The Impact of Micronutrition on the Response to Anti-VEGF Treatment for Neovascular Age-Related Macular Degeneration

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ABSTRACT

Objective: This study aims to investigate the impact of micronutrient supplements on treatment outcomes in patients with neovascular age related macular degeneration undergoing intravitreal injections.

Methods: Data from 63 patients with neovascular age related macular degeneration were analyzed retrospectively. Patients were divided into two groups based on micronutrient support. Best-corrected visual acuity measured by ETDRS charts, central macular thickness assessed by optical coherence tomography, and the number of anti-vascular endothelial growth factor injections were compared between the two groups. Statistical analyses were conducted employing Student's t-test, Mann-Whitney U test, and paired sample t-test.

Results: Among the 63 patients included, 33 received micronutrient support while 30 did not. The mean follow-up duration was 3.94±1.17 years in the supported group and 3.10±1.58 years in the unsupported control group. There was no significant difference either in age or gender distribution between the two groups (p= 0.44, p=0.10, respectively). Baseline best-corrected visual acuity (p=0.19) and central macular thickness (p=0.23) were similar. Patients receiving supplements had been on this regimen for approximately 4 years. No statistically significant distinctions were observed in the average alterations of best-corrected visual acuity (p=0.49), central macular thickness (p=0.09), and the number of anti-vascular endothelial growth factor injections (p=0.20) between the two groups.

Conclusion: This study found no significant difference in treatment response between neovascular age related macular degeneration patients receiving and not receiving micronutrient supplements. Despite previous preclinical evidence suggesting potential benefits of supplementation, clinical outcomes did not support their superiority in this cohort. Further research is warranted to elucidate the role of supplements in neovascular age related macular degeneration management.

Key words: Anti-vascular endothelial growth factor, micronutrition, supplement, wet type AMD

INTRODUCTION

Age related macular degeneration (AMD) is a progressive disease affecting older adults, leading to irreversible blindness in Western countries.[1] As the global population ages, the incidence of diseases among older individuals is on the rise.[2] While aging takes precedence among non-modifiable factors in the development of AMD, both non-modifiable elements such as genetics, gender, and ethnicity, as well as modifiable factors like smoking, physical activity, diet, education level, and BMI, play significant roles in AMD formation. [3]

When examining the pathophysiological factors in the development of AMD, one theory highlights the degeneration and thickening of Bruch's membrane[4], while another proposes reduced choroidal blood flow as a risk factor, showing correlation with atherosclerotic diseases such as carotid artery disease.[5] Moreover, oxidative stress

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stemming from the breakdown of protective antioxidant systems within the retina represents another theory. Across all three theories, the role of diet and supplementation intake is deemed to be a significant factor.[4]

The AREDS study is widely regarded for its comprehensive exploration of AMD and nutritional support. Their findings indicate that the original AREDS formulation, including vitamins C, E, beta-carotene, and zinc, led to an estimated 25% reduction in the 5-year risk of late AMD in at-risk individuals. Significantly, the addition of antioxidants plus zinc demonstrated a treatment benefit for neovascular AMD (nAMD) outcomes in intermediate and advanced groups (OR, 0.62; 99% CI, 0.43–0.90). AREDS2 aimed to assess if incorporating lutein, zeaxanthin, and/or omega-3 fatty acids to the original AREDS formulation would further reduce the risk of advanced AMD.[6] Adjustments in AREDS2 considered the risk of lung cancer with beta-carotene in smokers and established 25 mg as the maximum zinc dose. Preliminary results from AREDS2 did not show a significant impact on preventing advanced AMD in certain groups.[7] However, exploratory analyses indicated that lutein + zeaxanthin outperformed beta-carotene, reducing the risk of progression from intermediate to advanced stages by 10%. [8] While the influence of omega-3 usage was not evident in the AREDS 2 study, a majority of longitudinal population studies consistently show a decreased risk of AMD progression in individuals with elevated levels of EPA and DHA in their plasma or serum.[9,10]

The AREDS studies have yielded significant results, especially in early and intermediate stages of AMD, underscoring the positive influence of vitamin and mineral supplementation on the progression to advanced stages. However, with the growing elderly population and the considerable vision loss associated with advanced AMD, the necessity to explore and develop treatment options becomes indispensable for advanced stages. Recent advancements in treatment, especially intravitreal injections targeting vascular endothelial growth factor (VEGF), have revolutionized the management of nAMD. However, challenges arise due to the frequency of injections.[1] Despite the significant progress in vision preservation achieved with anti-VEGF agents, there is a critical need for innovations to reduce the burden of intravitreal injections and enhance outcomes, especially in patients who do not respond sufficiently to existing treatments. The favorable impact of nutritional supplements on the progression of the disease has led to investigations into their effectiveness on choroidal vascularization and intravitreal injection response in nAMD. [11]

This study aims to investigate the response of nutritional supplement support to treatment results in patients with neovascular AMD receiving intravitreal injections.

MATERIALS AND METHODS

This retrospective study was conducted to gather data on patients undergoing follow-up for neovascular AMD at the single tertiary clinic, between 2018 and 2023. The study strictly adhered to the principles outlined in the Declaration of Helsinki and received approval from the institutional review board of the Non-Invasive Human Research Ethics Committee (Hacettepe University Health Sciences Research Ethics Committee -SBA 24/422).

Patients were diagnosed and treated throughout the follow-up period by two experienced retinal specialists and, following a joint decision, were managed with a pro re nata protocol after three doses of monthly intravitreal anti-VEGF injections. Criteria for retreatment were; detection of intraretinal or subretinal fluid on OCT, observation of new or persistent hemorrhage, and decline in visual acuity.

Inclusion criteria comprised being over 50 years old, having neovascular AMD requiring treatment in one eye, the presence of dry or disciform scar in the other eye (requiring no anti VEGF treatment), regular intake of supplements containing the AREDS2 formulation (vitamin C and E, zinc, lutein+zeaxanthin, copper) plus omega 3 (Ocuvite Complete, Bausch & Lomb) twice daily within the specified duration reported by patients, regular attendance to visits, and not receiving any other vitamin or mineral support for any reason. Patients with retinal diseases other than AMD (i.e. choroidal nevus, angioid streaks, central serous choroidopathy, inherited degenerative retinal diseases, and diabetic retinopathy), opacities affecting imaging, irregular follow-up visits, and cases where retinal specialists did not reach a consensus on treatment management were excluded from the study.

All demographic information of patients, the type and number of injections administered were recorded. Best-

corrected visual acuity (BCVA) obtained with the ETDRS chart at the initial and final visits, as well as central macular thickness (CMT) measured by OCT (SPECTRALIS, Heidelberg Engineering, Heidelberg, Germany), were documented. The duration of micronutrient supplement intake was also inquired from patients.

Statistical Analysis

All parameters were subjected to normality testing via the Kolmogorov-Smirnov test. Normally distributed data were expressed as means with standard deviations. Group comparisons for continuous variables with normal distribution were conducted using Student's t-test, while non-parametric data were analyzed using the Mann-Whitney U test. BCVA, assessed using ETDRS charts, and CMT values underwent paired sample t-tests to evaluate intra and inter-group differences. Gender distribution and other eye conditions were assessed using the chi-square test. Statistical significance was established at p values < 0.05. The statistical analyses were carried out utilizing SPSS software (version 20.0; SPSS, Chicago, IL, USA).

RESULTS

A total of 63 eyes from 63 nAMD patients were included in the study. Thirty-three patients were receiving micronutrient support (M+), while 30 not receiving micronutrients comprised the control group M(-). The mean age in M (+) group was 72.96±8.38 years, and 71.03±11.22 years in M (-). Statistical analysis revealed no significant difference in age between groups (p=0.44). The gender distribution among the groups was found to be similar (p=0.10). When examining the status of the contralateral eyes of the patients, it was observed that the inclusion distribution in terms of eye conditions was statistically similar between M (+) and M (-). In M+ group, 66.6% exhibited dry-type AMD, and 33.3% had disciform scars, whereas in M- group, 70.9% had dry-type AMD, and 29.1% had disciform scars (p=0.71). No significant differences were observed between the two groups in terms of the baseline BCVA, CMT and number of administered anti-VEGF injections across the three types-bevacizumab (BVC), aflibercept (AFL), and ranibizumab (RBZ). (Table 1)

Table 1. Demographic and baseline clinical characteristics of the participants

Parameters	**Micronutrition (+) (n=33)**			**Micronutrition (-) (n=30)**			**p value**
Age (year) (mean ± SD) (range)	72.97 ±8.38 (59-93)			71.03 ±1.58 (53-98)			0.44
Gender (female/male)	15/18			8/22			0.10
BCVA, ETDRS (mean± SD) (range)	54.21± 19.77 (9-85)			49.90±24.97 (1-95)			0.19
CMT (µm) (Mean± SD) (range)	342.15 ±109.94 (233-674)			365.48±122.28 (249-682)			0.23
Number of anti-VEGF injections (mean± SD) (range)	8.79 ±7.42 (1-35)			11.55 ±9.57 (1-53)			0.20
Anti-VEGF agents	BVC	AFL	RBZ	BVC	AFL	RBZ	0.41
	4	18	11	1	18	11	
Fellow eye	SCAR	DRY-TYPE		SCAR	DRY-TYPE		0.71
	11	22		9	21		
Follow-up (year) (mean± SD) (min-max)	3.94 ±1.17 (1-6)			3.10 ±1.58 (1-5)			

Over the average follow-up duration of 3.94±1.17 years, no significant difference was noted between the initial (54.21± 19.77 letters) and final BCVA (51.52± 24.43 letters) (p=0.11) in M (+) group. Additionally, no significant difference was observed in CMT values during this period (p=0.47). The mean number of injections during the follow-up period was 8.79±7.42 and the average duration of micronutrition supplementation was 4.03±2.52 years in M (+) group.

Over the average follow-up duration of 3.10±1.58 years, a statistically nonsignificant difference was observed in CMT values within M (-) group. The CMT values showed a decrease from the initial (365.48±122.28) to the final visit (359.68±117.51) (p=0.12). No statistically significant difference was found in BCVA, with initial visit BCVA at 49.90±24.97 and final visit BCVA at 46.77±27.52 letters (p=0.32). The average number of injections during the follow-up period within M (-) group was 11.55±9.57.

There were no significant differences between the M (+) and M (-) groups in terms of changes in CMT, BCVA, and the number of injections administered during the follow-up period. (Table 2)

No significant differences were found in terms of changes in CMT, BCVA, and the number of injections administered when stratifying both groups (M (-) and M(+)) based on whether the contralateral eye had dry-type or disciform scar AMD, (p>0.05 for all comparisons).

DISCUSSION

With this study we wanted to investigate the effect of AREDS similar micronutrient support on outcomes of neovascular AMD. We have found no significant effect in terms of BCVA, CMT and the number of injections.

The retina is especially vulnerable to oxidative stress due to heightened oxygen pressure and exposure to ultraviolet and blue light, factors that stimulate the production of reactive oxygen species (ROS). Antioxidants, such as vitamins, carotenoids, and essential trace elements like zinc, are pivotal in augmenting the elimination and averting the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Consequently, they mitigate oxidative stress-induced damage in retinal cells.[12] This phenomenon has been substantiated by a 22% decrease in the risk of developing nAMD among participants who received antioxidant supplementation from the AREDS 2 formulation explanatory analysis. Specifically, this reduction was observed in individuals administered lutein plus zeaxanthin and the AREDS formula devoid of beta-carotene, compared to those who received no lutein plus zeaxanthin and the AREDS formula containing beta-carotene. [8] Additionally, a survey study has found lower antioxidant consumption among individuals with wet-type AMD.[13] These findings shed light on the necessity to investigate the effectiveness of supplement usage in our study, which solely includes participants with wet AMD. In daily practice, micronutrition is often recommended, particularly for intermediate and advanced stages of dry type AMD, aiming to halt the progression of the disease.[14] However, in the case of unilateral nAMD, where there is a high likelihood of the presence of dry AMD in the fellow eye, micronutrition may also be advised to prevent the progression. Recently, there has been growing interest in recommending micronutrition containing resveratrol due to its anti-angiogenic and antioxidant properties, especially for nAMD.[15]

Neovascular AMD represents the most severe form of AMD, characterized by a sudden onset and the imminent threat of vision loss. Despite the administration of anti-VEGF treatment, the progression of retinal damage persists unabated, and there is no restoration of healthy tissue,

Table 2. The mean differences between initial and final parameters

Parameters	**Micronutrition (+) (n=33)**	**Micronutrition (-) (n=30)**	**p value**
BCVA, ETDRS (mean± SD)	-2.69±8.12	-3.13±17.16	0.49
CMT (µm) (Mean± SD)	-10.36±80.61	-5.84 ±112.23	0.09
Number of anti-VEGF injections (mean± **SD)**	8.79±7.42	11.55 ±9.57	0.20

often leading to frequent relapses of nAMD.[16] To sustain treatment response, frequent intravitreal injections may be necessitated, thereby heightening the risk of complications such as stroke, fibrosis, endophthalmitis, retinal tears, and detachments. The therapeutic approach, involving potentially indefinite anti-VEGF injections in AMD patients, not only imposes a significant financial burden but also places a psychological strain on patients.[17] Taking into account all these negative parameters, additional methods are being explored to enhance the efficacy and mitigate the side effects of anti-VEGF agents, which are widely used and indispensable in treatment. In a preclinical study conducted on 60 mice with choroidal neovascularization (CNV), the effectiveness of oral supplementation and intravitreal anti-VEGF treatment was investigated. A decrease in enzymes and gene expressions involved in CNV development, as well as reductions in leakage and CNV size, were observed in mice receiving only oral supplementation and combined with anti-VEGF treatment. [11] The presence of resveratrol as an addition to the AREDS2 formulation distinguishes it from our research. However, in a previous preclinical study conducted on mice investigating the effectiveness of antioxidants (vitamin C, E, zinc) and zeaxanthin, it was demonstrated that antioxidant supplements reduce oxidative stress and VEGF expression in the RPE choroid. Moreover, the addition of zeaxanthin further intensified this effect.[18] Furthermore, studies conducted on omega-3 have demonstrated its anti-inflammatory and anti-angiogenic properties, along with its ability to reduce VEGF expression in mice.[19,20] These preclinical studies are compatible with the AREDS 2 formula used in our research and suggest positive outcomes of these supplements on nAMD. However, in this study, we did not observe any improvement in clinical findings of AMD patients with supplement use. The significant differences between preclinical studies and clinical trials, such as conducting experiments on animal models, study design, and stabilizing environmental conditions, could be the primary reasons for this disparity.

Out of 48 patients included in a clinical study, with unilateral CNV secondary to AMD without any exudative involvement of contralateral eye, were administered the original AREDS formulation (i.e, vitamin C, vitamin E, beta-carotene and zinc,manganese and selenium) while 45 individuals received the AREDS supplemented except beta-carotene, plus copper with DHA, lutein, zeaxanthin, resveratrol, and hydroxytyrosol. The study found that the supplemented formula did not have a significant differential effect on visual acuity compared to the original AREDS formulation at approved doses in Europe. However, the supplemented formula showed a significant, and in most cases, relevant effect in terms of reducing some inflammatory cytokines and achieving a greater improvement in the fatty acid profile and serum lutein concentration. Particularly, a significant decrease was observed in levels of cytokines like IL-1β, IL-6, and IL-8, which also play a role in inflammation and angiogenesis. Although our study had a different design, similar to this study, we did not observe a difference in visual acuity change between the groups receiving supplementation and those not. While we did not have the opportunity to analyze serum parameters in our study, there was no difference between the two groups in terms of CMT and injection frequency, which are indicators of disease activation. To attribute this difference to the agents resveratrol or hydroxytyrosol, which were used in supplementation and differ from our study, it would have been more accurate to have serum analysis results in our possession.[21]

In a group of patients with AMD treated with aflibercept, nutraceutical support (containing AREDS2 formulation and omega-3) demonstrated effectiveness in reducing the number of injections over a 12-months follow-up period ($p< 0.001$).[22] Although this finding was thought to be associated with the potentially negative impact of omega-3 on angiogenesis, as shown in preclinical studies, our study did not encounter this difference.[19] While this study only considered 1-year outcomes, our research extended over a period of 3-4 years, suggesting that the supplement addition may not create synergistic effects in the long term. Additionally, this study revealed a significant positive effect of non-steroidal anti-inflammatory drops on CMT. The absence of this data in our study perhaps indicates that the anti-inflammatory efficacy plays a more effective role in macular stability than micronutrition supplementation. For more definitive conclusions, combined observations on the efficacy of drops and supplements, along with validation of treatment efficacy through biochemical parameters, are necessary.

No significant differences were found in the mean change of BCVA and the number of injections administered

between the pre- and post-treatment periods in both our study groups. Perhaps, if contrast sensitivity testing could have been utilized as performed by Datseris et al., a difference could have been detected.[23] They reported increased sensitivity favoring patients using aflibercept in combination with resvega compared to those using aflibercept alone. The supplement used in this study differs in containing resveratrol and vitamin D, showing positive results on depression and anxiety in patients.[24] Enriching the supplement content may be another significant factor in enhancing the efficacy of intravitreal injections in wet AMD patients.

This study has several limitations, including its retrospective nature, the relatively small sample size, and the reliance on patient self-reporting to assess supplement intake, which may introduce recall bias and reduce the accuracy of compliance assessment.

In conclusion, this study demonstrates that there is no effect of micronutrition supplements in terms of treatment response. To the best of our knowledge, there is no other study in the literature that compares efficacy over such an extended period. Although obtaining real-world data through clinical studies in this field may be challenging due to the unique clinical characteristics of each patient, there is a need for more objective data that can support IVI treatments, which require frequent administration and can lead to significant financial and psychological burden.

DISCLOSURE OF INTEREST

No potential conflict of interest was reported by the authors.

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