Review

on

Prof. Marieta Ivanova Konareva-Kostianeva, MD, PhD

for a dissertation for awarding the educational and scientific degree "Doctor"

in the scientific specialty "Ophthalmology"

Author: **Dr. Konstantina Grigorova Kancheva-Bandramalieva**

Form of doctoral studies: **Full-time**

Chair: **Department of Ophthalmology and Visual Sciences, Medical University - Varna**

Topic: **"Place and role of food supplements in ophthalmological practice"**

Brief biographical data

Dr. Konstantina Grigorova Kancheva-Bandramalieva was born in 1985 in Petrich.

In 2005 she graduated from the high school with German language teaching "Johann Wolfgang von Goethe", Burgas. She graduated from the University of Duisburg-Essen, Germany with the acquisition of the Professional qualification of Doctor in 2012. The following year she started working as a doctor in SOBAL Burgas Ltd. and MCSP Dr. Ivanovi Mladost Ltd. Burgas. Since 2014 she has started training for acquiring a specialty in Ophthalmology at the Medical University Prof. Dr. Paraskev Stoyanov. In 2020 she was enrolled in the Doctoral Program: Ophthalmology at the Department of Ophthalmology and Visual Sciences, Medical University Prof. Dr. Paraskev Stoyanov, Varna.

She speaks German and English. She has very good computer literacy.

Relevance of the problem

The dissertation of Dr. Konstantina Kancheva is dedicated to the use of food supplements in glaucoma with a view to neuroprotection and preservation of visual functions beyond the reduction of intraocular pressure - a current problem in ophthalmology.

The development of new therapeutic strategies becomes a necessity in the fight against the leading causes of blindness, which, according to VISION 2020, are cataracts, glaucoma, insufficiently corrected refractive anomaly, age-related macular degeneration and diabetic retinopathy. The application of dietary supplements with antioxidant and neuroprotective properties is a possible and easily applicable concomitant therapeutic option. According to the

National Institutes of Health, dietary supplements are already being used in ophthalmological practice.

Currently, when it comes to the use of dietary supplements for glaucoma, the data are not so conclusive. The high frequency, as well as the irreversibility of changes in visual functions and the associated high disability rank glaucoma in the group of socially significant diseases. It is extremely important to develop new treatment strategies for patients with glaucoma to stop or slow down its progression without impairing the quality of life. to prove the place and role of neuroprotection in the management of glaucoma beyond the reduction of IOP. Glaucoma treatment will focus on preserving patients' visual function, both through neuroprotection and ocular hypotension.

The dissertation contains 173 pages, including 10 tables and 28 figures. 465 literature sources are cited, of which 5 are in Cyrillic and 460 in Latin. 22 more tables are added to the appendix. 7 chapters are presented, corresponding to the purpose and tasks set and meeting the requirements for the design of the dissertation.

The literature review is voluminous and informative. It occupies 53 pages of the work. The frequency and prevalence of primary open-angle glaucoma, as well as the risk factors for its onset and progression, are considered. Particular attention is paid to the pathogenesis of glaucoma, and the mechanical, vascular, immunological theories of this disease are exposed. Pathophysiological phases associated with glaucoma, such as alterations in axonal transport, oxidative stress, cytotoxins, glutamate-mediated excitotoxicity, anti-inflammatory cytokines, have been described in detail. This part of the literature review is most closely related to the topic of the dissertation. The main methods for diagnosing and monitoring glaucoma are also considered, and optical coherence tomography and computer perimetry are extensively described. The therapeutic options in the treatment of glaucoma are described, with an emphasis on neuroprotection and the drugs used in a common way in it. The literature review ends with a short summary, which is a transition to the goals and objectives.

The goal is formulated precisely, namely: To study and document the use of the dietary supplements Myelooptic and Cytisine, and to analyze the effect of their use as a concomitant therapy in patients with POAG.

The tasks set are 4. They are specific, clearly stated and ensure the fulfillment of the set goal.

The section "Material and Methods" was developed according to the rules of the dissertation. The work included 180 eyes of 90 patients (45 women and 45 men) aged 50-75 years with POAG, undergoing topical antiglaucoma therapy. The patients were randomly divided into three groups of 30 people (15 men and 15 women) and were followed for a period of 15 months. The IOP values of the respective patients were in the range of 14 - 21 mmHg.

The patients from the first group (GROUP A) took the combined dietary supplement Myelooptic, 1 ampoule per day orally (Myelooptic). Myelooptic has the following composition:

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 from the second group (GROUP B) did not take a dietary supplement.

Patients from the third group (GROUP C) took 2 tablets of Cytisine 250 mg, which is an intake of Citicoline 500 mg/24 hours. (2 x 1 tab./ 250 mg per day orally).

Food supplements were taken in 2 periods of 6 months, with an interval between them 3 months, for a total of 15 months. The criteria for inclusion and exclusion of patients with primary open-angle glaucoma are correctly defined. Patients in the formed groups are selected by similar age and sex, as well as by the degree of glaucoma damage. The correspondence in stage and duration of the disease could have an impact on the effect or lack of effect of the drugs studied.

The following research methods were performed: anamnesis of eye and general diseases, visual acuity examination with correction, Goldman tonometry, indirect ophthalmoscopy with +90 D lens, biomicroscopy, gonioscopy, OST pachymetry, as well as Standardized Computational Perimetry (SAP) and Optical Coherence Tomography (OCT). The effect of the application of dietary supplements was investigated by monitoring the functional and structural changes using standardized computer perimetry (SAP) and optical coherence tomography (OCT) in IOP within the normal range below the hypotensive local therapy used. The strategies in the last two examinations and the specifications of the devices with which they were performed are described in detail.

The results in the presented dissertation follow the tasks set and are precisely presented. First, in 4 tables, the average age and range for age, intraocular pressure and stage of glaucoma, as well as the topical medications used in the 3 groups are fixed.

On the first task, the author presented the functional results from SAP and structural results from OCT at the beginning, after the 6th and after 15th month of the followed eyes of 30 patients with POAG who received the dietary supplement Myelooptic according to the scheme. After 15 months, the mean values of MD decreased by 0.74 dB ($p<0.05$), the mean values of PSD decreased by 0.91 dB ($p<0.05$), mean RNFL Ave values increased by 3.43(μm) ($p<0.05$) and mean GCC Ave values increased by 3.62(μm) ($p<0.05$) compared to baseline. There was a statistically significant difference in the above indicators in a positive direction at the end of the follow-up.

On the second task , the mean values of the MD and PSD parameters, measured with SAP, and the RNFL and GCC parameters, measured with the OCT of the patients who did not take dietary supplements during the 15-month follow-up, were compared. A deterioration of the monitored parameters was found in this group and this deterioration was progressive - the studied indicators after the 15th month were statistically lower than the 6-month ones.

Under the third task , the mean values of the MD and PSD parameters, measured with SAP, and the RNFL and GCC parameters, measured with the OCT of the patients who also took the dietary supplement Cytisine according to the scheme for a period of 15 months, were compared. An improvement in the tracked parameters was found and the differences between the initial and final values of the studied indicators were statistically significant.

Patients from the second group (GROUP B) did not take a dietary supplement.

Patients from the third group (GROUP C) took 2 tablets of Cytisine 250 mg, which is an analogue of nicotine, 500 mg/24 hours, (2 x 1 tab/ 250 mg per day orally).

Food supplements were taken in 2 periods of 6 months, with an interval between them of 3 months, for a total of 15 months. The criteria for inclusion and exclusion of patients with primary open-angle glaucoma are correctly defined. Patients in the formed groups are selected by similar age and sex, as well as by the degree of glaucoma damage. The correspondence in structure and duration of the disease could have an impact on the effect or lack of effect of the drugs studied.

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On the fourth task, with the help of statistical methods, the results of functional and structural changes in the three groups were compared, which evaluated the effect of dietary supplements as a concomitant therapy in the treatment of POAG. In addition to descriptive and correlation analyses, the Student's test, the Wilkinson test and the one-factor analysis of variance were also used. This part is supported by multiple figures.

The ensuing discussion is extensive and very informative. The results of the dissertation work are correctly compared with the studies available in the literature.

In the summary, it was noted that the effect of taking Myelooptic was reported after the first 6-month period, while when taking Cytisine it was not so obvious in the first six months. Only in the next follow-up period was a more tangible effect of taking Cytisine reported - this suggests that this type of treatment needs time, to show relevant clinical results. No side effects or side effects have been reported as a result of taking the dietary supplements. For the entire follow-up period, there was an improvement in the parameters examined with SAP (MD and PSD) in the Myelooptic group and in the Cytisine group. taking food supplements Myelooptic and Cytisine, and in group B a deterioration of the relevant parameters was again reported.

The author points out that the long-term effect of the use of dietary supplements with neuroprotective properties on the functional and morphological characteristics of POAG has not been established, but in any case their addition to antiglaucoma therapy would not hurt. The dissertation determines that one of the limitations of the study is the heterogeneity of the glaucoma stage in the included patients, since the study is not limited to a certain stage of glaucoma. On the other hand, this characteristic provides a more realistic representation of the patient population. Another limitation of the study is the small sample analyzed, which predetermines the need for larger-scale studies on dietary supplements in the treatment of glaucoma.

It is concluded that additional studies with a longer follow-up period and carried out on a larger population will be useful for practice, as well as for clarifying the function of the optic nerve and optic pathways.

The 5 conclusions made, which are correctly and accurately presented on the basis of the results obtained, namely:

1. The intake of the dietary supplement Myelooptic by patients with POAG showed a statically significant improvement in all parameters tracked in the study.
2. In the absence of intake of food supplements within the observed period, a statistically significant deterioration of the parameters measured by SAP and OCT,
1. Taking the dietary supplement Cytisine resulted in a minimal but statistically significant improvement in MD and PSD parameters as measured by SAP and a slight increase in thickness of RNFL and GCC measured with OCT over the follow-up period.
2. The correlation analysis proved a statistically significant positive change for all group A and group C patients due to the intake of Myelooptic and Cytisine, respectively, and deterioration occurred in all group B patients within the observed 6 and 15-month periods.
3. The results of the analysis of variance show that in the three groups there is a change in the studied parameters, as in group A it is in the direction of moderate improvement, in group

On the future track, with the help of statistical methods, the results of functional and structural changes in the three groups were compared, which evaluated the effect of dietary supplements as a conservative therapy in the treatment of POAG. In addition to descriptive and correlation analysis, it is studied in the Wilkinson test and the one-factor analysis of variance were also used. This was supported by multiple figures.

The existing discussion is extensive and very informative. The results of the discussion were also correctly compared with the studies available in the literature.

In the summary, it was stated that the effect of taking Myclooptic was reported after the first 6-month period, while taking Cytisine it was not so obvious in the first six months. Only in the next follow-up period was a more tangible effect of taking Cytisine reported - this suggests that this type of treatment needs time to show relevant clinical results. No side effects or side effects have been reported as a result of taking the dietary supplements. For the entire follow-up period, there was an improvement in the parameters examined with SAP (MD and PSD) in the Myclooptic group and in the Cytisine group. Taking food supplements Myclooptic and Cytisine and in group B a deterioration of the relevant parameters was again reported.

The author points out that the long-term effect of the use of dietary supplements with neuroprotective properties on the functional and morphological characteristics of POAG has not been established, but in any case their addition to antiglaucoma therapy would not hurt. The author also determines that one of the limitations of the study is the heterogeneity of the glaucoma stages in the included patients, since the study is not limited to a certain stage of glaucoma. On the other hand, this characteristic provides a more realistic representation of the patient population. Another limitation of the study is the small sample analyzed, which predetermines the need for larger-scale studies on dietary supplements in the treatment of glaucoma.

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4. The correlation analysis proved a statistically significant positive change for all group A and group C patients due to the intake of Myclooptic and Cytisine, respectively, and deterioration occurred in all group B patients within the observed 6 and 15-month periods.
5. The results of the analysis of variance show that in the three groups there is a change in the studied parameters, as in group A it is in the direction of moderate improvement, in group

C - in the direction of a slight improvement and in group B - in the direction of deterioration of indicators.

Of the contributions indicated in the dissertation, the most valuable are those of a scientifically applied nature:

1. For the first time in Bulgaria, a prospective, long-term study has been conducted with the follow-up of functional and structural changes in patients with POAG who take the dietary supplements Myelooptic and Cytisine.

2. A comparative analysis of the rates of progression of POAG in patients with and without taking dietary supplements was made.

Dr. Konstantina Kancheva has presented 4 full-text publications related to the dissertation in scientific journals and 3 presentations at forums in Bulgaria.

Conclusion

The presented dissertation is definitely a novelty in Bulgarian ophthalmology and especially in the field of glaucomatology. It is a peek beyond the increased intraocular pressure and proves that progression in patients with POAG occurs even with well-controlled IOP. The presented work convincingly proves the benefits of using food supplements with neuroprotective and antioxidant properties as an additional option in order to slow down the progression of the disease. Modern established methods for diagnosis and monitoring of glaucoma such as computer perimetry and OCT have been applied. I consider it important that they are mastered and confirmed by the dissertation. Dr. Kancheva is well aware of the functional and structural changes that occur in the course of POAG, as well as imaging and functional studies and the available and potential drug options for POAG.

Analyzing the presented work of Dr. Kancheva, I believe that the dissertation demonstrates in-depth theoretical knowledge and clinical skills in the scientific specialty of ophthalmology. Dr. Konstantina Kancheva demonstrates the qualities for independent scientific research. She can also develop her capabilities to study the place and role of food supplements not only in the field of glaucoma, but also in other areas of ophthalmology. **"Place and Role of Food Supplements in Ophthalmological Practice"** is entirely positive and with this review I express my deep conviction that the work meets the accepted requirements for awarding the educational and scientific degree of "Doctor" in the Law on the Development of the Academic Staff in the Republic of Bulgaria.

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Plovdiv

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