Statement

By Assoc. Prof. Dr. Binna Nencheva, MD, PhD,

internal member of the scientific jury, appointed by the Order of the Rector of MU-Varna No. R-.109-404/20.11.2024 regarding the dissertation work of

Dr. Konstantina Grigorova Kancheva-Bandramalieva for the award of the educational and scientific degree "Doctor " in the scientific specialty "Ophthalmology," code 03.01.36 on the topic:

"Place and role of dietary supplements in the ophthalmology practice."

Brief Biographical Information

Dr. Konstantina Grigorova Kancheva-Bandramalieva was born on November 28, 1985, in Petrich, Bulgaria. She completed her primary education at "Kiril and Metodi" School in Burgas. In 2005, she graduated from the German Language High School "Johann Wolfgang von Goethe" in Burgas with excellent results and obtained a certificate in German – "Das Deutsche Sprachdiplom der KMK II," ranking fifth in Bulgaria based on her achievements.

After finishing her secondary education in 2006, she started her medical education at the University of Duisburg-Essen in Essen, Germany. In 2012, she obtained her professional qualification as a Medical Doctor from the same university. She practiced at the Specialized Eye Clinic "Provisus" in Essen, Germany, and at the University Clinic for Eye Diseases "Inselspital" in Bern, Switzerland.

In 2013, she returned to Burgas and started working as a physician at Eye Hospital Burgas Dr. Ivanovi Mladost. At the beginning of 2014, she began her training to obtain a specialty in Ophthalmology at the Medical University Prof. Dr. Paraskev Stoyanov - Varna and the University Specialized Hospital for Eye Diseases for Active Treatment in Varna, and in December 2020, she acquired the specialty "Ophthalmology."

Since the end of 2020, she has been enrolled as a PhD student in Ophthalmology at the Department of Eye Diseases and Visual Sciences, Medical University Prof. Dr. Paraskev Stoyanov - Varna. Dr. Kancheva has extensive experience in the field of ophthalmology in Germany, Switzerland, and Bulgaria, with acquired skills in working in ophthalmology outpatient clinics, inpatient care, and surgery, as well as proficiency with the necessary diagnostic and therapeutic equipment.

Relevance of the Problem

Blindness has always been a focus for ophthalmologists due to its significant social implications and the resulting consequences. Forecasts indicate that the loss of vision will increase by 55%, or 600 million people, over the next 30 years, primarily due to two factors: an aging population and lifestyle changes. The global population is expected to grow by 25% by 2050, reaching 9.7 billion. By 2050, the number of people over 65 will nearly double, and those aged 80 or older will triple. Vision loss increases with age due to the established link with a higher prevalence of cataracts, age-related macular degeneration (AMD), and glaucoma. Increased urbanization, education, sedentary lifestyles, lower quality of food sources, and resulting obesity have contributed to the rise in diabetes and myopia globally. This means that the demand for health services related to vision loss will increase in the coming years. In the near future, developing new therapeutic strategies to combat the leading causes of blindness will become increasingly necessary. According to VISION 2020, these causes include cataracts (15.2 million), followed by glaucoma (3.6 million), uncorrected refractive errors (2.3 million), AMD (1.8 million), and diabetic retinopathy (0.86 million). A possible and easily applicable adjunctive therapeutic option could be the use of dietary supplements with antioxidant and neuroprotective properties. Studies on age-related eye diseases (AREDS and AREDS2) suggest that supplements containing vitamins C and E, lutein and zeaxanthin, copper oxide, beta-carotene, and zinc may slow the progression of AMD. There is evidence that carotenoids lutein/zeaxanthin may be associated with reduced cataract progression in populations with limited dietary resources, but whether supplements would be beneficial for such populations requires further study. Some limited evidence suggests that omega-3 dietary supplements may play a role in managing dry eye, but more research is needed.

Structure of the Dissertation

The dissertation consists of 173 pages, including 10 tables and 28 figures. It cites 465 literary sources, 5 of which are in Cyrillic and 460 in Latin script. An additional 22 tables are included in the appendix. It is organized into 7 chapters, corresponding to the objectives and tasks set, meeting the requirements for dissertation formatting.

Literature Review

The literature review includes an analysis of glaucoma – its prevalence and incidence. The global prevalence of glaucoma varies between 1.18% and 4.16% for the population over 40 years old, depending on racial and ethnic background. Risk factors analyzed include intraocular pressure (IOP), advanced age, ethnicity, pseudoexfoliation syndrome, myopia, and reduced central corneal thickness. Systemic hypertension, vasospasm, and acute hypotension have been proposed as potential risk factors for glaucoma in clinical studies. Experimental studies show that the death of retinal ganglion cells (RGC) in glaucoma is an extremely complex process triggered by various molecular mechanisms, culminating in programmed cell death (apoptosis). Apoptosis (from Greek "apoptosis" meaning "falling off") is a phenomenon accompanied by numerous characteristic cytological signs. Pathogenetic theories regarding the mechanisms affecting retinal ganglion cells and inducing apoptosis include oxidative stress, inflammation, excitotoxicity, vascular damage, hypoxia, glial dysfunction, altered axonal transport, and others. Theories and factors for the development of glaucoma are discussed, including mechanical, vascular, and immunological

theories. Pathophysiological factors such as changes in axonal transport, oxidative stress, the effect of glutamate, and pro-inflammatory cytokines are analyzed. Methods for glaucoma diagnosis are presented: tonometry, central corneal thickness (CCT), gonioscopy, and fundus biomicroscopy.

In the treatment section, topical anti-glaucoma medications, prostaglandin analogs, beta-blockers, carbonic anhydrase inhibitors, pilocarpine, alpha-2 agonists, and neuroprotectors are introduced. Neurotrophic factors are proven to play a role in the pathogenesis of glaucoma. The goal of glaucoma treatment is to protect the patient from rapid disease progression during their remaining years of life or at least to prevent progression leading to serious visual field loss in the better eye. Alongside traditional treatment methods, neuroprotection has increasingly emerged as a promising direction, primarily aimed at preventing RGC death and slowing disease progression. These include anti-apoptotic substances, memantine, antiepileptic drugs (valproic acid and phenytoin), mesenchymal stem cells, citicoline, antioxidants like ginkgo biloba extract, coenzyme Q10 with vitamin E, and omega-3 fatty acids. Polyunsaturated fatty acids, polyphenolic flavonoids, curcumin, uridine monophosphate, lutein, and vitamins (A, C, and E), as well as vitamin B1 (thiamine), vitamin B3 (niacin), vitamin B6 (pyridoxine), vitamin B9 (folic acid), and vitamin B12 are also included.

Aim and Objectives

The aim of the research is to investigate and document the use of dietary supplements Mielooptik and Citicoline and to analyze their effects as adjunctive therapy in patients with primary open-angle glaucoma (POAG). To achieve this aim, the following tasks have been set:

1. To track functional and structural changes in the course of POAG using computer perimetry and optical coherence tomography (OCT) in patients undergoing topical anti-glaucoma therapy who take the dietary supplement Mielooptik over a period of 15 months.
2. To track functional and structural changes in the course of POAG using computer perimetry and OCT in patients undergoing topical anti-glaucoma therapy who do not take dietary supplements over a period of 15 months.
3. To track functional and structural changes in the course of POAG using computer perimetry and OCT in patients undergoing topical anti-glaucoma therapy who take the dietary supplement Citicoline over a period of 15 months.
4. To compare the results reflecting the progression of functional and structural changes in the three groups using statistical methods and to evaluate the effect of dietary supplements as adjunctive therapy in the treatment of POAG.

Material and Methods

Material

The study included 90 patients (45 women and 45 men) aged 50-75 years with POAG undergoing topical anti-glaucoma therapy. The patients were randomly divided into three groups of 30 individuals (15 men and 15 women) and were followed for a period of 15 months. The IOP values

of the respective patients ranged from 14 to 21 mmHg. Patients in the first group (GROUP A) took the combined dietary supplement Mielooptik, which consisted of: turmeric (100 mg), uridine monophosphate (50 mg), lutein (10 mg), vitamin B3 (10 mg NE), vitamin B6 (6 mg), vitamin B1 (4 mg), folic acid (400 µg), vitamin B12 (10 µg). Patients in the second group (GROUP B) did not take any dietary supplement. Patients in the third group (GROUP C) took 2 tablets of Citicoline at 250 mg, equating to a daily intake of 500 mg of Citicoline. The dietary supplements were administered in the form of products approved for use in Bulgaria: Citicoline (manufacturer - Laboratorios Virens SL Spain, importer - Bioshield LTD (Bulgaria)); Mielooptik (manufacturer - Plantapol Spain, importer - Naturpharma Bulgaria). They were taken in the standard dosage recommended by the manufacturer: 2 x 1 tablet/day Citicoline 250 mg orally, 1 ampoule/day Mielooptik orally.

Before starting the study, all patients underwent a complete ophthalmological examination, including:

- History of ocular and systemic diseases;
- Visual acuity testing with best correction for each eye separately;
- Goldmann tonometry;
- Indirect ophthalmoscopy;
- Gonioscopy;
- Pachymetry;
- Standardized Computer Perimetry (SAP);
- Optical Coherence Tomography (OCT).

The same examinations were conducted at the 6th and 15th months from the start of the study.

Methods

All participants in the study underwent a complete ophthalmological examination. Standardized computer perimetry was performed with the Humphrey Field Analyzer 2 (Carl Zeiss Meditec). To determine structural changes in this study, Optical Coherence Tomography (OCT) was used with the RTVue XR Model Avanti Scanner, Optovue, Version 2018.1.1.63. All analyses were performed using SPSS software (IBM Corp. Armonk, NY) version 24.0. For all tests, the significance level was set at $p < 0.05$. Descriptive analysis, variance analysis, graphical analysis, analysis of variance, and t-tests for comparing differences between groups and within groups, as well as Pearson correlation analysis, were used.

Results

Demographic data of the studied groups were analyzed before the start of the study, including IOP, stages of POAG according to the simplified classification of Hodapp, and topical therapy. In patients with topical anti-glaucoma therapy who took the dietary supplement Mielooptik over a period of 15 months, it was found that:

The first 6-month follow-up period of patients in group A showed effective improvement in observed parameters, with the mean MD decreasing by 11%, the mean PSD decreasing by 17%, and the average values of RNFL and GCC being statistically higher than the initial values by an average of 2%-3% over 6 months. In the subsequent 6-month period (after a 3-month pause of Mielooptik), patients in group A showed statistically significant improvement in all parameters studied. After 15 months, the average values of MD in group A decreased by 0.74 dB ($p < 0.05$), and the average values of PSD in group A decreased by 0.91 dB ($p < 0.05$) compared to the initial values. After 15 months, the average values of RNFL Ave in group A increased by 3.43 (μm) ($p < 0.05$), and the average values of GCC Ave increased by 3.62 (μm) ($p < 0.05$) compared to the initial values.

In patients with topical anti-glaucoma therapy who did not take dietary supplements over a period of 15 months, it was found that: During the first 6-month follow-up period, patients in group B experienced a deterioration in the observed parameters with 95% statistical significance, with the mean MD worsening by 4%, the mean PSD worsening by 7%, and all other parameters (RNFL Ave, RNFL inf, RNFL sup, GCC Ave, GCC inf, GCC sup) being statistically lower than the initial values, with RNFL Ave decreasing by 1%, RNFL inf decreasing by 1%, RNFL sup decreasing by 1.84%, GCC Ave – by 1.45%, GCC inf – by 1.5%, and GCC sup – by 1.5% over 6 months. In the subsequent 9-month period, patients in group B showed statistically significant deterioration in all parameters studied, with the mean MD worsening by an additional 1.7%, the mean PSD worsening by an additional 3%, and all other parameters (RNFL Ave, RNFL inf, RNFL sup, GCC Ave, GCC inf, GCC sup) being statistically lower than their 6-month values by an average of 1%-2%.

In patients with topical anti-glaucoma therapy who took the dietary supplement Citicoline over a period of 15 months, it was found that: The first 6-month follow-up period of patients in group C showed that MD decreased by 0.9%, the mean PSD of patients decreased by 0.3%, the mean RNFL worsened by 0.1%, and the mean GCC improved by 0.4% over 6 months. In the subsequent 6-month intake of Citicoline (after a 3-month pause), patients in group C showed statistically significant improvement in all parameters studied, with the mean MD decreasing by 4.7%, the mean PSD decreasing by an additional 10%, the mean RNFL improving by 1.7%, and the mean GCC improving by 2%. After 15 months, the average values of MD in group C improved by 0.31 dB ($p < 0.05$), and the average values of PSD in group C improved by 0.37 dB ($p < 0.05$) compared to the initial values. At the end of the period, the average values of RNFL in group C improved by 1.29 (μm) ($p < 0.05$), and the average values of GCC in group C improved by 1.89 (μm) ($p < 0.05$) compared to the initial values.

Discussion

In the discussion, Dr. Kancheva examines the effect of curcumin on the eye as an antioxidant that halts microglial damage and reduces the loss of retinal ganglion cells. The limited therapeutic potential of curcumin and ways to overcome this limitation through enhancers and nanocarriers are also presented. Data from similar studies on the effects of B vitamins in patients with glaucoma, showing improvements in contrast sensitivity and quality of life, are discussed. The available information on the effects of lutein is analyzed, revealing a statistically significant increase in mesopic contrast sensitivity. The information regarding the effects of antioxidant supplements in patients with glaucoma is quite controversial.

Numerous studies on the effects of Citicoline demonstrate its neuroprotective action through increased dopamine levels in the retina, enhanced anti-apoptotic effects, limited thinning of the retinal nerve fiber layer (RNFL), regeneration of neurites, protection against glutamate excitotoxicity, and minimization of RGC damage, thereby improving visual fields.

Dr. Kancheva also points out that several artifacts could affect the quality and subsequently of OCT images. Throughout the observation period, the dissertation reports improvements in parameters measured with SAP (MD and PSD) in the group taking Mielooptik and in the group taking Citicoline. In the group that did not take dietary supplements, a deterioration of the corresponding parameters was noted. Parameters measured with OCT (RNFL and GCC) also improved at the end of the observation period in patients taking dietary supplements Mielooptik and Citicoline, while in group B, a deterioration of the corresponding parameters was again reported, noting that the effect of Mielooptik was observed after the first 6-month period, whereas the effect of Citicoline was not as evident in the first 6 months.

In conclusion, Dr. Kancheva summarizes that the data from the study indicate that the dietary supplements Mielooptik and Citicoline have a positive effect on the progression of POAG at various stages of the disease.

Conclusions

1. The intake of the dietary supplement Mielooptik by patients with POAG showed statistically significant improvement in all parameters monitored in the study. The data observed in this study indicate a moderate improvement in the values of MD and PSD, measured with SAP, and a moderate increase in the thickness of RNFL and GCC measured with OCT after 6 and 15 months. The study demonstrated that the Mielooptik supplement has a positive effect on the progressive damage to the optic nerve in patients with glaucoma.
2. In the absence of dietary supplement intake during the observation period, a statistically significant deterioration of parameters measured with SAP and OCT was noted, despite the compensation of IOP with topical hypotensive treatment, indicating progressive damage to the optic nerve in patients with POAG.
3. The intake of the dietary supplement Citicoline led to minimal but statistically significant improvement in the parameters MD and PSD, measured with SAP, and a slight increase in the thickness of RNFL and GCC, measured with OCT during the observation period. No statistically significant effect on the parameters MD, PSD, and RNFL Ave was observed during the first 6-month period of intake. The change in observed parameters was more pronounced after the second 6-month intake of Citicoline, suggesting that a longer duration may be necessary to improve the condition and consequently slow the progression of POAG.
4. Correlation analysis demonstrated statistically significant positive changes for all patients in groups A and C due to the intake of Mielooptik and Citicoline, respectively, while deterioration of the parameters occurred in all patients in group B during the observed 6 and 15-month periods. The parameters of patients in group A improved to a greater extent compared to those in group C. A statistically significant strong correlation was observed

between the pairs of criteria MD-PSD and the average values of RNFL-GCC for all three studied groups.

5. Results from the analysis of variance indicated no distinguishable differences among the three groups regarding assessed parameters, both at baseline and after 6 and 15 months. Age, sex, and IOP were not determining factors for the three groups during the study period. Changes were observed in the studied parameters across the three groups, with group A showing moderate improvement, group C showing slight improvement, and group B showing deterioration in the observed parameters.

Contributions

1. An in-depth and analytical literature review of available literature dedicated to the pathogenetic factors, functional and structural changes occurring in the course of POAG has been conducted.
2. A detailed literature review of imaging and functional studies, as well as available and potential pharmacological options for POAG has been performed.

Scientific and Practical Contributions:

1. For the first time in Bulgaria, a prospective, long-term study has been conducted to monitor functional and structural changes in patients with POAG taking dietary supplements Mielooptik and Citicoline.
2. A comparative analysis of the rates of progression of POAG in patients with and without dietary supplement intake has been made.
3. Correlations of the observed parameters throughout the study have been investigated.

Confirmatory Contributions:

1. The utility of using dietary supplements with neuroprotective and antioxidant properties as an additional option for slowing progression in patients with POAG has been demonstrated.
2. It has been confirmed that disease progression occurs even with well-controlled IOP.
3. The diagnostic capabilities of OCT and SAP in the diagnosis and monitoring of POAG have been validated.

Glaucoma is a disease with many unknowns. Often, regardless of adherence to the algorithm, the disease does not follow a favorable course. Research on glaucoma is advancing in many directions—diagnosis, pathogenesis, and treatment. Dr. Kancheva addresses a topic that is still not fully developed, but the detailed presentation and analysis of results show that dietary supplements have their place in the treatment of glaucoma. This offers hope to ophthalmologists and patients with glaucoma for more successful treatment of the disease.

Dr. Konstantina Kancheva has 4 publications on the topic. The dissertation is a completed scientific work that meets the scientific criteria outlined in the Regulations for the Implementation of the Law on the Development of Academic Staff at MU-Varna.

The volume of the dissertation, the relevance of the problem, as well as the in-depth analysis provide grounds for me to propose to the Scientific Jury to vote positively for the awarding of the scientific degree "DOCTOR" to Dr. Konstantina Grigorova Kancheva-Bandramalieva.

Заличено на основание чл. 5, §1, б. „В“ от Регламент (ЕС) 2016/679

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