REVIEW

by Prof. dr. Zortnitsa Zlatarova, MD, PhD, DSc

appointed by order of the Rector of MU - Varna, No. R-109-170/ 28.04.2026 as a member of the Scientific Jury

regarding

the defense of the doctoral dissertation

submitted by

Dr. Maria Stoeva Stoeva-Milanova

entitled **„Control of myopia"**

for the award of the educational and scientific degree Doctor (PhD) in the scientific specialty Ophthalmology, code 03.01.36

Scientific supervisor: Prof. Christina Nikolova Grupcheva, DSc

Brief Biographical Information

Dr. Maria Stoeva graduated in Medicine from the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna in 2002. In 2003, she began her residency training at the University Specialized Eye Hospital for Active Treatment – Varna, where she obtained her specialty in Ophthalmology in December 2016 after successfully passing the state examination at the Military Medical Academy in Sofia. Since 2018, she has been a lecturer in the Department of Optometry and Occupational Diseases, Faculty of Public Health, Medical University of Varna. In January 2019, she joined the University Specialized Eye Hospital – Varna as an ophthalmologist. In the same year, following a competitive selection process, she was enrolled as a full-time PhD student in Ophthalmology at the Department of Ophthalmology and Visual Sciences at the Medical University of Varna. Dr. Stoeva has participated in numerous professional training courses, including vitreoretinal surgery, ophthalmologic ultrasound and laser applications, modern methods for the assessment of retinal structural changes (FA and OCT), amniotic membrane transplantation, intravitreal drug administration, and strabology. Her scientific interests focus on myopia and on modern approaches to the diagnosis, prevention, and treatment of anterior segment diseases. She has participated in congresses organized by the Bulgarian Society of Ophthalmology and the Bulgarian Glaucoma Society. She is a member of the Bulgarian Medical Association, the Bulgarian Society of Ophthalmology, and the European Society of Cataract and Refractive Surgeons (ESCRS). She is proficient in English and Russian and possesses excellent computer skills.

Relevance of the Topic

Myopia is a type of ametropia characterized by excessive refractive power of the ocular media and/or increased axial length of the eyeball. Due to its high prevalence worldwide, the World Health Organization considers myopia one of the leading causes of avoidable visual impairment, with uncorrected refractive errors affecting approximately 123.7 million people globally. High-grade myopia is associated with an increased risk of vision loss due to related ocular pathologies, including degenerative changes in the macula and peripheral retina, retinal detachment, myopic choroidal neovascularization, glaucoma, and cataract. Numerous studies predict a continued increase in myopia prevalence worldwide, leading to the so-called "myopia pandemic" by 2050, affecting approximately 5 billion people, or 50% of the global population. The prevalence of myopia among children has increased from 24.3% in 1990 to 35.8% in 2023.

The rapid rise in myopia prevalence, particularly in urbanized areas, together with its association with severe ocular complications, makes it a major public health concern. Consequently, myopia control has become the focus of extensive research and the development of various strategies aimed at slowing the disease progression. Pharmacological treatment with atropine, orthokeratology, bifocal and multifocal lenses, and peripheral defocus lens designs are among the most extensively studied and widely applied methods for control globally. In Bulgaria, however, there is still no national epidemiological study on myopia prevalence, nor a unified algorithm for slowing its progression.

Dr. Stoeva's dissertation addresses precisely these issues through the investigation of demographic characteristics, myopia severity, and the impact of different myopia-control methods on disease progression in children aged 6–16 years. This makes the study both timely and of considerable practical value.

Structure of the Dissertation

The dissertation is prepared in accordance with the contemporary academic standards and comprises of 225 pages, including: Abbreviations – 2 pages; Figures – 4 pages; Tables – 3 pages; Abstracts in Bulgarian and English; Introduction – 3 pages; Literature Review – 79 pages; Aim and Objectives – 1 page; Materials and Methods – 16 pages; Results – 40 pages; Discussion – 43 pages; Conclusions – 2 pages; Summary – 2 pages and Contributions – 1 page.

The dissertation contains 34 tables and 49 figures and cites 256 references, including 4 in Cyrillic and 252 in Latin.

The literature review is comprehensive, well-structured, and supported by appropriately adapted tables and figures. It provides a detailed analysis of the pathophysiology and epidemiology of myopia, the risk factors for its onset and progression, contemporary diagnostic methods, and current approaches to correction and myopia control worldwide. Special attention is devoted to the latest developments in the field. Three key conclusions are formulated, providing a sound rationale for the research presented in the dissertation.

The **aim** of the dissertation is **"to conduct a prospective investigation and analysis of the demographic characteristics and degree of myopia, and to evaluate the clinical efficacy of the applied myopia-control methods over a five-year period in patients aged 6–16**

years from the city of Varna who were treated at the University Specialized Eye Hospital – Varna."

To achieve this aim, the doctoral candidate has set the following 6 objectives:

1. To review the scientific literature regarding contemporary myopia-control methods and their effectiveness globally.
2. To determine the degree of myopia and its progression among the patients included in the study.
3. To analyze changes in axial eye length using optical biometry (IOLMaster 500, Carl Zeiss Meditec) and keratometric parameters using corneal topography (Pentacam®, Oculus).
4. To compare the effectiveness of the different myopia-control approaches applied in the study population.
5. To assess the participants' subjective symptoms, quality of life, and visual function before and during treatment.
6. To develop a questionnaire for children and parents regarding patients' subjective symptoms that could support eye-care professionals in clinical practice.

Materials and Methods

The study was conducted at the University Specialized Eye Hospital for Active Treatment – Varna between September 1, 2020, and September 1, 2025. A total of 92 patients were enrolled according to clearly defined inclusion criteria. Participants were verbal children from Varna aged 6–16 years with myopia and refractive error ≤ -2.00 D, astigmatism ≤ 1.00 D, anisometropia ≤ 1.50 D, no history of ocular surgery or trauma, no systemic diseases affecting vision, and no reported psychiatric disorders. Informed consent was obtained from their parents or guardians. The study was approved by the Ethics Committee of the Medical University of Varna (Protocol No. 129/06.04.2023). Patients were allocated to four therapeutic groups, each sufficiently large to allow statistical analysis. The mean age was 11.57 ± 2.52 years, with no statistically significant differences between groups ($p > 0.05$). The groups were also balanced regarding sex distribution and myopia severity, reducing the risk of systematic bias.

The methodology included **a documentary method** conducted by a literature analysis on the available scientific data on the approaches for myopia control and their efficacy, evaluation of the axial length progression and refractive error, assessment of the mechanisms of action of the said methods and indications for different myopia-control methods, and examination of emerging preventive approaches.

The **sociological method** comprised the development of a three-component questionnaire specifically for the aim of this dissertation due to the lack of a validated Bulgarian-language questionnaire assessing the quality of life in children and adolescents with myopia. The questionnaire was based on the Pediatric Refractive Error Profile (PREP) and the Screen for Child Anxiety Related Emotional Disorders (SCARED).

Clinical assessment included medical and family history taking, autorefractometry with keratometry, visual acuity testing, cycloplegic retinoscopy, optical biometry (ZEISS IOLMaster 700 with SWEPT Source Biometry®), and corneal topography (Pentacam®, Oculus).

Dr. Stoeva applied current **statistical methods** for data processing, which guarantee the reliability of the obtained results, namely analysis of variance (ANOVA, MANOVA), variation, correlation, regression and comparative analysis, and risk assessment analysis (OR, RR). In all analyses, an acceptable level of significance of $p<0.05$, $p<0.01$, $p<0.001$ at a standard confidence interval of 95% is assumed. The data were statistically processed using SPSS v.20, using descriptive indicators for quantitative and qualitative variables, presented in tabular and graphical form.

Results

1. Results from the analysis of the socio-demographic characteristics of the patients with myopia.

Among the participants included in the study, 40 were male (43.48%), and 52 were female (56.52%). The mean age of myopic patients was 11.57 years, with the lowest being 8 years and the highest being 17 years of age. In terms of the spherical equivalent (SE), 78% of the participants had low-grade myopia, and nearly 82% had astigmatism, with mean values of SE -4.27 D and Cyl -0.82 D. A predominance of the female gender was established, as well as of patients spending between 3 and 6 hours a day working at a close range distance and between 1 and 3 hours outdoors. A familial burden of myopia was found in 56 of the studied patients, with both parents being myopic in 31 cases.

2. Results on the quality of life before and after myopia-control interventions

The Cronbach's alpha of the questionnaires was higher than 0.6, indicating acceptable internal consistency. Higher quality of life scores were reported in patients using multifocal contact lenses and Ortho-K lenses. Participants with myopia above -6.00 D demonstrated higher levels of anxiety and lower visual quality compared to the other groups. The distribution of patients concerning the corrective device and the results of the anxiety questions showed the worst results in the groups of patients with glasses (median - 26) and atropine drops (median - 15), and the best results in the group of children and adolescents fitted with MCL (median - 2) and Ortho-K (median - 2). According to the distribution of patients with the lowest quality of life, represented by the worst scores on the Quality of Vision and Mood Disorders Questionnaire and anxiety levels, the results were calculated for each group separately and represented 36.96% of all participants (34 out of 92 patients). The worst results were reported in the monofocal glasses group – 44.12%, followed by the atropine drops group – 35.29%, 3 from the Ortho-K group – 8.83%, and 4 from the MCL wearers – 11.76%. Patients with myopia above -6.00 D had the highest anxiety scores and lower visual quality among all participants with myopia.

3. Results of the assessment of subjective symptoms of myopic patients included in the study.

In the study of patients with myopia, the following indicators were used to assess subjective symptoms: blurred vision, headache, and pain. The results show that nearly 20% of patients experience pain before the application of a certain method for myopia control, 57.61% have blurred vision, 26.09% headache. A significant impact on the pain syndrome, followed by blurred vision, was observed already at the sixth month after randomization in a certain group, with only 4.35% reporting pain, 14.13% for blurred vision, and 9.78% for headache. A statistically significant difference was found in the perceptions of pain and blurred vision in patients with different degrees of myopia, regardless of the method for controlling myopia before treatment and after randomization in a certain group.

It is striking that a large proportion of patients in the atropine drops group continued to report blurred vision and headache, which is probably due to the side effects of the drop therapy, in terms of blurred vision at the sixth month – 69.23% of all reported patients using atropine drops (n=9), and in terms of headache – 77.77% (n=7). In the first year of the study, 3.26% had pain, 10.87% had blurred vision (atropine drops group: n=6), and 7.61% had headache, with the largest proportion again being patients in the atropine therapy group (n=5). In the second year, patients did not report pain, 7.61% had blurred vision, and 4.35% had headache, with the observed data again being highest in the pharmacological agent group (n=4 and n=2, respectively) ($p<0.001$).

A statistically significant difference was found in the perceptions of blurred vision and pain in patients with different degrees of myopia ($p<0.001$). The most prominent subjective symptomatology before randomization to a certain group was reported in patients with high-degree myopia – 83.33% of all patients with myopia ≥-6.00 diopters reported pain at the beginning of the study (n=15 out of 18), 37.74% for blurred vision (n=20 out of 53), and 79.16% for headache (n=19 out of 24).

4. Results of the analysis of the efficacy of the approach used to control myopia.

The lowest progression of axial length (AL) for the right and left eyes was observed in patients with Ortho-K lenses and on atropine therapy, while the highest progression was found in the spectacle control group ($p<0.001$). The Ortho-K lens group showed a statistically significant lowest progression of both AL and SE, followed by the atropine therapy group, especially compared to patients using soft contact lenses and spectacles. Spectacles showed the highest axial growth and refractive error shift, suggesting that they are the least effective in progression control. Atropine and MCL fall in the middle, with atropine showing better control of SE than AL. The greatest retention of values was observed up to the first year of application of the introduced control method. In terms of effect sizes, Ortho-K lenses and atropine drops showed a truly large effect compared to the control group. An average effect was reported when comparing the groups of patients with Ortho-K lenses and atropine drops – 0.61 for the right eye and 0.70 for the left eye, respectively. Glasses and MCL show a wider range, which means greater variability and less effective control than Ortho-K lenses. Visual acuity remains almost unchanged for all groups, which indicates the safety of the applied therapeutic methods. The analysis of variance shows that the applied methods for myopia control have a statistically significant effect. No statistically significant difference was found

with respect to the time of application of the specified control approaches, nor with respect to the combination of a certain method and time of action.

There is a tendency towards an increase in AL, more pronounced after the first year of application of the respective method for myopia control, as well as an expected deepening of the negative values of SE with progressive myopia. Faster progression of SE and AL was found in patients between the ages of 8 and 12 years, as well as in females.

5. Results of the analysis of data obtained from the highly specialized research conducted.

Various ocular biometric parameters, including axial length (AL), central corneal thickness (CCT), anterior chamber depth (ACD), corneal curvature (CC), corneal curvature radius (CR), and axial length to corneal radius ratio (AL/CR ratio), were measured using optical biometry and corneal topometry. At baseline, the mean values measured for ACD were 3.57±0.33 mm and 19.96±1.42 mm for vitreous depth. After 2 years of follow-up, a trend towards greater myopization and axial elongation was observed in all age groups. Younger participants had significantly ($p<0.001$) higher levels of myopic shift and axial elongation compared to older participants (>16 years).

The results also showed a significant increase in AL, AL to CR ratio, and ACD in both low and high-grade myopia groups. CC also showed increased mean values, while decreased values were observed in CCT and CR values.

In the low-grade myopia group, ACD values were greater with the increasing of AL (Pearson coefficient=0.338, $p<0.01$). In the high-grade myopia group, no correlation was found with AL (Pearson coefficient=0.057, $p=0.233$). Similar CC values were obtained for both eyes, and a correlation was found between refractive error and AL (Pearson coefficient=−0.579, $p<0.001$), but not with CC.

The results obtained from IOLMaster and Pentacam regarding the measured values of anterior chamber depth, keratometry, and astigmatism were compared and evaluated by a paired t-test. Both devices demonstrated no statistically significant difference in determining the anterior chamber depth ($p=0.270$). IOLMaster demonstrated steeper K1 values and higher mean ▲K values than Pentacam ($p=0.001$; $p<0.001$). No statistically significant difference was observed between the two devices when measuring patients with astigmatism ($p=0.476$).

6. Results of determining the risk profile of the studied patients with myopia and predicting the risk of progression.

From the obtained data, it was suggested that the risk profile for myopia progression is female gender, having a familial burden of two myopic parents, annual progression rate in SE ≤ - 1.00 D, younger age of onset ≤ 13 years, and spherical equivalent (SE) values ≤ - 6.00 D. No statistically significant difference was reported in terms of intensive near-distance activity, nor in time spent outdoors. From the surveys conducted, the average hours per day spent working at near-distance of the study patients were 6.65±3.78 hours/day, and time spent in outdoor activities was 2.15±1.73 hours/day. The highest number of parents chose soft contact lenses for myopia control (n=30), with the results for the other types of methods being similar

- atropine drops (n=23), Ortho-K (n=20), and 19 parents noted that they were not sufficiently informed.

In the chapter "**Discussion**", the authors' results are consistently and thoroughly examined, analyzed, and compared to the studies of other authors, indicating the similarities and differences between them.

Dr. Stoeva makes 7 well-founded conclusions in her dissertation paper, as follows:

1. Myopia control requires a personalized approach to patients, an examination of their subjective symptoms and quality of life, as well as the attitude of parents/guardians. In order for any approach for progression control to be successful, eye specialists must compare the individual benefit-to-risk ratio for specific patients.

2. Myopia progression correlates with the age of the patient and the onset of myopia, as well as with the severity of ametropia.

3. Female gender (OR 1.83), both parents having myopic refraction (OR 2.57), annual progression in SE≤-1.00D (OR 3.43), and early age of onset ≤13 years. (OR 4.19) and the absolute value of SE≤-6.00D (OR 6.43) emerged as risk factors for myopia progression.

4. After 2 years of follow-up, there was a trend towards greater myopization and axial elongation in all age groups. Younger participants had significantly higher levels of myopic shift and axial elongation compared to older participants.

5. After analyzing the objective progression by performing highly specialized studies to record changes in AL values, it became clear that the data from the study were similar to the results of other authors - the most effective for controlling axial progression were Ortho-K lenses, followed by atropine drops and MCL. Identical results were also reported for SE values.

6. The assessment of the subjective symptoms of the patients included in the study shows that pain, blurred vision, and headache had the strongest impact on the visual function and normal perception of the participants. The results improved significantly already at the sixth month of the introduction of the respective control method. However, a large part of the atropine drops group continued to report persistent symptoms, which decreased by the second year of observation.

7. The best results regarding the quality of life were reported by the group of patients corrected with multifocal and Ortho-K lenses. Increased levels of anxiety among the representative sample of patients were observed among the control group, followed by the patients on atropine drops. The lowest quality of life related to vision and increased levels of anxiety were obtained by the patients with monofocal glasses and/or myopia of -6.00D.

The following can be mentioned as important **contributions** of the dissertation work of a cognitive, scientifically applied and practical nature:

1. A detailed analysis of the available data in the scientific literature on the methods of myopia control, their individual efficacy and application, their advantages and disadvantages related

to the annual progression in SE and AL, the subjective symptoms of the patients and their quality of life on a European and global scale.

2. For the first time in our country, an assessment of the subjective signs and quality of life children and adolescents with myopia, who underwent observation at USEHEDAT-Varna, was made.

3. An analysis of the subjective symptoms, quality of life related to vision, anxiety levels and annual progression in the values of SE and AL and their relationship with socio-demographic characteristics, habits and method of myopia control was carried out.

4. The advantages of myopia control using Ortho-K lenses in the areas of subjective symptoms, quality of life and slowing of axial progression have been established, as a more reliable and safer method for controlling this socially significant ametropia.

5. A risk profile for myopia progression has been created for children and adolescents with myopia from the city of Varna.

Publications Related to the Dissertation

Dr. Stoeva-Milanova has presented two publications related to the dissertation topic, one as a first author and one as a sole author, thereby fulfilling the minimum scientometric requirements for obtaining the educational and scientific degree of Doctor (PhD).

The **dissertation abstract** consists of 94 pages and is prepared in accordance with the applicable requirements. Its content accurately reflects the dissertation.

I have known Dr. Stoeva since the beginning of her residency training at the University Specialized Eye Hospital – Varna. Throughout the years, she has consistently demonstrated herself to be a highly conscientious and dedicated physician and educator. She is cooperative, capable of working effectively within a team, and strongly committed to professional development and lifelong learning.

In conclusion, I believe that the dissertation presented by Dr. Maria Stoeva Stoeva-Milanova on the topic "Control of Myopia" is relevant, with a strong scientific and applied significance. The dissertation fully meets the requirements for awarding the educational and scientific degree "doctor" specified in the Act on the Development of the Academic Staff in the Republic of Bulgaria and the Regulations for its implementation at MU-Varna. All this provides me with a reason to grant my positive assessment and to propose to the esteemed Scientific Jury to award Dr. Maria Stoeva Stoeva-Milanova the educational and scientific degree "doctor" in the scientific specialty "Ophthalmology".

04.06.2026

Varna

Reviewer:

Prof. Zornitsa Zlatarova, MD, PhD, DSc