Review

Of a dissertation for the award of an educational and scientific degree "DOCTOR" in the scientific specialty "Ophthalmology" on the topic:

Place and role of nutritional supplements in the ophthalmology practice

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Brief biographical data:

Dr. Konstantina Grigorova Kancheva – Bandramalieva was born in 1985 in Petrich. She completed her primary education at Secondary School "Kiril and Metodiy" - Burgas. In 2005, she graduated from the German Language High School "Johann Wolfgang von Goethe" - Burgas with excellent marks and obtained a certificate in German – "Das Deutsche Sprachdiplom der KMK II". In 2006, she began her medical education at the University of Duisburg-Essen in Essen, Germany. In 2012, she obtained her professional qualification as a physician from the same university. She practiced at a Specialized eye clinic in Essen, Germany, and at the University Eye Clinic "Inselspital" – Bern, Switzerland. In 2013, she returned to Burgas and began working as a physician at SOBAL Burgas, Dr. Ivanovi Mladost. She immediately started her training to obtain a specialty in ophthalmology at the Specialized Hospital for Active Treatment of Eye Diseases in Varna, and in December 2020, she acquired the specialty "Ophtalmology". In 2020, she was enrolled as a PhD student in Ophthalmology at the Department of Eye Diseases and Visual Sciences, Medical University Prof. Dr. Paraskev Stoyanov - Varna. She has attended numerous congresses and courses in Bulgaria and abroad, participating in several national ophthalmological forums. Dr. Kancheva has extensive experience in the field of ophthalmology in Bulgaria and Europe. In addition to Bulgarian, she is proficient in German and English. My personal impressions of her are good communication skills and an individual approach to each patient. She is married, has two children, and has clinical and scientific ambitions.

Nutritionism is progressively developing and is entering both medical prescriptions and the daily lives of patients. In recent years, nutrition has also gained attention in ophthalmology practice. In

the near future, the development of new therapeutic strategies in the fight against the leading causes of reduced vision and adequate hygiene-epidemiological measures, including dietary recommendations, will become increasingly necessary. One possible and easily applicable adjunctive therapeutic option would be the use of dietary supplements with antioxidant and neuroprotective properties. This is also the idea of the dissertation author.

Dr. Kancheva has conducted an analysis of the National Institute of Health in the USA and correctly noted that dietary supplements are already finding their application in ophthalmological practice. Findings from the Age-Related Eye Disease Studies (AREDS and AREDS2) suggest that supplements with vitamins C and E, lutein and zeaxanthin, copper oxide, beta-carotene, and zinc may slow the progression of AMD. There is also some evidence that for populations with more limited dietary resources, carotenoids lutein/zeaxanthin may be associated with a reduction in the progression of cataracts, but whether supplements would be beneficial for such populations requires further study. Dietary supplements with vitamin B12 are not recommended for the treatment of cataracts, although there is some data suggesting that such supplements may slow or prevent the development of the disease. There is some limited evidence suggesting that omega-3 dietary supplements may play a role in managing dry eye, but more research is needed. However, current data are not as conclusive regarding the application of dietary supplements in glaucoma. The latter is ranked as the second leading cause of blindness and the fourth leading cause of moderate and severe visual impairment, thus being the most common cause of irreversible blindness and the second most common cause of irreversible moderate and severe visual impairment. Experimental studies show that the death of retinal ganglion cells in glaucoma is an extremely complex process triggered by various molecular mechanisms. Regardless of the primary impact, the result is a process of programmed cell death (apoptosis). The wide range of pathogenetic theories regarding the mechanisms affecting retinal ganglion cells and triggering apoptosis includes: oxidative stress, inflammation, excitotoxicity, vascular damage, hypoxia, glial dysfunction, altered axonal transport, and others. It is becoming increasingly clear that these factors do not contribute to glaucoma independently but can rather be viewed as a complex in which each factor has its contribution to the damage of the axons of the retinal ganglion cells. Among the already known factors leading to optic neuropathy are also impaired microcirculation, ischemia/reperfusion injury, oxidative stress, deprivation of neurotrophic growth factor, mitochondrial dysfunction, and activation of autoimmunity. Lowering intraocular pressure is currently the main biomarker of the disease, while functional (perimetry) and structural (optical coherence tomography) changes are also monitored. In addition to medical, laser, and surgical treatment, neuroprotection is increasingly entering the field in recent years, which is a very promising direction aimed at preventing the death of retinal ganglion cells and slowing the progression of the disease. Neuroprotection is a therapeutic approach aimed at preventing, delaying, or reducing the death of nerve cells. A large number of preclinical and clinical studies show promising results regarding the effectiveness of several neuroprotective molecules in reducing the loss of retinal ganglion cells in glaucoma. Therefore, the author's attempt to study the effect of two dietary supplements on patients diagnosed with primary open-angle glaucoma is not only interesting but also an innovative concept. The topic is interesting and relevant as it focuses on seeking new therapeutic opportunities in the fight against a chronically progressive disease that leads to irreversible vision loss.

The dissertation is well-structured and contains 173 pages, including 10 tables and 28 figures. A total of 465 literary sources are cited, 5 of which are in Cyrillic and 460 in Latin script. An additional 22 tables are included in the appendix. Seven chapters are presented, corresponding to the objectives and tasks set and meeting the requirements for the formatting of the dissertation.

Aim:

The **aim** is formulated correctly: to study and document the use of dietary supplements Mielooptik and Citizin, and to analyze their effect as adjunctive therapy in patients with primary open-angle glaucoma (POAG).

To achieve this goal, four well-formulated **tasks** have been set:

1. To track the functional and structural changes in the course of POAG using computer perimetry and optical coherence tomography in patients receiving topical antiglaucoma therapy who also take the dietary supplement Mielooptik for a period of 15 months.
2. To track the functional and structural changes in the course of POAG using computer perimetry and optical coherence tomography in patients receiving topical antiglaucoma therapy who do not take dietary supplements for a period of 15 months.
3. To track the functional and structural changes in the course of POAG using computer perimetry and optical coherence tomography in patients receiving topical antiglaucoma therapy who take the dietary supplement Citizin for 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.

To achieve this ambitious goal and the associated tasks, two dietary supplements with neuroprotective properties were chosen – Mielooptik and Citizin. The first is taken at a dose of one ampoule daily, orally, and contains: Curcumin 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. Curcumin is increasingly used as a neuroprotector and is a phytochemical compound extracted from the popular Indian spice turmeric, known for its anti-inflammatory, antioxidant, and antitumor properties. Lutein is also well-known for its antioxidant properties, while B vitamins are important for providing energy to cells and are factors in numerous metabolic reactions involving amino acids, glucose, and lipids.

The other chosen dietary supplement is Citizin, which contains 250 mg of citicoline, and for the purpose of this specific study, two tablets were taken orally per day. Citicoline (cytidine 5'-diphosphocholine) is a naturally occurring (endogenous) compound. It has demonstrated positive effects in several neurodegenerative diseases of the CNS, such as Parkinson's disease and Alzheimer's disease, as well as in amblyopia. Citicoline has the ability to regenerate nerve cells through the biosynthesis of structural components of the cell membrane. Additionally, it prevents the accumulation of free fatty acids caused by ischemia, leading to anti-apoptotic and neuroprotective effects.

The author examines the effect of the two potential supplements and states the hypothesis that the addition of neuroprotective and antioxidant medications and dietary supplements may lead to the preservation of the visual field and prevention of glaucoma progression.

Materials and Methods

The study included results from 180 eyes of 90 patients, randomized into 3 groups (A, B, and C), each consisting of 15 women and 15 men aged 50 to 75 years, diagnosed with POAG and undergoing topical antiglaucoma therapy. The study was conducted at SOBAL Burgas, with the approval of the Ethics Committee of Scientific Research at MU-Varna – Protocol/Decision No. 103 dated 27.05.21. Patients in the first group (GROUP A) took the combined dietary supplement Mielooptik. Patients in the second group (GROUP B) did not take dietary supplements that could affect the study results (control group). Patients in the third group (GROUP C) took the dietary supplement Citizin. Before the start of the study, at the 6th and 15th months, all patients underwent a complete ophthalmological examination. Goldmann tonometry was performed between 2 PM and 4 PM. Standardized computer perimetry (SAP) was conducted using the Humphrey Field Analyzer 2 (Carl Zeiss Meditec), with stimulus size III, using the standard Swedish interactive threshold algorithm (SITA) and program 30-2. For determining structural changes, Optical Coherence Tomography (OCT) was used with the RTVue XR Model Avanti Scanner, Optovue, Version 2018.1.1.63.

The effect of dietary supplements was investigated by tracking the dynamics of functional and structural changes occurring in the course of POAG using computer perimetry (SAP) and optical coherence tomography (OCT) over a total period of 15 months, while maintaining intraocular pressure (IOP) within constant limits.

Results

The three groups were evenly distributed by gender (15 women/15 men), approximately equal in age, and had similar IOP values, with no statistically significant changes throughout the observation period. The average age for Group A was 65.76 years, for Group B was 64.5 years, and for Group C was 65.7 years. The average IOP values for the entire 15-month period were: Group A – an average of 14.7 mmHg, Group B – an average of 14.1 mmHg, and Group C – an average of 14.4 mmHg.

In the first 6-month follow-up period, patients in Group A showed effective improvement in the observed parameters, with the average MD decreasing by 11%, the average PSD decreasing by 17%, and the average values of RNFL and GCC being statistically higher than the baseline by 2%-3% over 6 months. In the subsequent 6-month period (after a 3-month pause in Mielooptik), patients in Group A showed statistically significant improvements in all examined parameters, with the average MD decreasing by 4%, the average PSD decreasing by another 7%, and the average values of RNFL and GCC being statistically higher than their 6-month values by an average of 1%-2% over 9 months. After 15 months, the average MD values for Group A decreased by 0.74 dB ($p<0.05$), and the average PSD values for Group A decreased by 0.91 dB

($p<0.05$) compared to the baseline. After 15 months, the average RNFL Ave values for Group A increased by 3.43 (μm) ($p<0.05$), and the average GCC Ave values increased by 3.62 (μm) ($p<0.05$) compared to the baseline. In the first 6-month follow-up period, patients in Group B experienced a deterioration in the monitored parameters with statistical significance of 95%. After 15 months, the average MD values for Group B worsened by 0.22 dB ($p<0.05$), and the average PSD values worsened by 0.35 dB ($p<0.05$) compared to the baseline. The first 6-month follow-up period for patients in Group C showed that MD decreased by 0.9%, the average PSD decreased by 0.3%, the average RNFL worsened by 0.1%, and the average GCC improved by 0.4% over 6 months. After 15 months, the average MD values for Group C improved by 0.31 dB ($p<0.05$), and the average PSD values for Group C improved by 0.37 dB ($p<0.05$) compared to the baseline.

After the first 6-month intake of Mielooptik, a statistically significant effect was demonstrated for all parameters in Group A compared to the baseline, although this effect was less pronounced for the parameters GCC Ave, GCC Inf, and GCC Sup. A statistically significant improvement effect for Group C was observed after the second 6-month intake of Citizin. After the 15-month observation period, a statistically significant improvement in the monitored parameters was observed in Group A, which was stronger than the statistically significant improvement in Group C. In Group B, a clear statistically significant effect indicating deterioration was noted for all parameters. The author conducted numerous statistical analyses to substantiate this hypothesis.

According to the results from applying ANOVA regarding the rates of change of parameters for the three studied groups, Group A showed a statistically significant ($p<0.05$) positive change in parameters, Group C also showed a statistically significant ($p<0.05$) but to a lesser extent, while Group B showed a statistically significant ($p<0.05$) deterioration in all parameters over the 15-month study period.

Discussion

The results are discussed by analyzing over 70 sources of published literature. The author finds no publications in the reviewed databases regarding the dietary supplement Mielooptik and its effects in patients with POAG, but the effects of the components of the combined dietary supplement concerning neurodegenerative diseases are present in numerous publications. Curcumin, due to its anti-inflammatory, antioxidant, and antitumor properties, has been widely studied in vitro and in vivo in the context of many inflammatory, autoimmune, and degenerative diseases of both the anterior and posterior segments of the eye. According to the author's analysis, the potential of Citicoline concerning POAG is better studied, with similar studies dating back to the year 1999. Citicoline has been administered both orally and locally (in the form of drops), and it has been observed that the thickness of RNFL has statistically significantly higher values after 6 months of supplement intake. Among the many studies analyzed, the author also notes one by Lanza et al. demonstrating a neuroprotective effect of oral Citicoline that slows down the progression of POAG. The author correctly points out a meta-analysis conducted by

Prinz J et al., which found insufficient evidence supporting the notion that Citicoline slows the progression of glaucoma.

- Reviewing the main publications in the databases, the author concludes that there are numerous studies in the global literature noting improvements in parameters measured by computer perimetry after dietary supplement intake by glaucoma patients, but only a few studies report improvements in parameters measured by OCT. This makes Dr. Kancheva's study even more significant, as she demonstrates that:
- The intake of the dietary supplement Mielooptik by patients with POAG showed statistically significant improvements in all monitored parameters and a positive effect on the progressive damage to the optic nerve in glaucoma patients.
- The intake of the dietary supplement Citizin leads to minimal but statistically significant improvements in parameters.

The results are confirmed by well-conducted statistical correlation and variance analyses. 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. Age, gender, and IOP were not determining factors for the three groups during the study period. The author correctly notes that the long-term effects of dietary supplements with neuroprotective properties on functional and morphological characteristics in POAG cannot be established, but in any case, their addition to antiglaucoma therapy would not be harmful. The placebo effect for patients suffering from this chronic progressive disease should not be overlooked either. The author concludes that long-term studies and follow-ups are necessary for a more precise assessment of the results.

The dissertation has numerous **contributions** of a confirmatory, scientific, and applied nature, with the more important ones being as follows:

1. For the first time in Bulgaria, a prospective, long-term study has been conducted tracking the functional and structural changes in patients with POAG who take the dietary supplements Mielooptik and Citizin.
2. A comparative analysis of the rates of progression of POAG in patients with and without dietary supplement intake has been made, investigating the correlations of the parameters observed during the study.
3. The benefits of using dietary supplements with neuroprotective and antioxidant properties as an additional option to slow progression in patients with POAG have been proven, without harmful effects.

The author has 4 publications related to the dissertation, which presents an innovative, non-standard approach following contemporary trends for comprehensive personalized therapy through changes in the lifestyle and habits of patients. Proper nutrition and the intake of dietary supplements is a good opportunity in any chronic disease, including glaucoma. For the first time, a popular dietary supplement in Europe with neuroprotective effects has been studied, and these studies should continue to prove the effects over time and compare them with other supplements and combinations.

I know Dr. Kancheva as a resident and colleague ophthalmologist and have always been impressed by her punctuality, unconventional thinking, and especially her dedication to patient care.

Based on the analysis of the dissertation, the critical view of the publications, and the assessment of the role and place of dietary supplements in the therapeutic approach to primary open-angle glaucoma, I believe that the dissertation meets the criteria and rules of the institution and the law, and I recommend that the esteemed scientific jury votes positively for the awarding of the educational and scientific degree "DOCTOR" to Dr. Konstantina Grigorova Kancheva – Bandramalieva.

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Varna

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