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 micronutrition 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, subspecialty knowledge about micronutrition preference for prescribing micronutrition to age related macular degeneration patients, and the reason for this preference. If a participant indicated that he or she prescribed micronutrition, 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 micronutrition. The most frequent prescribing subgroup was general ophthalmology (22%), followed by the retina-uvea subspecialty (13.9%). The micronutrition 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 micronutrition. Among the ophthalmologists prescribing micronutrition, 57.1% of them did not use the Age-Related Eye Disease Study-1 (AREDS) criteria, and only 31.3% prescribe micronutrition 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 micronutrition preference in age related macular degeneration was low in ophthalmologists in Turkey. Additionally, retina specialists have a lower rate of prescribing micronutrition. 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

RESUMO

Objetivo: *Avaliar o conhecimento e comportamento dos oftalmologistas na Turquia sobre o suporte micronutricional em pacientes com degeneração macular relacionada à idade (DMRI).*

Método: *Este estudo continha 1.845 oftalmologistas, e uma pesquisa científica foi enviado a todos os participantes por e-mail. O levantamento abrangeu as seguintes informações: características demográficas, conhecimento na subespecialidade sobre a preferência micronutricional para a prescrição micronutrientes a pacientes com degeneração macular relacionada à idade, e a razão por trás dessa preferência. Se um participante respondeu que prescreveu micronutrientes, foi solicitado que indicasse a origem do tratamento, bem como tratamentos suplementares.*

Resultados: *Duzentos e quarenta e nove de 1.845 oftalmologistas responderam à pesquisa. Destes oftalmologistas 9% (22) nunca haviam usado micronutrição, 43% (107), utilizava eventualmente, 37% (92) usavam com frequência, e 11% (27) sempre usou. O subgrupo de prescrição mais frequente era composto por oftalmologistas gerais (22%), seguido por subespecialistas em retina e/ou úvea (13,9%). A frequência de prescrição de micronutrientes foi de 54,8% dentre os subespecialistas em retina e/ou úvea quando resultados de resposta foram combinados em "frequente" e "sempre." Não houve diferença estatisticamente significativa entre os subgrupos com relação à prescrição de micronutrientes. Entre os oftalmologistas que prescreviam micronutrição, 57,1% deles não usavam os critérios* The Age-Related Eye Disease Study-1 (*AREDS*) *e 31,3% deles prescreviam de acordo com critérios AREDS. A utilização dos critérios teve distribuição semelhante entre os oftalmologistas gerais e os especialistas, 56,3% vs 20,2%, e 54,1% vs 36,1%, respectivamente. A micronutrição não era recomendada pelas seguintes razões: preço (55,4%), baixa expectativa de paciente (40%), nenhum efeito (30%), e baixa aderência do paciente à droga (25,4%). Além disso, 55,2% dos clínicos recomendam a atividade física, mudanças na dieta, e cessação do tabagismo; 7,3% deles não recomendam estas mudanças comportamentais.*

Conclusão: *Este estudo demonstrou que a preferência por micronutrientes em degeneração macular relacionada à idade foi baixa dentre os oftalmologistas da Turquia. Além disso, os subespecialistas da retina têm uma menor taxa de prescrição. Apoio micronutricional e outras recomendações (cessação do tabagismo, mudanças na dieta, etc.) devem ser lembrados mais em pacientes com degeneração macular relacionada à idade.*

Descritores: *Degeneração macular/prevenção & controle; Suplementos dietéticos; Vitaminas/administração & dosagem; Luteína/administração & dosagem; Guias como assunto; Turquia*

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%[6]. In recent years, a number of alternative treatments, such as anti-VEGF therapy, have increased the hope of curing neovascular ARMD[7-9]. 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[10].

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[11-15]. 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[16]. The Age-related Eye Disease Study-1 (AREDS) is a comprehensive, prospective, placebo-controlled study monitoring 4757 participants. Its first results were published in 2001[17]. This study demonstrated that high doses of vitamin and mineral supplements prevent progression to the advanced stages of ARMD (choroid neovascularization or central geographic atrophy) at a rate of 25%, and decrease the risk of serious vision loss. The authors of these and other studies (such as those conducted by American Academy of Ophthalmologists) have recommended micronutrition support for category 3, and 4 patients, as long as no contraindication exists. Outcomes of the AREDS 2 study were published in 2013[18]; the results suggest that enrichment of the diet with lutein and zeaxanthin has a protective role in ARMD progression.

A few published studies showed that patients receiving vitamin supplements complied poorly with the recommendations of their ophthalmologists. However, a large-scale study which evaluates the amount of supplements recommended by ophthalmologists has not been conducted yet[19-24]. The primary objective of this study is to evaluate the frequency of micronutrition recommendations made by ophthalmologists to ARMD patients in Turkey, and to assess the criteria used by ophthalmologists when making such recommendations.

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 responders and their responses would not be disclosed. The participants 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.

Statistical analysis

For statistical analysis, all data were entered into a database in SPSS v. 18, followed by descriptive analyses. The significance level between groups was assessed by the χ^2 test; $p<0.05$ was considered as significant.

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 questionnaires. 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. Table 1 and table 2 show demographic characteristics of the participants, and their specialty areas.

Of the participants, 43% preferred use of micronutrition occasionally, 37% frequently, 11% always, and 9% never. General ophthalmologists (26.4%) and professors (7.9%) were the most common groups of participants to select "frequently" and "always." Associate professors prescribed micronutrition at a minimal level (1.6%). Micronutrition was most commonly recommended by general ophthalmologists (22%) and retina-uvea specialists (13.9%). The micronutrition prescribing ratio was 54.8% in retina-uvea specialists when the "frequent" and "always" response results were combined. Table 3 shows the distribution of micronutrition use according to subspecialty and gender of the participants. There was no statistically significant difference between subspecialty groups (p=0.308).

When asked about the type of AREDS criteria used for recommendation of micronutrition, 57.1% of the participants indicated that they had not used AREDS criteria. Instead, they relied on their clinical experience. Only 31.3% recommended micronutrition for their AREDS category 3-4 patients (Table 4). Based on the responses, 56.3% of the general ophthalmologists who prescribed micronutrition did

Table 1. Demographic characteristics of participants

			Affiliation			
Academic degrees	**Responses, %**	**Age (mean SD)**	**Private hospitals**	**Training and research hospitals**	**State hospitals**	**University-foundation hospitals**
Assistant	28 (11)	28.3 ± 1.5	0	8	0	20
Specialist	151 (62)	38.6 ± 8.0	47	28	62	11
Asst. prof	22 (9)	36.5 ± 3.6	0	2	0	20
Assoc. prof	11 (5)	43.0 ± 5.9	2	2	0	7
Professor	31 (13)	52.9 ± 6.8	4	2	0	25
Total	243 (100)	-	53 (22)	42 (17)	62 (26)	83 (35)

SD= standard deviation; Asst. prof= assistant professor; Assoc. prof= associate professor.

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 mic ronutrition 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.

Table 2. Distribution of participants by subspecialty

Subspecialty	n	%
General ophthalmology	121	48.8
Glaucoma-oculoplasty	19	7.7
Cornea-refractive surgery	26	10.5
Retina-uvea	62	25.0
Other	19	7.7
Total	247	99.6

Table 3. Prescribing rates of micronutrition according to gender and subspecialty

	Recommendation of micronutrition			
	Never n (%)	Occasionally n (%)	Frequently n (%)	Always n (%)
Gender				
Male	16 (6.6)	76 (31.4)	51 (21.1)	14 (5.8)
Female	5 (2.1)	30 (12.4)	38 (15.7)	12 (5.0)
Subspecialty				
Retina & uvea	4 (1.6)	24 (9.8)	26 (10.6)	8 (3.3)
Other	18 (7.3)	82 (33.4)	65 (26.4)	19 (7.7)
Total	22	106	91	27

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[25]. 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, currently 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[26]. 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[27,28]. 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[29]. Survey research in the UK revealed that almost all optometrists and ophthalmologists recommend micronutrition supplements (92.8%)[20].

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 micronitrution.

Table 4. Prescribing rates of micronutrition according to the AREDS criteria with respect to subspecialty

Subspecialty	I do not use AREDS n (%)	Category 1-2 n (%)	Category 3-4 n (%)	Category 5 n (%)
General ophthalmology	67 (56.3)	12 (10.1)	24 (20.2)	2 (1.7)
Glaucoma & oculoplasty	12 (66.7)	3 (16.7)	2 (11.1)	0 (0.0)
Cornea & refractive surgery	16 (64.0)	3 (12.0)	2 (8.0)	0 (0.0)
Retina & uvea	33 (54.1)	2 (3.3)	22 (36.1)	0 (0.0)
Other	9 (52.9)	1 (5.9)	6 (35.3)	0 (0.0)
Total	137 (57.1)	21 (8.8)	56 (23.3)	2 (0.8)

AREDS1 and AREDS2 studies are multi-centered, placebo-controlled, randomized, double-blind studies concerning micronutrition[18,30]. 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[19]. 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[20].

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[19]. 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 to our patients the longevity of the treatment and its protective value against vision loss. Even though a statistically significant difference was not found between the educational levels of the participants who were in favor or against micronutrition, nearly one third of the general ophthalmologists and the retina specialists had negative opinions about its benefits. Though the outcomes of AREDS 2 study demonstrated the benefits, some physicians have some reservations. The newly published AREDS 2 study suggesting the necessity of performing larger scale long-term studies may possibly explain some of these reservations.

Many studies have shown that 36-43% of patients do not sufficiently comply with recommendations of the physicians[19,22]. Hochstetler et al. showed that the main reason for poor compliance was failure to recommend micronutrition for suitable patients[19]. In other words, in addition to lower compliance of the patients who had been given relevant recommendations, some patients did not receive any recommendation.

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[23]. Additionally, a separate study indicated that nearly one third of the patients did not receive adequate doses[24]. In this study, 62% of the patients used correct doses[23]. 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[31-33]. 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[23]. 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 physicians 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 survey 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.

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