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Changes of eye's functions among patients with age-related macular degeneration during the use of vitamin D medications

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Aim. To increase the effectiveness of the treatment of age-related macular degeneration (AMD), dry form, in postmenopausal women by determining the level of serum vitamin D and correcting its deficiency.

Materials and methods. The study was conducted on the basis of the Department of Ophthalmology at Bogomolets National Medical University, was prospective, case-control, included 88 women (88 eyes) aged 72.0 ± 10.1 years, who were divided into 2 groups: control group – 20 patients (20 eyes) without AMD and study group – 68 patients (68 eyes) with AMD, dry form.

Results. Supplemental vitamin D did not significantly improve visual acuity, but slowed the deterioration of contrast sensitivity. Deficiency of vitamin D is associated with lower visual acuity, negatively affects contrast sensitivity, more strongly than its insufficiency. The results of the treatment in the AREDS-2 + vitamin D group after 12 months showed a probable double increase in the content of 25(OH)D in patients with AMD, dry form ($p < 0.05$). Visual acuity after 12 months decreased by 7.56 % (from 0.19 ± 0.06 to 0.20 ± 0.06) in women who took only AREDS-2 drugs, and by 6.78 % (from 0.18 ± 0.07 to 0.19 ± 0.08) in the group where vitamin D medications were additionally prescribed ($p > 0.05$). Logarithmic indicators of contrast sensitivity after treatment had a slight negative trend in both groups, decreased by 2.80 % in women in the AREDS-2 group, and by 2.25 % in women who additionally took vitamin D medications ($p > 0.05$).

Conclusions. Irreversible vision loss is a global problem with both medical and socioeconomic consequences. Age-related macular degeneration is one of the main diseases that lead to blindness, especially in people over 50 years old. Additional prescription of vitamin D to AREDS-2 may be beneficial in slowing the progression of AMD. Further studies are needed to confirm these results.

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Зміни функціональних показників органа зору у пацієнтів із віковою дегенерацією макули за умов застосування вітаміну D

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Мета роботи – підвищити ефективність лікування вікової дегенерації макули (ВДМ) сухої форми у жінок постменопаузального віку шляхом визначення рівня сироваткового вітаміну D та корекції його недостатності.

Матеріали і методи. Дослідження здійснили на базі кафедри офтальмології Національного медичного університету імені О. О. Богомольця. Дослідження проспективне, випадок – контроль. Залучено 88 жінок (88 очей) віком 72,0 ± 10,1 року, яких поділили на 2 групи: контрольна – 20 пацієнток (20 очей) без ВДМ; група дослідження – 68 пацієнток (68 очей) з ВДМ сухої форми.

Результати. Додаткове приймання вітаміну D не спричинило значного покращення гостроти зору, однак уповільнило погіршення контрастної чутливості. Дефіцит вітаміну D пов'язаний із нижчими показниками гостроти зору, впливає на контрастну чутливість істотніше, ніж його недостатність. Результати лікування у групі AREDS-2 + вітамін D через 12 місяців показали вірогідне підвищення (вдвічі) вмісту 25(OH)D у пацієнток з ВДМ сухої форми ($p < 0,05$). Гострота зору через 12 місяців знизилася на 7,56 % (з 0,19 ± 0,06 до 0,20 ± 0,06) у жінок, які отримували лише препарати AREDS-2, та на 6,78 % (з 0,18 ± 0,07 до 0,19 ± 0,08) у групі, де додатково призначали препарати вітаміну D ($p > 0,05$). Логарифмічні показники контрастної чутливості після лікування мали незначну негативну динаміку в обох групах, знизилися на 2,80 % у жінок із групи AREDS-2 та на 2,25 % у жінок, які додатково отримували препарати вітаміну D ($p > 0,05$).

Висновки. Незворотна втрата зору – глобальна проблема, що має і медичні, й соціально-економічні наслідки. Вікова дегенерація макули є одним з основних захворювань, що призводить до сліпоти, особливо у людей, старших за 50 років. Додаткове приймання вітаміну D разом із AREDS-2 може бути корисним для уповільнення прогресування ВДМ. Потрібні наступні дослідження для підтвердження цих результатів.

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Irreversible vision loss is a worldwide problem that goes beyond medical issues and has a profound impact on the socio-economic sphere. People with visual impairment require expensive care, which places a significant burden on both the state budget and their families.

More than 2.2 billion people worldwide suffer from visual impairment, and half of these cases are preventable or treatable [1].

Major diseases leading to visual impairment and blindness include cataracts (94 million cases), refractive anomalies (88.4 million), age-related macular degeneration (8 million), glaucoma (7.7 million), and diabetic retinopathy (3.9 million). These conditions cause significant economic losses, for example, the annual loss of work productivity due to visual impairment is estimated at US $411 billion [1].

Visual impairment affects people of all age groups but is particularly common in those aged 50 and above [1]. By 2030, the world population aged 60 and over is projected to grow from 962 million in 2017 to 1.4 billion, while the number of people over 80 is expected to increase from 137 million to 202 million [2]. This demographic transition will consequently elevate the prevalence of severe eye diseases.

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries and is the third leading cause of blindness worldwide, behind cataract and glaucoma. By 2019, approximately 196 million individuals worldwide were diagnosed with AMD [2]. AMD cases are expected to increase 1.5 times in the United States by 2050, despite efforts to prevent and treat neovascular form of AMD [3].

The prevalence of age-related eye diseases is expected to increase. The number of people diagnosed with AMD is projected to increase 1.2 times to approximately 243.3 million by 2030. In Europe, the number of AMD patients was around 67 million in 2020 and is projected to increase to 77 million by 2050 [2]. The prevalence of AMD is projected to increase by 15 % and the incidence by 75 % by 2050 [4]. By 2040, Europe is expected to have 14.9–21.5 million cases of early-stage AMD and 3.9–4.8 million cases of late-stage AMD [5].

Clinical studies indicate that more than 10 % of people aged 65–74 have symptoms of AMD, this figure rises to 25 % among people aged 75 and over and exceeds 30 % among people over 85. Notably, if AMD is diagnosed in one eye, the other eye is usually affected within 5 years [6].

AMD is a complex disease influenced by various factors. Although the role of vitamin D in the development of this disease is widely discussed in the current literature, a definitive conclusion remains inconclusive.

Certain studies suggest a correlation between vitamin D deficiency and an elevated risk of AMD [7,8,9,10,11,12]. On the contrary, other research does not find such an association [13]. The precise mechanism by which vitamin D influences AMD remains unclear and requires further study.

It is critical to recognize that vitamin D deficiency is widespread throughout the world [14]. According to the World Health Organization (WHO), 50–80 % of the world's population have insufficient level of this vitamin [14]. In Poland, nearly 90 % of the population has low level of vitamin D [15]. Similarly, in Ukraine, over 90 % of the population suffers from vitamin D deficiency, according to Povoroznyuk [16]. Moreover, among 24.6 million women in Ukraine, more than half are postmenopausal [16]. According to WHO data for 2015, women aged 45 years and older accounted for 46 % of the world's total female population [2].

Vitamin D insufficiency can adversely affect health, contributing to the onset of various pathologies, including immune and autoimmune disturbances, cardiovascular diseases, metabolic disorders, and cancer [17].

Aim

To increase the effectiveness of the treatment of age-related macular degeneration, dry form, in postmenopausal women by determining the level of serum vitamin D and correcting its deficiency.

Materials and methods

The study was conducted at the clinical base of the Department of Ophthalmology of the Bogomolets National Medical University and was a prospective, case-control study.

All studies were conducted in accordance with the bioethical requirements of the Declaration of Helsinki adopted by the General Assembly of the World Medical Association on the ethical principles of scientific medical research involving human subjects (1964, with subsequent additions, including the 2000 version), the European Convention of Human Rights and Biomedicine (1977), the corresponding provision of the World Health Organization, the International Council of Medical Scientific Societies, the International Code of Medical Ethics (1983), the laws of Ukraine, and the order of the Ministry of Health of Ukraine No. 690 dated by 09/23/2009. Conducting of this study was agreed and approved by the Commission on Bioethical Expertise and Ethics of Scientific Research at the Bogomolets National Medical University.

Women (88 people, 88 eyes) aged 72.0 ± 10.1 years were included in the study.

The criteria for including patients in the study were as follows: women in the postmenopausal period; presence of confirmed age-related macular degeneration, dry form (main group) or its absence (control group); presence of confirmed decrease in vitamin D level.

All patients evaluated in the study were divided into the following groups: group I – 20 patients (20 eyes) without age-related macular degeneration in both eyes (control group). We used data obtained from control group patients to establish reference values; group II – 68 patients (68 eyes) with age-related macular degeneration, dry form (study group).

Similarly to patients in the study group, patients in the control group also had vitamin D deficiency and insufficiency in the blood.

Depending on the chosen approach to patient care, individuals with age-related macular degeneration, dry form (study group), were divided into the following groups:

– AREDS-2 group – 34 patients (34 eyes) diagnosed with age-related macular degeneration, dry form, underwent treatment with medications following the AREDS-2 formula. The treatment

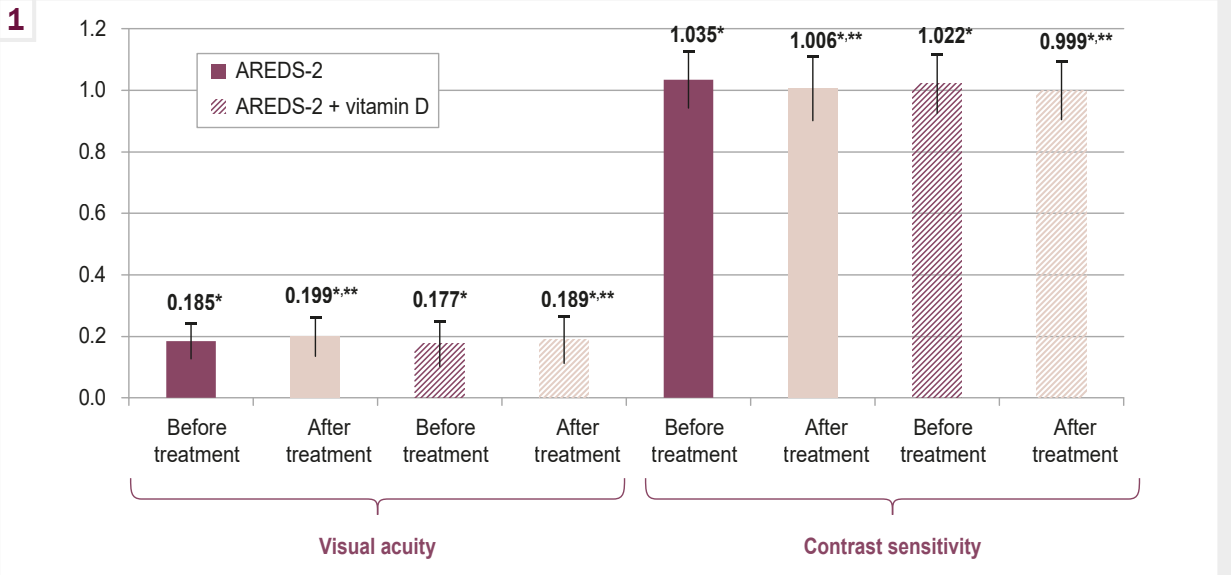

Fig. 1. Changes in visual functions among patients with age-related macular degeneration, dry form, during treatment (X ± σ). ***:** p > 0.05 when comparing groups; ****:** p < 0.05 when comparing before / after within the group.

regimen involved taking 1 capsule twice daily for 2 months, with a 3-month interval between courses. This cycle was repeated three times a year;

– AREDS-2 and vitamin D group – 34 patients (34 eyes) diagnosed with age-related macular degeneration, dry form, received a combination of AREDS-2 drugs and vitamin D supplements for treatment purposes. Additionally, to the traditional therapy with AREDS-2 drugs, these patients were also prescribed vitamin D supplements at a dosage of 6000–8000 IU per day for 2 months, with a 3-month interval between courses of treatment. This regimen was maintained until optimal levels of vitamin D in the blood were achieved.

To present the research findings, descriptive statistical methods were used. Quantitative variables taken from the electronic primary database are presented as mean values with standard deviations. The Student's t-test was applied for normally distributed quantitative variables, while non-parametric tests were used for data that did not follow a normal distribution. Specifically, the Mann–Whitney U test assessed the significance of differences between means in independent populations. Also, routine indicators of visibility were used to compare the indicators obtained in different observation groups (to compare indicators in dynamics – growth / decrease rates). For analysing time-based changes in related samples, one-factor ANOVA was used for normally distributed data, and the Wilcoxon signed-rank test for non-normal distributions. Correlation analysis methods included Pearson's linear correlation coefficient for normal distributions and Spearman's rank correlation coefficient for non-normal distributions to determine relationships between quantitative indicators. Statistical significance was evaluated at a threshold of no more than 5 % ($p < 0.05$). Statistical processing of primary data was conducted using MedStat V5.2 and EZR (R-Statistics) software packages.

Results

Following treatment, the visual acuity of women who received medication according to the AREDS-2 formula was measured at 0.20 ± 0.06 *(Fig. 1)*. Conversely, the visual acuity of women from the AREDS-2 and vitamin D group was recorded at a level of 0.19 ± 0.08 *(Fig. 1)*.

Contrast sensitivity indicators after the course of treatment were 1.01 ± 0.10 and 1.00 ± 0.09, respectively *(Fig. 1)*.

It can be observed from the data that the visual acuity indicators within the specified research groups showed minor variances, remaining relatively stable compared to the baseline ($p < 0.05$).

There was a decrease of 7.56 % in visual acuity among women who only took AREDS-2 drugs, and a decrease of 6.78 % in the group additionally prescribed with vitamin D drugs. However, no significant differences in the deterioration of visual acuity were noted when comparing the groups ($p > 0.05$) *(Fig. 1)*.

Following the treatment, the logarithmic contrast sensitivity indicators exhibited a slight decline in both groups, although a more pronounced decrease was noted among women in the AREDS-2 group.

Specifically, contrast sensitivity decreased by 2.80 % among women from the AREDS-2 group, whereas in those who also received vitamin D medications, the decrease was only 2.25 %. Nevertheless, upon comparing the groups, these differences did not reach statistical significance ($p > 0.05$) *(Fig. 1)*.

Upon analyzing the results of the dynamic observation two months after initiating treatment, no significant changes were observed in visual acuity and contrast sensitivity indicators ($p > 0.05$) both within the groups and between them ($p > 0.05$) *(Table 1)*.

However, starting from the fifth month of the study, a notable decline in visual acuity was noted among women who solely received AREDS-2 drugs ($p < 0.05$), whereas women who were additionally administered vitamin D preparations did not

Table 1. Observation of visual functions over time in patients with age-related macular degeneration, dry form, during treatment, X ± σ

Parameter, units of measurement	Examination terms	AREDS-2 group	AREDS-2 + vitamin D group	Level of difference between groups, p
Visual acuity	In 2 months	0.19 ± 0.06	0.18 ± 0.07	>0.05
	In 5 months	0.19 ± 0.06	0.18 ± 0.09	>0.05
	After 12 months	0.20 ± 0.06	0.19 ± 0.08	>0.05
	Level of difference between groups, p (2 months – 12 months)	<0.05	<0.05	
Contrast sensitivity	In 2 months	1.03 ± 0.10	1.02 ± 0.09	>0.05
	In 5 months	1.02 ± 0.10	1.02 ± 0.10	>0.05
	After 12 months	1.01 ± 0.10	1.00 ± 0.09	>0.05
	Level of difference between groups, p (2 months – 12 months)	<0.05	<0.05	

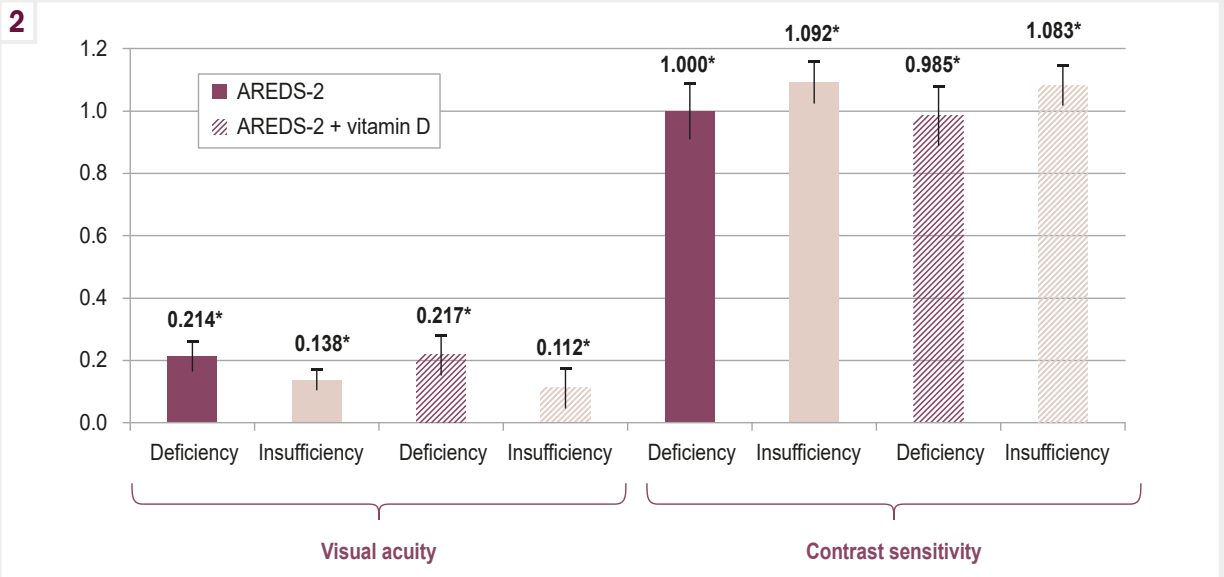

Fig. 2. Comparison of visual acuity and logarithmic contrast sensitivity indicators among patient groups with varying levels of vitamin 25(OH)D supply, during treatment (X ± σ). ***:** p > 0.05 when comparing groups.

experience alterations in visual acuity. Moreover, no significant alterations were observed in contrast sensitivity indicators, both between groups and within the groups (p > 0.05) *(Table 1)*.

Upon examination conducted 12 months after initiating treatment for age-related macular degeneration using the conventional regimen and with the incorporation of vitamin D supplements, it was observed that the progression of visual acuity and contrast sensitivity decline was slightly more pronounced among women receiving only traditional therapy *(Table 1)*.

Upon comparing the visual acuity levels among groups of patients with varying levels of vitamin 25(OH)D, it was observed that in women receiving only traditional treatment, those with vitamin D deficiency exhibited lower acuity compared to those with insufficiency (p < 0.05) *(Fig. 2)*.

Among women prescribed AREDS-2 formula drugs, maximum corrected visual acuity was 0.21 ± 0.05 for those with vitamin D deficiency, slightly higher (at 0.14 ± 0.03) for those with insufficiency. A similar trend was noted among women who supplemented with additional vitamin D medications: 0.28 ± 0.06 and 0.11 ± 0.06 respectively.

Comparing the groups based on their vitamin D levels, it was observed that visual acuity was lower among individuals with a deficiency compared to those with insufficiency *(Fig. 2)*.

When examining logarithmic contrast sensitivity indicators among patient groups with varying levels of vitamin 25(OH)D supply, we observed differences. In the group receiving vitamin D medications alongside traditional therapy, contrast sensitivity was higher in patients with vitamin D insufficiency (1.08 ± 0.06) compared to those with deficiency (0.99 ± 0.09, p < 0.05).

This trend was similarly observed in the group undergoing only traditional therapy (1.09 ± 0.07 and 1.00 ± 0.09, respectively, p < 0.05) *(Fig. 2)*.

However, comparing the vitamin D levels between the groups revealed similar levels of contrast sensitivity.

Discussion

Age-related macular degeneration stands as a significant retinal ailment impacting millions of individuals globally. Its prevalence is on a steady rise, currently reaching 8.7 %. Predictions suggest that by 2040, AMD could afflict up to 288 million people [18].

In the United States, AMD holds a prominent position among the leading causes of blindness, trailing only glaucoma and cataracts [19]. The annual economic toll resulting from AMD-induced vision loss is estimated at $4.6 billion solely for medical expenses in the US [20].

AMD profoundly impacts quality of life, complicating tasks like reading, using electronic devices, driving, and recognizing familiar faces, potentially leading to depression [20].

In the prospective multicenter randomized clinical trial AREDS (Age-Related Eye Disease Study), it was revealed that over 10 % of individuals aged 65–74 exhibit symptoms and signs of AMD [6]. This figure escalates to 25 % among those over 75 years old and surpasses 30 % among individuals over 85 years old.

The dry form of AMD constitutes 85–90 % of all AMD cases globally. However, approximately 80 % of vision loss is due to the wet form of AMD [21]. Measures that correct pathogenetic changes and slow down the transition of the dry form to the wet form are relevant.

Regrettably, there is a lack of current data regarding the prevalence and incidence of AMD in Ukraine. The most recent official statistics, dating back to 2017 and published on the Ministry of Public Health website, focus on retinal diseases. According to these figures, approximately 1.5 million adults are afflicted with ocular and appendage disorders, with around 30 % of them grappling with retinal ailments [22].

The war in Ukraine has caused serious disruptions in the country's healthcare system, making it difficult for the population to access proper medical care, including ophthalmological care. This can lead to delays in the diagnosis and treatment of AMD, potentially exacerbating its course and increasing the risk of vision loss.

Certain scientific research has established a correlation between vitamin D levels and its protective role against various eye conditions, including refractive errors, diabetic retinopathy, dry eye syndrome, and choroidal inflammation [23]. Nonetheless, the precise mechanism by which vitamin D levels influence the pathogenesis and progression of AMD is still under investigation.

Scientific literature suggests that receptors for vitamin D are distributed across more than 38 tissues in the body. Vitamin D plays a crucial role in regulating essential genes associated with bone metabolism, oxidative stress, chronic ailments, and inflammation [24]. It is also known to affect angiogenesis, reducing its manifestations [25,26].

Receptors for vitamin D are also identified in the retina, particularly in the pigment epithelium and choroid, hinting at the potential involvement of this vitamin in retinal disorders [25]. Thus, we can assume the possibility of a negative effect of reduced vitamin D level on the retina, limiting its potential protective functions.

In 2007, findings from the third National Health and Nutrition Examination Survey (NHANES III) revealed a potential protective link between vitamin D levels and AMD [27]. Since then, scientists from all over the world have conducted a number of studies, but the results are of the opposite nature [28,29,30].

Experimental research has focused on exploring the impact of vitamin D metabolites on AMD. In 2016, findings were released indicating a notable inverse association between vitamin D levels and advanced stages of AMD [31].

The significance of diet in AMD was initially highlighted in the outcomes of the National Health and Nutrition Examination Survey (NHANES) conducted in 1988 [32]. This study identified that a diet rich in vitamin A from vegetables and fruits was correlated with a reduced risk of AMD.

Subsequent research has confirmed the significance of dietary factors, prompting clinical trials to assess the impact of specific antioxidant vitamins, omega-3 fatty acids, and minerals such as zinc and copper in AMD management [27,29]. To conduct research in this area, the AREDS was established. Initial clinical investigations from AREDS (AREDS-1) revealed that the administration of a compound containing beta-carotene, vitamins C, E, and zinc decelerates AMD progression, particularly its advanced wet form [33].

Further advancements in nutritional supplements for AMD emerged with the formulation of AREDS-2, comprising 500 mg of vitamin C, 400 IU of vitamin E, 10 mg of lutein, 2 mg of zeaxanthin, 80 mg of zinc as zinc oxide, and 2 mg of copper as copper oxide [33].

Currently, there exists no unanimous consensus on the impact of vitamin D supplements in preventing or slowing down the progression of AMD. The majority of studies are experimental in nature, and clinical findings present varying perspectives on this matter.

Thus, there are currently no unified methods for the primary or secondary prevention of AMD by correcting vitamin D levels, despite the high prevalence of vitamin D deficiency or insufficiency in the general population, especially among people over 65 years of age and postmenopausal women [15,16].

Conclusions

1. Following 12 months of treatment, the AREDS-2 + vitamin D group showed a likely twofold increase in 25(OH)D levels among patients with age-related macular degeneration, dry form ($p < 0.05$). Visual acuity, however, experienced a decline of 7.56 % (from 0.19 ± 0.06 to 0.20 ± 0.06) in individuals receiving only AREDS-2 drugs, and 6.78 % (from 0.18 ± 0.07 to 0.19 ± 0.08) in those additionally prescribed vitamin D preparations, although without statistical significance ($p > 0.05$). Contrast sensitivity exhibited a minor downward trend in both groups post-treatment, with a decrease of 2.80 % in the AREDS-2 group and 2.25 % in the group receiving vitamin D supplements ($p > 0.05$).

2. The use of vitamin D preparations slows down the progression of contrast sensitivity, which can be used in the treatment and prevention of age-related macular degeneration.

Prospects for further research. The studies should aim to establish definitive evidence on the effectiveness of vitamin D supplementation in improving or maintaining visual functions in AMD patients.

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