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RESEARCH ARTICLE

Assessment of the effectiveness of micronutrient therapy in patients with neovascular age-related macular degeneration unable to receive intravitreal therapy due to COVID-19 pandemic constraints*

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ABSTRACT

Aim: The aim of this study was to evaluate the efficacy of micronutrient therapy for individuals with neovascular age-related macular degeneration (nAMD) who were unable to undergo intravitreal therapy due to the COVID-19 pandemic.

Material and Method: Patients diagnosed with neovascular age-related macular degeneration (nAMD) between March 2020 and July 2021, who were ineligible for intravitreal therapy, had their medical records reviewed retrospectively. Those who met the inclusion criteria were divided into two groups. Group-1 received regular micronutrition therapy for at least six months, while Group-2 did not. Variables including age, gender, duration without intravitreal treatment, intraocular pressure (IOP), best-corrected visual acuity (BCVA), and central macular thickness (CMT) were recorded. Data obtained were compared between the two groups.

Result: Of the 183 nAMD patients screened, 125 were excluded due to missing data or irregular use of micronutrition tablets. Of the 58 patients who met the inclusion criteria, 27 were included in Group-1 and 31 in Group-2. The BCVA and CMT values at the beginning of the pandemic were 0.69±0.72 logMAR, 343.6±106.4 µm, respectively, for Group-1; and 0.85±0.82 logMAR, 381.3±93.7 µm, respectively, for Group-2 (p value 0.211, 0.153 respectively). The BCVA and CMT values obtained at the first examination were 0.74±0.76 logMAR and 330.3±148 µm, respectively, for Group-1; and 1.39±1.30 logMAR and 396.0±151.7 µm, respectively for Group-2 ($p<0.001$ and $p=0.102$, respectively).

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Conclusion: The administration of micronutrient therapy did not lead to significant changes in the central macular thickness (CMT) levels between the groups. However, it did slow down the progression towards a poor prognosis in terms of best-corrected visual acuity (BCVA). We believe that for individuals with non-alcoholic fatty liver disease, micronutrition therapy could potentially serve as an adjunctive treatment to intravitreal therapy. These findings highlight the importance of adequate micronutrient intake in the medical treatment of patients with neovascular age-related macular degeneration (nAMD).

Keywords: central macular thickness, micronutrition, neovascular age-related macular degeneration, visual acuity

INTRODUCTION

Age-related macular degeneration (AMD) is formed by fibrovascular tissue that starts from the choriocapillaris and passes through the impaired Bruch's membrane and extends under the retinal pigment epithelium (RPE) or into the cavities in the subretinal space (1). The global prevalence of AMD is predicted to be 8.7%, and it is projected to double by 2040 (2). According to the AREDS study, the severity scale of AMD is divided into three stages as early, intermediate, and advanced. Advanced AMD is classified as either geographic atrophy affecting the fovea or exudative AMD (3). AMD is categorized into two types: the wet type, characterized by the development of choroidal neovascular membrane, and the dry type which features drusen and retinal pigment epithelial anomalies. The dry type constitutes 85-90% of AMD cases and the wet type 10-15%. Advanced AMD results in subretinal fibrosis or geographic atrophy, which can cause severe vision loss in 10-12% of patients with non-neovascular AMD and 88% of patients with neovascular AMD (nAMD) (4).

There are several studies in the literature that focus on nAMD, especially regarding the treatment of this disease. One of the most important steps in this regard is the use of anti-vascular endothelial growth factor (VEGF) drugs in recent years (5). However, the high cost of these drugs and the need for frequent re-administration are their most significant disadvantages. Combining intravitreal anti-VEGF with different treatment modalities aims to reduce the number of repeated intravitreal injections, costs, and associated complications.

In the pathogenesis of AMD, inflammation resulting from oxidative stress and reduced cellular antioxidant protective effects are important. Chronic oxidative stress and inflammation increase the accumulation of lipofuscin by reducing the RPE's capacity for phagocytosis, lysosomal activation, and autophagy. In contrast, omega-3 polyunsaturated fatty acids, especially in Mediterranean-type diets, prevent inflammation, angiogenesis, and apoptosis, thereby preventing the onset and progression of AMD (6,7). Molecules such as lutein and zeaxanthin, which are components of macular carotenoids obtained through a normal diet, absorb short-wavelength light and help protect against photochemical damage. In addition, they block reactive oxygen radicals that can affect the lipid and protein structures of cells, including the cell nucleus (8). In the AREDS study, high doses of oral antioxidant vitamins such as vitamins C and E, lutein, zeaxanthin, and zinc were shown to reduce the risk of late AMD progression in the fellow eye by 25% in patients with moderate or advanced AMD in one eye (9).

Some patients treated with anti-VEGF for nAMD were unable to visit the hospital for follow-up or treatment due to the COVID-19 pandemic conditions, resulting in severe vision loss in some cases. In this study, we aimed to analyze the effect of micronutrient therapy on the prognosis, anatomical and functional outcomes of nAMD in patients who could not receive intravitreal anti-VEGF treatment during the pandemic.

MATERIAL AND METHOD

This study was designed as a retrospective cohort study. The records of patients who were diagnosed with nAMD at Ümraniye Training and Research Hospital Eye Clinic between March 2020 and July 2021 but could not receive intravitreal treatment due to pandemic conditions, were retrospectively analyzed. Patients who met the inclusion criteria were divided into two groups: Group-1, consisting of patients receiving regular micronutrient therapy, and Group-2, consisting of patients not receiving regular micronutrient therapy. The data collected were compared between these two groups. Initially, changes in central macular thickness (CMT) and best-corrected visual acuity (BCVA) were compared and analyzed across both groups.

Approval was obtained from SBÜ Ümraniye Training and Research Hospital Clinical Research Ethics Committee with the number B.10.1.TKH.4.34.H.GP.0.01/247 on 05.08.2021. Patients were informed that the information contained in the medical records would be used for scientific research and that all personal information would be kept confidential. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Content and use of micronutrition therapy:

The patients in Group-1 were instructed to take a micronutrition tablet with the following contents at least once a day:

1- Omega-3, minimum 300 mg

2- Docosahexaenoic acid (DHA), minimum 360 mg

3- Vitamin C, 60 mg

4- Vitamin E, 10 mg

5- Zinc, 7.5, mg

6- Lutein, 5, mg

7- Zeaxanthin, 1 mg

Inclusion criteria: Advanced stage (stage 4) nAMD diagnosed according to AREDS criteria, at least three doses of anti-VEGF therapy for neovascular AMD, no history of intravitreal anti-VEGF treatment within the last six months during the pandemic period despite the presence of indications, regular micronutrition therapy applied according to AREDS-2 criteria for at least six months, for moderate or advanced AMD (category 3 or 4) in the fellow eye, age range 60-80 years.

Exclusion criteria: Non-neovascular AMD, irregular micronutrition therapy, presence of other concomitant ocular diseases (e.g., diabetic retinopathy, uveitis, glaucoma, and retinal vein occlusion), ocular trauma, previous pars plana vitrectomy surgery, and smoking.

Statistical analysis

Statistical Package for the Social Sciences (SPSS, Version 21, Chicago, IL) was used for statistical analysis at a 95% confidence level. Descriptive statistics, mean, and standard deviation were used to analyze the data. Quantitative data were analyzed using the chi-square test, independent-samples t-test, and paired-samples t-test. Statistical significance was considered at $p < 0.05$

RESULTS

Of the 183 screened patients with nAMD, 125 were excluded from the study due to missing data or irregular use of micronutrition tablets. Among the 58 patients who met the inclusion criteria, 27 were assigned to Group-1 (receiving micronutrition therapy) and 31 to Group-2 (not receiving micronutrition therapy). In Group-1, 12 patients were male and 15 were female, while in Group-2, 14 were male and 17 were female. The mean age was 74.5±7.6 years for Group-1 and 74.1±7.2 years for Group-2. No significant differences in age and gender were observed between the groups (p=0.803 and 0.178, respectively). The baseline and demographic characteristics of the patients are presented in Table 1.

No significant differences were observed between the groups in terms of BCVA, central macular thickness and intraocular pressure values at the patients' final examination while under intravitreal treatment (p=0.211, 0.153, and 0.402, respectively). The time

Table 1. Comparison of demographic characteristics, BCVA and CMT between the groups

Variables	Group-1	Group-2	p
Number of patients (male/female)	27 (12/15)	31 (14/17)	0.178
Age (years)	74.5±7.6	74.1±7.2	0.803
Time without IVI treatment (months)	9.19±3.10	8.42±2.77	0.325
IOP (mmHg)	13.9±3.5	14.7±3.7	0.402
BCVA [logMAR] (pre-pandemic)	0.69±0.72	0.85±0.82	0.211
CMT µm (pre-pandemic)	343.3±106.4	381.3±93.7	0.153
BCVA [logMAR] (post-pandemic)	0.74±0.76	1.39±1.22	<0.001
CMT µm (post-pandemic)	330.3±148	396.0±151.7	0.102

Group-1: patients receiving micronutrition therapy, Group-2: patients that did not receive micronutrition therapy, IVI: intravitreal injection, IOP: intraocular pressure, BCVA [logMAR]: best-corrected visual acuity, CMT µm: central macular thickness.

Independent-samples t-test, chi-square test.

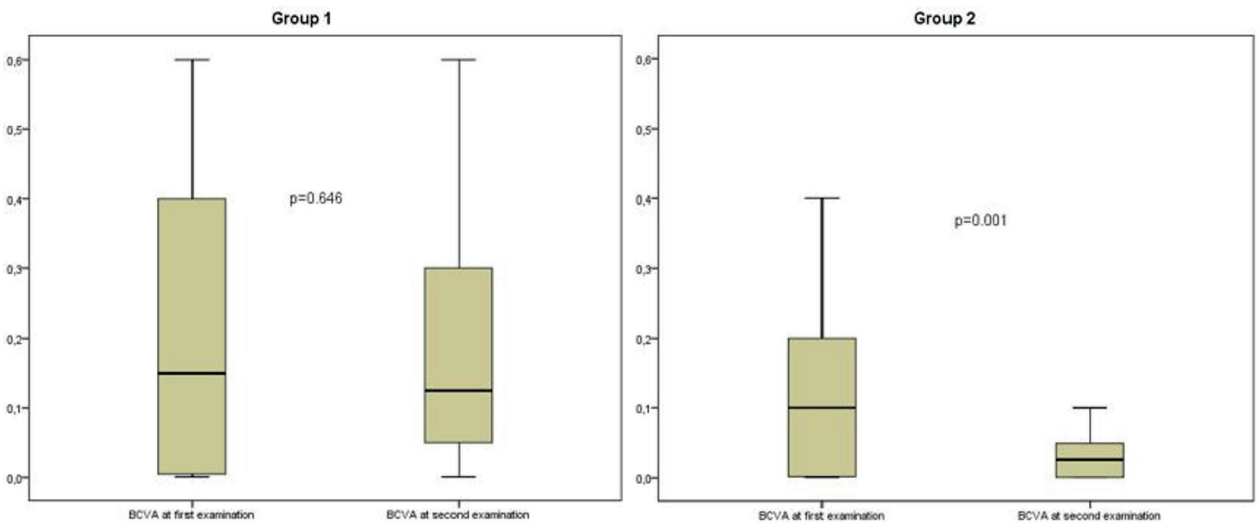

Figure 1. Best corrected visual acuity progression of Group-1 and Group-2 during the pandemic period.

from diagnosis of nAMD to the initiation of intravitreal treatment was 9.19±3.10 months in Group-1 and 8.42±2.77 months in Group-2. No significant difference was observed between the groups regarding the duration without treatment (p=0.325). At the first visit after the period without intravitreal treatment, the BCVA values of Group-1 and Group-2 were measured as 0.74±0.76 and 1.39±1.22 logMAR, respectively, indicating a significant difference between the groups (p < 0.001). No significant difference was observed in terms of CMT or intraocular pressure (p=0.102, 0.402, respectively) (Table 1).

Although there was a decrease in the BCVA values of both groups compared to the pre-pandemic period, the decrease in the BCVA value of Group-1 was not statistically significant (p=0.646). The BCVA value of Group-2 was significantly reduced compared to the pre-pandemic period (p=0.001) (Figure 1). The changes in the CMT values, as measured by optical coherence tomography, were not statistically significant for either group (p=0.542 for Group-1 and p=0.541 for Group-2) (Figure 2).

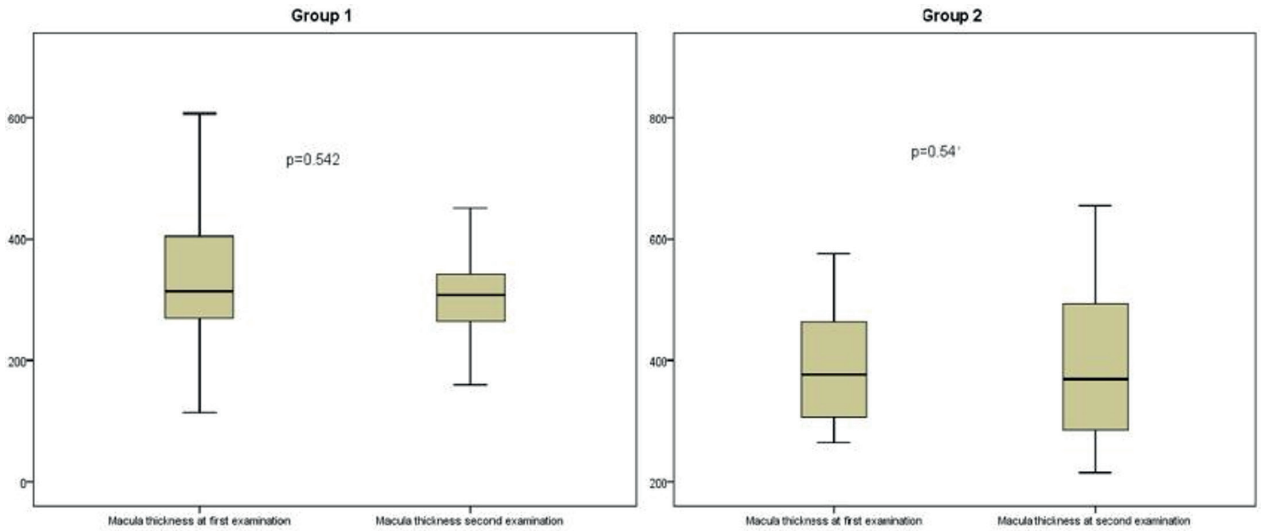

Figure 2. Macular thickness progression of Group-1 and Group-2 during the pandemic period.

DISCUSSION

Age-related macular degeneration is a degenerative condition that affects the macula, which is responsible for central vision, and is the leading cause of blindness in people over the age of 55 (10). The most important risk factors for AMD are advanced age and diet (11). It is known that diet also affects the aging process in the whole body. Similarly, age-related nutritional deficiencies may also predispose the retina to oxidative damage. This highlights the importance of adequate nutrition and nutritional supplements. In our study, we determined that micronutrition therapy had no effect on CMT but slowed down the decline in BCVA in these patients.

Inflammation and reduced antioxidant levels, induced by oxidative stress, are significant factors in the pathogenesis of AMD. Omega-3 polyunsaturated fatty acids have been shown to mitigate inflammation, angiogenesis, and apoptosis, thereby preventing the development and progression of AMD. Studies have shown that in societies with a high intake of long-chain omega-3 fatty acids, the risk of advanced AMD development decreases by approximately 30% (6,7). The AREDS 2 study showed that a combination of antioxidants (vitamins C, E, lutein and zeaxanthin) and zinc supplementation reduced the risk of AMD and vision loss in humans beyond what is achievable through diet alone (7,9). This combination was suggested to be the most valid supplemental therapy for atrophic AMD in patients with intermediate and late stage AMD.

Oxidative stress and inflammation play an important role in the pathophysiology of AMD; therefore, antioxidant vitamins are known to have protective effects. Lutein and zeaxanthin are potent antioxidants found in high concentrations in the retina and reduce oxidative damage by filtering phototoxic blue light, and protect the retinal pigment epithelium. Low levels of lutein and zeaxanthin increase the risk of AMD, while supplementation increases macular pigment density, improves visual function, and may slow disease progression. Other antioxidants such as zinc, vitamins C and E, B vitamins, and vitamin D also support retinal health and are effective in reducing the risk of AMD. In particular, the AREDS 2 study showed that a combination of these compounds reduced the risk of progression to late-stage AMD (12).

Anti-VEGF therapy protects retinal tissue in diseases such as AMD by preventing the development of abnormal blood vessels in the retina. This treatment prevents neovascularization and reduces inflammation by blocking VEGF. In particular, new generation drugs such as Aflibercept, Ranibizumab, Faricimab provide a more effective treatment by blocking Angiotensin

2, which has pro-angiogenic and pro-inflammatory effects together with VEGF. Micronutrition therapy protects retinal cells against oxidative stress with lutein, zeaxanthin, and antioxidant vitamins, reduces inflammation and supports vascular stability. In this way, micronutrition enhances the effectiveness of anti-VEGF therapy, provides better retinal protection, and may contribute to slowing disease progression (13).

In the AREDS 2 study, high doses of antioxidants (zinc, lutein, zeaxanthin, and vitamins C and E) in AMD patients led to a reduced risk of progression to an advanced stage of AMD in the fellow eye. For patients with advanced AMD in one eye, this treatment reduced the risk of developing advanced AMD in the fellow eye from 28% to 20%, and also reduced the rate of moderate vision loss from 29% to 23%. According to AREDS 2 report number 30, patients with high omega-3 intake had a 30% lower risk of developing geographic atrophy or nAMD (6). The AREDS 2 study, on the other hand, was designed to test whether the original AREDS formulation could be made safer and more effective by replacing B-carotene (15mg/day) with omega-3 fatty acids, lutein (10mg/day), and zeaxanthin (2mg/day). This study concluded that while the modified formulation was safe, it did not provide an overall additional benefit (14). In our study, the BCVA of the patients with nAMD received preparations containing at least 300 mg of omega-3, a minimum of 360 mg DHA, 80 mg EPA, 5 mg lutein, 1 mg zeaxanthin, 10 mg vitamin E, 60 mg vitamin C, and 7.5 mg zinc. Our findings showed that the decline in the BCVA of patients with neovascular type AMD who received micronutrition therapy was better preserved than the group that did not undergo this treatment.

According to the Eye Disease Case-Control Study Group, carotenoid intake reduced the risk of developing neovascular AMD by 43%, and the combination of lutein and zeaxanthin had a very strong association with reducing the risk of AMD (15). Similarly, the Waterford study found that macular pigment optical density was lower in all patients with AMD, but macular pigment density increased with oral lutein intake (16).

In the Nutritional AMD Treatment (NAT)-1 study, it was stated that the efficacy of EPA 720 mg/day and DHA 480 mg/day in patients with drusenoid pigment epithelial detachment was not significantly different from that of the placebo group (17). According to the NAT-2 study, the risk of developing nAMD was not different in the group receiving DHA (840 mg/day) and EPA (270 mg/day) compared to the group receiving a placebo. A 68% reduction in the risk of nAMD was reported in patients with high DHA+EPA levels (18). According to the Blue Mountains Eye Study, dietary intake of lutein and zeaxanthin reduced the risk of nAMD by 65%, high zinc intake reduced this risk by 44% for all stages of AMD and by 46% for early-stage AMD; and excess omega-3 intake reduced the risk of developing nAMD by 37% (19). In our study, the micronutrient formulation included a minimum of 5 mg lutein, 1 mg zeaxanthin, 7.5 mg zinc, and 300 mg omega-3. Although there were differences in intraretinal and subretinal fluid between patients receiving micronutrients and those not receiving this therapy, the lack of relative deterioration in BCVA raises concerns about the importance of decontamination therapy in maintaining retinal cell function.

A Mediterranean-style diet is linked to a reduced risk of developing advanced age-related macular degeneration (AMD) and large drusen, with fish consumption being a contributing factor to this protective effect (20). Other studies have indicated that low dietary zinc intake is associated with increased intraretinal fluid and macular thickness in patients with neovascular AMD (nAMD) (12,21). In our study, although no significant differences in central macular thickness (CMT) were observed between the two groups, we found that dietary intervention slowed down the progression towards a poor visual prognosis. These results suggest that adhering to evidence-based dietary recommendations may provide protective effects against nAMD.

Limitations of the study include the lack of a group of patients using micronutrients along with intravitreal therapy, the inability to compare patients with nAMD using micronutrient molecules with different contents (e.g., resveratrol, coenzyme Q, and astaxanthin), the small number of patients, and the short follow-up period.

In summary, we believe that micronutrition therapy has the potential to slow the progression towards poor prognosis in patients with neovascular age-related macular degeneration (nAMD) and may serve as a supportive treatment alongside intravitreal therapy. These results underscore the importance of micronutrient intake in patients with nAMD who are receiving clinical care.

Ethical approval

This study has been approved by the Ümraniye Training and Research Hospital Clinical Research Ethics Committee (approval date 05.08.2021, number B.10.1.TKH.4.34.H.GP.0.01/247). Written informed consent was obtained from the participants.

Author contribution

Concept: EB; Design: UL; Data Collection or Processing: BİSA; Analysis or Interpretation: GT, GTD; Literature Search: EB, GTD; Writing: EB, GT. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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