Approach of Turkish ophthalmologists to micronutrition in age-related macular degeneration

Abordagem dos oftalmologistas turcos em relação a micronutrição na degeneração macular relacionada à idade

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ABSTRACT

Purpose: To evaluate the knowledge and behaviors of ophthalmologists in Turkey concerning micronutrient support in patients with age related macular degeneration (ARMD).

Methods: This study involved 1,845 ophthalmologists. A scientific poll was sent to all participants by email. The survey covered the following: demographic features, specialty knowledge about micronutrient preference for prescribing micronutrient to age related macular degeneration patients, and the reason for this preference. If a participant indicated that he or she prescribed micronutrient, the participant was also asked to indicate the source of the treatment and supplemental treatments.

Results: Of 1,845 ophthalmologists, 249 responded to the survey. Of the respondents, 9% (22) never, 43% (107) sometimes, 37% (92) frequently, and 11% (27) always used micronutrient. The most frequent prescribing subgroup was general ophthalmology (22%), followed by the retina-uvea subspecialty (13.9%). The micronutrient prescribing ratio was 54.8% in retina-uvea specialists when the “frequent” and “always” responses were combined. There was no statistically significant difference between subgroups with respect to prescribing micronutrient. Among the ophthalmologists prescribing micronutrient, 57.1% of them did not use the Age-Related Eye Disease Study-1 (AREDS) criteria, and only 31.3% prescribe micronutrient according to AREDS criteria. The results for the general ophthalmologist and retina-uvea specialist subgroups were similar, 56.3% vs 20.2%, and 54.1% vs 36.1%, respectively. Micronutrition was not recommended for the following reasons: expensive (55.4%), low patient expectancy (40%), no effect (30%), and low patient drug compliance (25.4%). Moreover, 55.2% of the clinicians recommended physical activities, dietary changes, and smoking cessation; 7.3% did not recommend these behavioral changes.

Conclusion: This survey demonstrated that micronutrient preference in age related macular degeneration was low in ophthalmologists in Turkey. Additionally, retina specialists have a lower rate of prescribing micronutrient. Micronutrition support and behavior such as smoking cessation, dietary changes, etc. should be recommended more often to patients with age related macular degeneration.

Keywords: Macular degeneration/prevention & control; Dietary supplements; Vitamins/administration & dosage; Lutein/administration & dosage; Guideline as topic/standards; Turkey

INTRODUCTION

Age-related macular degeneration (ARMD) is the most frequent cause of vision loss in patients over 50 years of age in developed countries[1,2]. In these populations, many factors including prolonged life expectancy, the need for independence in daily activities, and economic burden on family and society are related to the quality of life, and thus to severity of the disease[3,4]. Although the etiopathogenesis of ARMD is not fully understood, it indisputably appears as the combination of factors such as familial predisposition, family history, aging, and smoking[5]. A limited study

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on women suggested protective factors such as a healthy life style, modification of dietary habits, and improved physical activity decrease the incidence of development of ARMD at a rate of 71%. In recent years, a number of alternative treatments, such as anti-VEGF therapy, have increased the hope of curing neovascular ARMD. However, important disadvantages of these treatments include their higher costs, need for reinjection, loss of workforce, and extra hours spent by the physicians. Currently, there is no curative treatment for dry type ARMD. Therefore, serious attempts have been made to protect patients from ARMD risk factors, and to prevent progression to advanced ARMD. Use of micronutrition in ARMD represents a large scientific scope, which is the subject of various investigations. However, an increasing proportion of patients using micronutrition led to an estimated expenditure of nearly 27 million dollars.

Conflicting results in the literature show that ophthalmologists have widely differing preferences regarding the use of dietary supplements. The increased vulnerability of retinal injury due to increased oxidative stress and free radical generation with aging has been demonstrated. Several studies were conducted to investigate the effect of dietary intake of anti-oxidant agents and vitamins on the retina. In the European Eye, a significant correlation was found between neovascular ARMD patients consuming a low-density diet containing lutein and zeaxanthin pigments, and subsequent cumulative visible light damage. The Age-related Eye Disease Study-1 (AREDS) is a comprehensive, prospective, placebo-controlled trial using lutein and zeaxanthin supplements, and subsequent cumulative visible light damage. The study encompassed ophthalmologists working in state hospitals, training and research hospitals, university hospitals, foundation hospitals, and private hospitals. Emails were sent to the participants twice, for example in June and September 2013. The first part of the 9-item questionnaire asked for demographic characteristics such as age, gender, title, and employer. The second part comprised of questions about the specialty/subspecialty, subject matter topics of interest, and ARMD (wet/dry) cases seen in practice. In the last part of the questionnaire, we asked the clinicians about their prescribing practices in ARMD patients, their use of the AREDS classification system, and the reasons for their prescribing preferences. The last part of the survey asked for the clinicians’ sources of information on micronutrition and their additional recommendations for ARMD patients. The responses were tabulated in an excel format and analyzed.

**METHODS**

After obtaining approval of the Presidency of Ethics Committee of the Dicle University Faculty of Medicine, questionnaire forms were sent to the email addresses of ophthalmologists. The participants were informed that the study was a scientific survey, and that the results were not allowed to change their responses after submission. The participants were free to respond or not respond to any question. The study encompassed ophthalmologists working in state hospitals, training and research hospitals, university hospitals, foundation hospitals, and private hospitals. Emails were sent to the participants twice, for example in June and September 2013. The first part of the 9-item questionnaire asked for demographic characteristics such as age, gender, title, and employer. The second part comprised of questions about the specialty/subspecialty, subject matter topics of interest, and ARMD (wet/dry) cases seen in practice. In the last part of the questionnaire, we asked the clinicians about their prescribing practices in ARMD patients, their use of the AREDS classification system, and the reasons for their prescribing preferences. The last part of the survey asked for the clinicians’ sources of information on micronutrition and their additional recommendations for ARMD patients. The responses were tabulated in an excel format and analyzed.

**RESULTS**

Email addresses of 1845 ophthalmologists were found on the internet. We could not contact 643 ophthalmologists because of outdated email addresses. The remaining 1202 ophthalmologists were emailed, but only 249 responded to the questionnaire. Those 249 (20.7%) participants (males, n=158; 65%; females, n=85; 35%) had a mean age of 39.4 ± 9 (25-67 yrs) years. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question. The participants were free to respond or not respond to any question.
not use AREDS criteria, and only 20.2% employed AREDS criteria for their category 3-4 patients. More than half (54.1%) of the retina-uvea specialists did not use AREDS criteria, and only 36.1% used them for their category 3-4 patients.

The responses to the question "Why didn't you prefer to use micronutrition in ARMD?" by percent were: "It is expensive" (55.4%); "It does not satisfy the expectations of the patients (40%); "I don't think that it is beneficial (30%); and "patient compliance is very poor" (25.4%).

Analysis of micronutrition use based on the employer of the participants revealed it was mostly used in private hospitals (56.6%), followed by university hospitals and foundation hospitals (51.2%), and then by state and training and research hospitals (39%), without any statistically significant difference between groups.

When asked about micronutrition information, 41% of the participants responded that they had read 2-5 articles about micronutrition. Of the remaining participants, 39% had read more than 5, 9% had read one, and 12% had not read any. We found no statistically significant difference between the categories of responders and the number of articles read.

We asked the participants about additional measures recommended for ARMD patients. The responses included modification of only dietary habits (29.4%), quitting smoking (35.5%), increased physical activity (0.4%), and all of the above (55.2%); 7.3% did not recommend any additional measures.

**DISCUSSION**

If prophylactic or definitive treatment of ARMD is not discovered within the next 20 years, the incidence of ARMD is expected to rise up to nearly 50 percent in the USA and Europe. Introduction of new treatments for neovascular ARMD (i.e., anti-VEGF therapy) brings some important disadvantages, such as cost and interventional procedures requiring reinjection. In addition, there is no therapy available for dry type ARMD. However, lower-cost treatment modalities which slow down progression to advanced ARMD have a crucial impact. These include micronutrition, modification of dietary habits, exercise, and smoking cessation.

In our survey we tried to investigate general perspectives, attitudes, and behavioral patterns of ophthalmologists in Turkey related to the use of micronutrition and recommendations offered to ARMD patients.

Retinal photoreceptors are exposed to intense oxidative stress induced by oxygen and light. Consequently, every night 10% of the outer surface of the photoreceptor layer desquamates. The task of retinal pigment epithelium (RPE) is to remove desquamated debris, and to sustain nutrition of photoreceptors. With adequate nutritional support, RPE can achieve turnover of photoreceptors. Prior studies clearly demonstrate that prophylactic measures (i.e., antioxidant intake) are effective against development of ARMD.

Various studies have demonstrated that higher doses of vitamins and mineral supplements decrease the risk of ARMD in elderly populations. In particular, placebo-controlled randomized double-blind studies (AREDS 1, and AREDS 2) showed that higher doses of vitamins and mineral supplements slow down progression of the disease to advanced ARMD in 25% of cases. Survey research in the UK revealed that almost all optometrists and ophthalmologists recommend micronutrition supplements (92.8%).

However, in our study we found that only about half of ophthalmologists are in favor of micronutrition (52% in favor and 48% against). General ophthalmologists were the most common group to recommend micronutrition (26.4%), followed by professors (7.9%). The rate of micronutrition recommendation for ARMD was very low. It is possible that these rates are even lower than observed. Additionally, when looking at the differences between specialties, general ophthalmologists and retina-uvea specialists used micronutrition most commonly (22%, and 13.9%, respectively). However, these differences were not statistically significant. Although follow-up and treatment of ARMD patients were realized by retina specialists, our study suggests that a lower number of retina specialists preferred micronutrition.

<table>
<thead>
<tr>
<th>Subspecialty</th>
<th>n (%)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>General ophthalmology</td>
<td>121</td>
<td>48.8</td>
</tr>
<tr>
<td>Glaucoma-ocularplasty</td>
<td>19</td>
<td>7.7</td>
</tr>
<tr>
<td>Cornea-refractive surgery</td>
<td>26</td>
<td>10.5</td>
</tr>
<tr>
<td>Retina-uvea</td>
<td>62</td>
<td>25.0</td>
</tr>
<tr>
<td>Other</td>
<td>19</td>
<td>7.7</td>
</tr>
<tr>
<td>Total</td>
<td>247</td>
<td>99.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subspecialty</th>
<th>I do not use AREDS</th>
<th>Category 1-2</th>
<th>Category 3-4</th>
<th>Category 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>General ophthalmology</td>
<td>67 (56.3)</td>
<td>12 (10.1)</td>
<td>24 (20.2)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Glaucoma &amp; oculoplasting</td>
<td>12 (66.7)</td>
<td>3 (16.7)</td>
<td>2 (11.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Cornea &amp; refractive surgery</td>
<td>16 (64.0)</td>
<td>3 (12.0)</td>
<td>2 (8.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Retina &amp; uvea</td>
<td>33 (54.1)</td>
<td>2 (3.3)</td>
<td>22 (36.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (52.9)</td>
<td>1 (5.9)</td>
<td>6 (35.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Total</td>
<td>137 (57.1)</td>
<td>21 (8.8)</td>
<td>56 (23.3)</td>
<td>2 (0.8)</td>
</tr>
</tbody>
</table>
AREDS1 and AREDS2 studies are multi-centered, placebo-controlled, randomized, double-blind studies concerning micronutrition\textsuperscript{[6,9-11]}. Publication of AREDS 1 outcomes started in 2001, publication of AREDS 2 results started in 2013. These publications contain recommendations for management of ARMD. Another study demonstrated that patients often did not use recommended AREDS formulations at adequate doses\textsuperscript{[12,13]}. The same study indicated that patients who complied with the recommended doses correctly received those recommendations from retina specialists. According to a survey among optometrists and ophthalmologists, a relatively higher percentage of ophthalmologists used recommended AREDS formulations. However, according to the results of this survey, ophthalmologists rarely recommended micronutrition supplements containing macular carotenoids\textsuperscript{[14,15]}. In our study however, more than half (56.3\%) of the general ophthalmologists who recommended micronutrition did not use AREDS criteria. Only one fourth of the participants (20.2\%) indicated that they had used AREDS criteria for category 3-4 patients. Also, a little over half (54.1\%) of the retina-uvea specialists who recommended micronutrition used AREDS criteria, and only 36.1 \% of them responded that they had used these criteria for their category 3-4 patients. This finding demonstrates that two important groups of physicians, general ophthalmologists and retina specialists, do not use AREDS criteria. Additionally, only one third of the users of these criteria employ them for category 3-4 patients. Assuming that a number of patients did not comply adequately, it is likely that the number of patients who received appropriate AREDS-based treatment is even smaller.

According to our survey, retina specialists did not prefer micronutrition mostly because of its higher treatment cost (67.8\%) and failure to meet the expectations of the patients (39.2\%). Additionally, they were not convinced of the benefits (32.1\%), and they indicated that only limited patient compliance was achieved (28.5\%). The general ophthalmologists showed similar perspectives. A past study demonstrated that patients do not prefer micronutrition for similar reasons\textsuperscript{[16,17]}. These reservations demonstrate the numerous complaints of the patients to their physicians concerning higher cost and lack of benefit of the treatment. Our study also shows that we, the physicians, must explain some of these reservations.

Many studies have shown that 36-43\% of patients do not sufficiently comply with recommendations of the physicians\textsuperscript{[18,19]}. Hochstetter et al. showed that the main reason for poor compliance was failure to recommend micronutrition for suitable patients\textsuperscript{[18]}. In other words, in addition to lower compliance of the patients who had been given relevant recommendations, some patients did not receive any recommendations.

Poor patient compliance with micronutrition recommendations may indirectly cause a relaxed attitude of the physicians about offering necessary recommendations in the first place. However, according to another study, if recommendations were offered for ARMD patients the majority of these recommendations would be followed by the patients\textsuperscript{[20]}. Additionally, a separate study indicated that nearly one third of the patients did not receive adequate doses\textsuperscript{[21]}. In this study, 62\% of the patients used correct doses\textsuperscript{[22]}. The authors indicated that general ophthalmologists should use required doses, and they should raise awareness of the selected patients on this issue. Physicians should always give these recommendations to the patients irrespective of the degree of the patient compliance. Indeed, the patients should be reminded of these recommendations more often. In particular, patients with poor compliance should be reminded for a longer period of time, and patients with high compliance should be reminded at control visits.

Various studies have determined that nutritional factors, modification of dietary habits, increased physical activity, and smoking cessation are cost-effective and applicable prophylactic measures in ARMD\textsuperscript{[3,5-10]}. In our study, little more than half (55.2\%) of participants recommend a combination of diet, smoking cessation, and physical activity to their ARMD patients. A small number of participants did not give any recommendations about modifiable risk factors. This scarce number of recommendations concerning modifiable risk factors might be attributed to inadequate time for patient counseling in the ophthalmologists’ busy schedules. Even though the patients did not comply with micronutrition in some studies, other studies show that the majority of the patients did comply with recommendations\textsuperscript{[11-13]}. We suggest that the clinicians do not allocate enough time for the patients so as to offer such simple additional recommendations on an ambulatory basis. Moreover, we speculate that ophthalmologists do not believe the therapeutic effects of additional recommendations for ARMD patients, or they may not understand or be convinced of its necessity.

Therefore, we think that ophthalmologists should be made more aware on this subject, especially specialists in general ophthalmology and retinal diseases.

Our study has some limitations. First, inherent to the questionnaire design of our study, we received inadequate feedback. Second, ophthalmologists might respond keeping “examination mood” in mind. Third, participants might give responses that interviewers want to hear. Fourth, they might give responses which the interviewers either wanted to hear or did not want to hear, or they may give exaggerated responses. Finally, the survey was realized on a relatively local basis, and in a developing country. Despite all of these limitations, however, in the present study we wanted to demonstrate perspectives of the ophthalmologists in Turkey concerning the use of micronutrition in ARMD.

REFERENCES