitograms showed progression from a "high-backed chair" to a "double-humped camel" pattern with advancing FECD, especially in men (100% in the 80–89 group). The thinnest corneal point was predominantly in the inferior temporal quadrant, with Y-axis displacement in women aged 50–59 and 60–69 ($p<0.014$). Loss of regular isopachs increased with age, from 0% in women aged 50–59 to 68.75% in those aged 80–89, and 100% in men aged 80–89. CCT, measured by Pentacam (e.g., 552.875 ± 25.159 μm in women aged 50–59) and specular microscopy (562.75 ± 21.191 μm), showed higher values with the latter, with significant differences in women aged 60–69 ($p=0.046$) and men aged 70–79 ($p=0.020$). Visual quality deteriorated with age, with 57.14% of women in the 50–69 groups and 100% in the 70–89 groups reporting blurred vision, glare, and photophobia; all men reported complaints. Family history was noted in 7 women and 2 men, with higher awareness in women (11 vs. 3 men). Comorbidities (hypertension, diabetes) were prevalent (90.3% in women, 75% in men). The study confirms that specular microscopy is critical for FECD diagnosis and monitoring but is limited in advanced edema, while Scheimpflug tomography detects subclinical edema and predicts progression via densitometry and isopachs. Emerging technologies, including artificial intelligence, promise enhanced diagnostics but require validation.

Summary:

FECD is a prevalent corneal dystrophy associated with endothelial cell loss, more frequent in women, manifesting in advanced age, and a leading cause of corneal transplantation in the USA.

Its pathogenesis, though not fully elucidated, involves autosomal dominant inheritance with variable expressivity and incomplete penetrance. Understanding FECD is crucial, as its progression reduces lens transparency, necessitating cataract surgery, which risks exacerbating the dystrophy. Comprehensive preoperative assessment is essential to mitigate adverse outcomes. This dissertation reviews the application of various visualization technologies for assessing corneal changes in FECD patients. Diagnostic methods include biomicroscopy, which can detect early corneal changes and monitor progression (stromal edema, subepithelial/epithelial bullae, fibrosis, neovascularization, reduced transparency), with technological advancements enabling photographic documentation. Single CCT measurements are not reliable indicators of disease severity due to anatomical variations but serve as progression markers in longitudinal follow-up. Scheimpflug tomography tracks CCT, loss of parallel isopachs, thinnest point displacement, posterior surface focal depression, and densitometry. Specular and confocal microscopy are key for corneal imaging; specular microscopy, a non-invasive standard, provides data on endothelial cell count, shape, and size but requires corneal transparency, while in vivo confocal microscopy (IVCM) visualizes all corneal layers regardless of transparency. Anterior segment optical coherence tomography (AS-OCT) offers detailed insights into the endothelium and Descemet's membrane, aiding in diagnosis, staging, and follow-up of FECD patients.

Conclusions:

1. Higher disease prevalence was confirmed in women.
2. Disease severity worsens with advancing age.
3. Greater corneal changes were observed in men compared to women with disease progression.
4. Microstructural corneal analysis in FECD patients showed significant endothelial cell density reduction with disease progression.
5. Densitometry results confirmed increased light backscatter from corneal layers with advancing disease.
6. With aging in FECD patients, greater displacement of the thinnest corneal point relative to the pupil center and disruption of regular isopach patterns on topographic maps were observed using Pentacam Scheimpflug tomography.
7. Single CCT measurements are not reliable indicators of disease severity due to anatomical variations but can serve as progression markers in FECD follow-up.

8. Lack of screening and diagnosis for the disease was noted.
9. Low patient awareness of the disease was observed.

Contributions:

Cognitive Contributions:

1. A comprehensive review of scientific literature on corneal changes in FECD patients was conducted.
2. Contemporary diagnostic methods for FECD were analyzed.

Scientific-Applied Contributions:

1. Detailed analysis of corneal changes in FECD patients was performed.
2. Microstructural differences in the endothelium between FECD patients and healthy controls were described.
3. The first study in Bulgaria analyzing specular microscopy and Pentacam Scheimpflug tomography results in FECD patients, stratified by age and gender, was conducted.

Practical Contributions:

1. Microstructural analysis of the endothelium in FECD patients hospitalized for various reasons at USBOBAL Varna was performed.
2. The advantages of specular microscopy for early diagnosis of endothelial changes in FECD patients were established.
3. The advantages of Pentacam Scheimpflug tomography for early diagnosis of endothelial changes in FECD patients were established.

Publications Related to the Dissertation:

1. Fuchs Endothelial Dystrophy and Phacoemulsification in Cataract
2. Eye Health During the COVID-19 Pandemic

Statement:

The dissertation of Dr. Vladislava Yotsova addresses a highly significant and complex topic related to Fuchs endothelial corneal dystrophy (FECD), which holds substantial medical and social importance due to its high prevalence (4-7% of the population) and its role as a leading cause of corneal transplantation. Affecting primarily individuals over 40–50 years, especially women, FECD leads to progressive visual impairment, requiring precise diagnostics, innovative technologies, and a multidisciplinary approach for effective management. Dr. Yotsova's work provides a current and in-depth perspective on the issue, delivering valuable data on morphological and functional corneal changes analyzed via specular microscopy and corneal tomography in 89 individuals (47 with FECD and 42 healthy controls). The dissertation, spanning 179 pages and illustrated with 43 figures and 34 tables, is distinguished by clearly formulated aims and objectives, precision in expression, and systematic presentation of results. Of particular interest are the scientific-applied contributions, including the first study in Bulgaria analyzing specular microscopy and Scheimpflug tomography results in FECD patients stratified by age and gender, as well as the finding of more pronounced disease progression in men. Significant reductions in endothelial cells and hexagonality with age, increased coefficient of variation, and progressive light backscatter, particularly in the anterior corneal layer, were noted, with densitograms showing a characteristic shift. The visual quality analysis revealed deterioration in 100% of patients in advanced age groups, with men reporting more severe symptoms (blurred vision, glare, photophobia). The work highlights the need for improved screening and awareness, as only 11 women and 3 men were aware of their condition. The dissertation's scope, the problem's relevance, the thorough analysis, and the practical applicability of the results provide grounds for me to recommend that the Scientific Jury vote positively for awarding Dr. Vladislava Yotsova the educational and scientific degree "Doctor."

Assoc. Prof. Dr. Mladena Radeva, MD, PhD, FEBO