DERLEME / REVIEW

The Effect of Nutriton and Lifestyle on Age-related Macular Degeneration

Beslenme ve Yaşam Tarzının Yaşa Bağlı Makula Dejenerasyonuna Etkisi

Ahsen ERİK, Aylin SEYLAM KÜŞÜMLER
İstanbul Okan Üniversitesi, Sağlık Bilimleri Fakültesi, Beslenme ve Diyetetik Bölümü, İstanbul, Türkiye

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Sorumlu Yazar/Corresponding Author:

Ahsen ERİK, Dyt.
İstanbul Okan Üniversitesi, Sağlık Bilimleri Fakültesi, Beslenme ve Diyetetik Bölümü, İstanbul, Türkiye
E-posta: ahsennerik@gmail.com
ORCID: 0000-0003-1324-5771

Aylin SEYLAM KÜŞÜMLER, Dr. Öğr. Üyesi
ORCID: 0000-0003-4705-8042

Abstract

Age-related macular degeneraton is an eye disease that is one of the biggest causes of blindness worldwide. Age-related macular degeneration is a complex and multifactorial disease. Although there are many risk factors both environmental and genetic such as ethnicity, age, genetics, family history, and oxidativestress, the most effective and modifiable risk factor in preventing age-related macular degeneration is smoking. In addition, the fact that nutrition is a potentially modifiable risk factor suggeststhat it may reduce the risk of age-related macular degeneration. In many epidemiological studies, especially Age-Related Eye Disease Studies, the specific effect of vitamins and minerals, which are nutritional components, on age-related macular degeneration has been investigated as they prevent oxidativestress due to their antioxidant effect. In this review, the effects of diet and lifestyle change on age-related maculardegeneration are explained.

Anahtar Kelimeler: Macular degeneration, risk factors, eye diseases, dietary supplements.

Öz

Yaşa bağlı makula dejenerasyonu, tüm dünyada körlüğün en büyük nedenlerinden biri olan göz hastalığıdır. Yaşa bağlı makula dejenerasyonu karmaşık ve çok faktörlü bir hastalıktır. Hem çevresel hem genetik olarak hastalığa yol açan etnik köken, yaş, genetik, aile öyküsü, oksidatif stres gibi birçok risk faktörü bulunsa da yaşa bağlı makula dejenerasyonunu önlemede en etkili, değiştirilebilir risk faktörü sigara içmektir. Bunun yanında, beslenmenin de potansiyel değiştirilebilir bir risk faktörü olarak karşımıza çıkması, yaşa bağlı makula dejenerasyonu oluşturma riskini azaltabileceğini düşündürmektedir. Beslenme ve/veya besin bileşenleri takviyesinin yaşa bağlı makula dejenerasyonu üzerinde olumlu etki yaratabileceği düşünülmüş, bununla ilgili birçok çalışma yapılmıştır. Yaşa bağlı göz hastalıklarını inceleyen birçok epidemiyolojik çalışmada, antioksidan etkisinden dolayı oksidatif stresi engellediği için vitamin ve minerallerin, makula dejenerasyonu üzerindeki spesifik etkisi araştırılmıştır. Bu derlemede, diyet ve yaşam tarzı değişikliğinin yaşa bağlı makula dejenerasyonu üzerindeki etkisi anlatılmaktadır.

Keywords: Makula dejenerasyonu, risk faktörleri, göz hastalıkları, diyet takviyeleri

1. Introduction

Most elderly individuals suffer from age-related macular degeneration (AMD), which is characterized by structural changes in the Bruch membrane, deposition of lipofuscin in the retinal pigment epithelium (RPE) and is the leading cause of irreversible relative loss (1). Thickening of the RPE and/or enlargement of the new blood vessel between the Bruch membrane and retina can cause both geographic atrophy and choroidal neovascularization, which are types of AMD (2). AMD, the main cause of central vision loss, affects approximately 10% of individuals older than 65 years and 25% of individuals older than 75 years in the world (2). There is no prevalence data for AMD in Turkey. However, in a meta-analys is conducted in 2015, the percentage of AMD for individuals aged 50 and over in North Africa and Middle East group, including Turkey, was 3.2% (3). In Europe, it is estimated that the number of individuals with early AMD will vary between 14.9-21.5 million and the number of individuals with advanced AMD will vary between 3.9-4.8 million in 2040 (4). Int he United States, approximately 9 million individuals over the age of 40 are affected by different types and severity of AMD. However, this numbers are estimated to double in 5-10 years (5). Both the prevalence and incidence of allt ypes of AMD increase in direct proportion with age(6). Although the exact pathogenesis is still unknown, oxidative stress is thought to be one of the main components of AMD, as the retina is susceptible to oxidative processes (7). Many modifiable and non-modifiable factors cause AMD risk. Ethnicity, age, gender, and genetic predisposition can be given as examples of non-modifiable factors, and lifestyle changes such as diet and smoking can be given as examples of potentially modifiable risk factors. The modifiable risk factors are of great importance in the prevention or treatment of the disease and especially to reduce vision loss (6).

In the most important Age-Related Eye Disease Studies (AREDS and AREDS2) investigating the role of nutrition in the treatment of AMD, it was seen that red meat consumption may be a risk factor for AMD depending on the dose. On the other hand, it was concluded that fruit consumption may be a protective factor due to its antioxidant effects such as lutein, zeaxanthin, beta-carotene, vitamin B, C, D, E, and zinc (9).The AREDS study is the only large-scale commendation still with a grade A for the prevention of AMD.

The AREDS formula, containing beta-carotene, vitamin C, vitamin E, copper, and zinc, has shown that it slows disease progression over a 5-year period in patients with moderate or advanced AMD. In addition, zinc or other antioxidants alone have less effect on AMD, the effect of the combination of supplements was observed to be more effective (10).

Although the antioxidant-effective nutritional components have positive effects in patients with AMD, they do not eliminate the risk in healthy individuals. Therefore, even if nutritional supplementation is recommended, people should be informed about the possibility of AMD risk and other modifiable risk factors. Additionally, the side effects of the supplements used in AREDS formulation should not be forgotten due to the excess amount and the length of time they are used (6).

1.2.Age-related Macular Degeneration

Age-related macular degeneration, which was previously overlooked and not well understood despite medical and surgical interventions, but has now become a major public health problem, is a disease characterized by mild to moderate vision loss. This disease, which significantly reduces the quality of life, is the first cause of blindness in Western countries (11). On the other hand, it is thought that the number of people with AMD could increase by 40% worldwide from 2020 to 2040 (12).

The hallmark of AMD is that the drusen structure accumulates in clusters (10). Drusen is the yellowish deposit of oxidized lipids, proteins, and inflammatory residues located between the basement membrane of the RPE and the Bruch's membrane. It has been observed that as people age, the accumulation of plasma lipids such as cholesterol and triglycerides in the Bruch membrane can contribute to the formation of drusen, and drusen may also become calcified with age (6). Drusen are further classified by size [small (<63 μm in diameter), medium (63-124 μm), and large (> 124 μm)]. It may also appear hard or soft along the edges (13). While the presence of drusen is a risk factor for blindness, the presence of small (<63 μm) and hard drusen is not a risk factor for AMD development alone (2). AMD has two subtypes with different prognoses. It is mostly classified as neovascular AMD with minimal visual impact and atrophic AMD. Neovascular AMD, also known as choroidal neovascularization, is caused by the abnormal growth of new blood vessels in the retinal tissue, a condition characterized by subsequent seepage and bleeding of the vessels. It is associated with a partially reversible rapid vision loss. Atrophic AMD, which causes a more gradual loss of vision and for which treatment options are limited, is another subtype of AMD. In addition, current treatments for atrophic AMD do not prevent vision loss, they delay disease progression. After the less serious neovascular and atrophic AMD, the early and intermediate stages of AMD could occur and cause more serious impairments. In early AMD, the larger the area of drusen, the higher the risk of turning late-stage disease. While early AMD is defined by the presence of soft or in distinct drusen (14), late-stage AMD consists of a dry form characterized by central geographic atrophy and a wet form characterized by the presence of neovascular AMD (15). Approximately 10% of patients with early AMD progress to the late AMD stage, which causes severe visual impairment (16). At the same time, it is known that AMD can switch from the dry (non-exudative) form to the wet (exudative) form, as well as the opposite (15).

The visual result of the last period of wet ADM causes permanent loss of central vision. According to the AREDS study, the categories of AMD are classified into four 4 categories: 1) If the number of drusen is less than 5 or less, the individual does not have AMD, 2) If there is a large number of small drusen or at least 1 medium-sized drusen, mild AMD in the individual, 3) Moderate AMD if the individual is classified with medium-sized drusen intensive, more than one large drusen or decent ralized geographic atrophy (GA), 4) If there is central GA or choroidal neovascularization (CNV) causing vision loss in one of the eyes, the individual has developed AMD (2). This loss of vision in patients with AMD means that it will prevent daily routine activities such as reading and writing, using computers, watching TV, or driving a car, and this disability can cause an increase in personal costs and a serious increase in the burden on health care resources (17).

Age-related macular degeneration, its multifactorial nature, the complexity of the visual system, and the uncertainty of the aging process make the disease a complex pathology (18). Although there is no single cause of AMD, there are many reasons such as age, genetic predisposition, ethnic origin, family history, oxidative stresses and environmental factors (6). The effort to identify risk factors for AMD is extremely important to prevent the development or progression of the disease (14).

1.3. AMD Risk Factors

1.3.1. Genetic Predisposition & Ethnicity

Knowledge about the photo-mechanisms of AMD is increasing since genetic risk factors were first identified 10 years ago (15). About 20 genes have been identified and the most important ones are component 2 (C2), complement factor B (CFB), component 3 (C3) genes, complement factor H related genes (CFHR4, CFHR5),CHF, ARMS2, FB, and F13B. The CHF and Y4O2H polymorphism, has been strongly proven to be associated with AMD, is thought to play an almost 60% role at the population level due to the increased risk varying between two and four times for heterozygous carriers and three to seven times for homozygotes (15, 18). The genetic predisposition of the individual may also affect the response to treatment (2). In addition, genetic testing has been reported to be particularly important in individuals with a family history of AMD (18).

Ethnicity greatly influences an individual's risk of developing AMD; alltypes of AMD are found most frequently in Caucasians (39%) and blacks (30%). The prevalence of AMD is the lowest in Asians (7%) (18).

1.3.2. Age and Gender

The most important unchangeable risk factor for the increase in the incidence and prevalence of AMD is aging. Age significantly increases the risk of AMD by affecting drusen due to dyslipidemia, atherosclerosis, and contributing to theatrophy of photoreceptors (18). While the risk of acquiring AMD is rare in individuals younger than 50 years of age, this risk increases more than three fold in individuals over the age of 75. According to a study, the prevalence of late AMD is 1.4% in individuals aged 70, 10% in individuals older than 80, and increases up to 20% in individuals aged 90 (18). In addition, individuals with a genetic predisposition to late AMD may be exposed to disease at a younger age (19).

Researchers have suggested that women have a higher risk of AMD compared to men, thus, the effect of gender may also be a risk factor (2). While considering the higher prevalence of AMD among women, their longer life expectancy should also be taken into account (4, 20, 21).

1.3.3. Oxidative Stress

The retina becomes susceptible to oxidative stress and damage, especially due to exposure to intense light and high oxygen concentration. Increasing oxidative damage and other retinal modifiers during aging are known to be characteristic features of early AMD, which can progress to advanced AMD-related pathology and visual impairment (4).

1.3.4. Other Risk Factors

In addition to all these known risks, multiple risk factors are thought to cause the development of AMD. These risks should be considered modifiable risks. Obesity (BMI >30 kg/m2) (especially abdominal obesity in men) or being overweight (BMI >25 kg/m2) are associated with body mass index (BMI) and anthropometric measurements such as waist circumference are among these modifiable risk factors (18). In AREDS, individuals with a higher BMI were found to be at greater risk of geographic atrophy, a type of AMD (5). However, more studies on this subject need to be designed (14). In addition to anthropometric measurements, physicalactivity (PA) was considered another potentially modifiable risk factor, as both early and late AMD types were lower in individuals with above-average PA (19).

Some studies have shown that certain diseases may be a risk for AMD (1,5). Atherosclerotic vascular diseases is thought to contribute to the development of AMD since it is similar to drusen accumulation and affects the pathophysiology of RPE(14). In addition, in a study found that C-reactive protein was associated with AMD (5). High pulse pressure is thought to be another factor associated with an increased risk of AMD, although conclusive evidence is not yet available. Diabetes, hyperlipidemia, previous cataract surgery, and hyperopia are other risk factors thought to play a role in AMD risk (18).

A non-negligible, potentially modifiable risk factor for AMD is smoking. Smoking is known to be the only causative factor of AMD, as it increases oxidative stress, is associated with higher fibrinogen levels and decreased antioxidant levels. According to the report of AREDS, it has been officially proven that individuals who smoke are more likely to progress to advanced AMD (7). In another study, individuals who currently smoke found to have an increased risk of AMD by 1.9 fold, while individuals who used to drink but currently do not have an 1.7 fold increased risk (7).

1.4. The Relationship Between Diet and AMD

While some new drug treatments have proven effective in controlling neovascular AMD in recent years, the current cost of these drugs is quite high as patients require multiple injections. This is why overcoming AMD with prevention is considered to be more economical and more reliable (7). Antioxidative measures, known to both patients and physicians, are of great interest as they are beneficial in delaying the progression of AMD (22). It is known that diet and/or dietary supplements will prevent AMD by reducing oxidative stress with its antioxidative effect (11). There are two of the most important studies looking at the role of nutrients in AMD (6, 23). The first is AREDS, a multi center randomized trial that showed that treatment with vitamin and mineral supplementation reduced progression to advanced AMD (6). AREDS2, another multi center and randomized study following this study, showed that lutein and zeaxanthin supplements rather than omega-3 fatty acids further reduced the risk of progression to AMD (23, 24).

The main ingredients of the AREDS formula, which remains the only A-rated recommendation for AMD, are vitamin C, vitamin A (the beta-carotene form), vitamin E, and zinc. The idea that these vitamins and minerals play a role in the prevention of AMD comes from their antioxidant properties, resulting in a protective effect on retinal cells by resisting oxidative stress. The result of the study showed that daily intake of thea mount of antioxidant and zinc included in the formula reduced the risk of progression to advanced AMD by 25% (10). It is also of great importance that the amounts of these supplements are much higher than the Dietary Reference Intake (DRI), known as the nutritional recommendation system. For example, the amount of vitamin C for a healthy adult should only be 90 milligrams according to the DRI, while in the AREDS formula this amount is 500 milligrams (7). At the same time, taking supplements regularly for a long time comes with some potential risks. Excessive amounts of vitamin C causing kidney stone formation, decreased thyroid function due to vitamin E, stomach pain due to zinc, and increased lung cancer due to beta-carotene, especially in smokers, are examples of potential risks in AREDS formula (7). Since the risk of beta-carotene-induced lung cancer is 4-5 timeshigher in smokers than in non-smokers, AREDS formula is not considered suitable for AMD patients who are smokers (21). In addition, it is an inevitable fact that AMD can develop in patients who apply the AREDS formula (7).

Age-Related Eye Disease Study 2 was designed to maket he AREDS formula more effective. AREDS2 is a study designed to evaluate whether adding lutein/zeaxanthin and omega-3 fatty acids (EPA and DHA) to the original AREDS formula would be effective on the risk of developing AMD (25). However, as a result of the study, the addition of lutein+zeaxanthin, EPA, and DHA to the AREDS formula did not reduce the risk of patients developing advanced AMD. Also, in AREDS2, lutein, and zeaxanthin were not associated with this increase, unlike beta-carotene in the AREDS formula, which was associated with lung cancer in smokers. Although the high intake of DHA found in oilyfish was associated with a decrease in the risk of neovascular AMD, it was observed that the addition of DHA and EPA to the original AREDS formulation did not alter the risk of developing AMD (9). Some researchers have criticized the fact that they could not detect the effect of omega-3 supplementation due to factors such as patient selection, insufficient treatment time, insufficient dose (11). Another possible explanation for these inconsistent results is the complex interaction between nutritional components and other environmental factors (9). Despite all this, researchers think that, given the available evidence, it makes sense for AMD patients to consume dietary fatty fish or fish oil supplements (11).

In both studies (AREDS and AREDS2), it was concluded that consumption of red meat may be a risk factor for AMD, depending on the dose, while fruit consumption may be a protective factor because it contains components such as vitamin C, vitamin E, beta-carotene and zinc. Again, both studies emphasized the importance of modifiable risk factors for late AMD and proved a good distinction between the absence of AMD and advanced AMD, with a diet tailored to age, gender, body mass index, alcohol, and cigarette intake (2, 9).

1.4.1. Dietary Micronutrients

Carotenoids (lutein+zeaxanthin, beta-carotene), vitamins (vitamin A, E, C, D, B) with antioxidant effect; dietary fatty acids (omega-3, omega-6, PUFA, etc.), and minerals such as zinc are the dietary components that are thought to affect on AMD (2). In a study, it was investigated whether a diet rich in vitamins and minerals had an effect on AMD, and it was found that an above-average intake of vitamin C, vitamin E, beta-carotene, and zinc reduced the risk of AMD by 35% (12). The literature shows that the combination of other nutritional components with antioxidant effects and antioxidants further increases the effect on AMD (13).

The increase in the intake of lutein and zeaxanthin, which are the most studied carotenoids for AMD, reduces the risk of developing AMD by protecting the retinal tissue from photo-oxidative damage (13). However, as the human body cannot synthesize lutein, the only source of lutein is foods (vegetables such as kale, spinach) and/or supplements (12). As a result of the AREDS study, it has been shown that a higher intake of lutein + zeaxanthin from foods reduces the risk of developing early or neovascular AMD within 5-10 years (21).

Beta-carotene, which is the most common serum carotenoid, is called provitamin A because it is broken down by some enzymes after absorption and contributes to vitamin A activity in humans (13). It has been suggested that beta-carotene, which is found in green leafy vegetables and fruits, can be included in multivitamin supplements due to its antioxidant effect and may reduce the risk of AMD (26). However, according to the epidemiological findings, it was seen that beta-carotene supplements did not provide any protection against oxidative stress-related AMD or even cancer(26). However, its use is not recommended for the prevention of AMD because of its potential side effects, such as lung cancer, especially in smokers (13).

Although low intake of vitamin C, which is found in the entire retina and was thought to reduce the risk of AMD, was associated with a higher risk of AMD, adequate consumption did not significantly affect the risk of AMD (26). In addition, vitamin E, which is the most effective scavenger of freeradicals, is known as a vitamin whose deficiency increases with age. Because its deficiency causes photoreceptor loss and retinal damage, researchers speculated that consumption of vitamin E would have a positive effect on the progression of AMD (26). In addition to conflicting results in studies, it has been observed that vitamin E consumption has no adverse or protective effect on the prevention of AMD (13). Since vitamin D has anti-inflammatory properties, it has been investigated whether it has a specific effect on AMD. One study found that high doses of dietary vitamin D were associated with smaller drusen size and less severe AMD (13). B group vitamins that play an important role in cell metabolism and change homocysteine levels when taken with diet are folic acid, vitamin B6, and vitamin B9. High plasma homocysteine has been seen in people with exudative AMD, also called dry AMD (13). In a study, homocysteine, vitamin B12, and folate levels were compared and a relationship was found between serum homocysteine and AMD (21). A similar relationship is seen when vitamin B12 intake is low, but this is not the case for folate levels. In another study conducted later, it was seen that folicacid and B12 deficiencies, followed for 10 years, increasing the risk of developing AMD, and this was supported (13).

Zinc is an essential trace element with an important role in retinal pathophysiology and is also these cond most abundant metal in the retina afteriron (26). According to the Food and Drug Administration in the United States, the daily zinc intake is 11 milligrams for men; 8 milligrams for women (11). However, although sea food such as clams contains more zinc perserving than other nutrients, it is known that there commended amount of zinc is difficult to obtain from diet alone (22). While zinc concentration in the human retina decreases with age, zinc concentrations influence the progression of AMD (26). Taking 80 mg of zincoxide alone or in combination with antioxidants was seen in the AREDS study, which reduced the risk of progression to advanced AMD in individuals with moderate AMD (11). Although the results of some studies have found mixed results regarding the effect of zinc on AMD, the value of zinc supplementation has generally been supported (13).

Another nutritional component associated with the reduction of AMD is polyunsaturatet fattyacids (6). In a cohort study conducted in Australia, which included a large population, it was observed that consuming one portion of fish per week or consuming 2 servings of nuts per week, due to its EPA and DHA content, reducedthe risk of AMD after 10 years in patients (23). In a study, although an inverse relationship was found between EPA and DHA intake and AMD, it was observed that the risk of advanced AMD (geographicatrophy and neovascularatrophy) increased in patients with high dietary total fat intake (4). Foods such as pork, beef, and especially those containing α-linolenic acid are the foods most associated with an increased risk of AMD. In the AREDS study, although EPA and DHA added to the AREDS formulation did not have a protective effect on AMD, the opposite was seen in a subsequent study on the AREDS population (27).

2. Conclusion and Recommendations

In conclusion, a healthy dietary pattern was found to be effective in preventing or delaying the progression of AMD. While no specific dietary supplement is available as primary prevention for AMD in healthy individuals and individuals at moderate to severe risk of AMD, the most reliable evidence exist for the supplements included in the AREDS formulation. Although more studies are needed for daily servings of clinically recommended supplements, many observational studies show that increased dietary or supplemental intake of nutritional components such as carotenoids, B vitamins, zinc, omega-3 fattyacids is beneficial. As seen in recent studies, it has been proven that the consumption of vegetables and fruits reduce sthe risk of developing AMD as they contain vitamins and minerals.

Recommended dietary supplements should be part of a healthy and varied diet. For example, for a daily intake of 10 mg of lutein, the US Department of Agriculture states that the patient should eat half a cup of cooked kale or 1 cup of cooked spinach every day. Despite all this, it is an inevitable fact that the possibility of AMD risk should not be forgotten even in individuals who apply AREDS formulation and the patient should be warned about potentially modifiable risk factors (smoking, etc.) that may cause AMD.

3. Contribution to the Field

In this review, the nutrition was considered a modifiable risk factor for AMD, which is one of the biggest causes of blindness, and that nutrition or nutritional supplementation could have a positive effect. it will offer new ideas to researchers in ophthalmology studies.

Conflict of Interest

This article did not receive any financial fund. There is noconflict of interest regarding any person and / or institution.

Authorship Contribution

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References

1. Bringmann A, Hollborn M, Kohen L, Wieddemann P. Intake of dietary salt and drinking water: Implications for the development of age-related macular degeneration. Mol Vis [Internet]. 2016 May [cited 2016 Dec 22];22:1437–1454. Available from:http://www.molvis.org/molvis/v22/1437/

2. Zamil W, Yassin S. Recent developments in age-related macular degeneration: A reciew. Clin Interv Aging [Internet]. 2017 Jun [cited 2017 August 22]; ;12:1313-1330. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5573066/ DOI: 100.2147/CIA.S143508

3. Flaxman S, Bourne R, Resnikoff S, Ackland P, Braithwaite T, Cicinelli M, et al. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. Lancet Glob Health [Internet]. 2017 Oct [cited 2017 Dec];5(12):e1221-e1234. Available from: https://pubmed.ncbi.nlm.nih.gov/29032195/ DOI:10.1016/S2214-109X(17)30393-5

4. Colijn JM, Buitendijk G, Prokofyeva E, Alves D, Cachulo M, Khawaja A, et al. Prevalence of age-related macular degeneration in europe: the past and the future. Ophthalmology [Internet] 2017 July [2017 Dec 1];124(12):1753-1763. Available from: https://pubmed.ncbi.nlm.nih.gov/28712657/DOI:10.1016/j.ophtha.2017.05.035.

5. Wul J, Uchino M, Sastry S, Schaumberg D. Age-related macular degeneration and the incidence of cardio vascular disease: A systematic review and meta-Analysis. PloSOne [Internet]. 2013 April [cited 2014 Mar];9(3):e89600. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3969321 DOI:10.1371/journal.pone.0089600

6. Gorusupudi A, Nelson K, Bernstein P. The age-related eye disease 2 study: Micronutrients in the treatment of macular degeneration. Adv Nutr. 2017 Jan;8;40-53.

7. Wong I, Koo S, Chan C. Prevention of age-related macular degeneration. Int Ophthalmol [Internet]. 2010 Jan [cited 2010 Sep];31, 73-82 (2011). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3021198/ DOI:10.1007/s10792-010-9397-5

8. Merle B, Silver R, Rosner B, Seddon J. Associations between vitamin D intake and progression to incident advanced age-related macular degeneration. Invest Ophthalmol Vis Sci. 2017 Sep;58, 4569-4578

9. Ersoy L, Ristau T, Lechanteur Y, Hahn M, Hoyng C, Kirchhof B, et al. Nutritional risk factors for age-related macular degeneration. Biomed Res Int[Internet]. 2014 April [cited 2014 July 3];(2):413150. Available from: https://www.hindawi.com/journals/bmri/2014/413150/ DOI: 10.1155/2014/413150

10. Gregori N, Goldhardt R. Nutrition supplements for age-related macular degeneration. Curr Ophthalmol Rep[Internet]. 2015 Feb [cited 2015 Mar 3]; (1):34-39. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7015456/ DOI: 10.1007/s40135-014-0059-z

11. Gregoire A, Merle B, Korobelnik J, Rougier B, Delyfer M, Goff M, et al. Olive oil consumption and age-related macular degeneration: The Alienor Study. PloSOne [Internet]. 2016July [cited 2016 July 28];11(7): e0160240. Available from:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4965131/ DOI: 10.1371/journal.pone.0160240

12. Zampatti S, Ricci F, Cusumano A, Marsellaa L, Novelli G, Giardina E. Review of nutrient actions on age-related macular degeneration. Nutr Res [Internet]. 2013 May [cited 2013 Oct 28]; 34 (2014) 95 – 105. Available from: https://core.ac.uk/download/pdf/53853165.pdf / DOI: 10.1016 /j.nutres.2013.10.011

13. La T, Cho E, Kim E, Kang S, Jee D. Prevalence and risk factors for age-related macular degeneration: Korean National Health and Nutrition Examination Survey 2008–2011. Curr Eye Res [Internet]. 2013 Aug [cited 2014 April 22];39:12, 1232-1239. Available from: https://www.tandfonline.com/doi/full/10.3109/02713683.2014.907431?scroll=top&needAccess=true / DOI:10.3109/02713683.2014.907431

14. Schmidl D, Garhofer G, Schmetterer L. Nutritional supplements in age-related macular degeneration. Acta Ophthalmol [Internet]. 2015 Jan [cited 2015 Mar];93(2):105-21. Available from: https://onlinelibrary.wiley.com/doi/epdf/10.1111/aos.12650/ DOI:10.1111/aos. 12650

15. Hwang I, Bae J, Kim J, Lee J, Nguyen Q. Adult body height and age-related macular degeneration in healthy individuals: A nation wide population-based survey from Korea. PloSOne [Internet]. 2020 Jan [cited 2020 May 1);1;15(5):e0232593. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7194362/ DOI: 10.1371/journal.pone.0232593

16. Tang D, Mitchell P, Flood V, Kifley A, Hayes A, Liew G, et al. Dietary intervention in patients with age related macculardegeneration: Protocol For A RandomisedControlled Trial. BMJ Open [Internet]. 2018 Jun [cited 2019 Feb 5];9: e024774. Available from: https://bmjopen.bmj.com/content/bmjopen/9/2/e024774.full.pdf/ DOI: 10.1136/bmjopen-2018-024774

17. Layana A, Lopez F, Arumi J, Barquet L, Moreno J. Early and intermediateage-related macular degeneration: Update And Clinical Review. Clin Interv Aging [Internet]. 2017 May [cited 2017 Oct];12:1579-1587. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5633280 /DOI:10.2147/CIA.S142685

18. Heinemann M, Welker S, Li J, Wintergerst M, Turski G, Turski C, et al. Research article: impact of visual impairment on physical activity in early and lateage-related macular degeneration. PloS One [Internet] 2019 Aug [cited2019Oct 21];14(10): E0222045.Available from:https://pubmed.ncbi.nlm.nih.gov/31634374/ DOI: 0.1371/journal.pone.0222045

19. Ampati J, Ampati B, Yoo SH, Ianchulev S, Adamis A. Age-related macular degeneration: Etiology, pathogenesis, and therapeutic strategies. Surv Ophthalmol. 2003 May;48(3):257-93.

20. Evans JR. Risk factors for age-related macular degeneration. Prog Retin Eye Res. 2001 March;20(2):227-53.

21. Sin H, Liu D, Lam D. Lifestyle modification, nutritional and vitamins supplements for age-related macular degeneration. Acta Ophthalmol. 2012 Feb];91(1):6-11.

22. Andreatta W, Sherbiny S. Evidence-based nutritional advice for patients affected by age-related macular degeneration. Acta Ophthalmol 2014 Feb 1;231(4):185-90

23. Broadhead G, Grigg J, Chang A, McCluskey P. Dietary modification and supplementation for the treatment of age-related macular degeneration. NutrRev2015 Jul;73(7):448-62

24. Raimundo M, Mira F, Cachulo M, Barreto P, Ribeiro L, Farinha C, et al. Adherence to a mediterranean diet, lifestyle and age-related macular degeneration: The coimbra eye study- report 3. Acta Ophthalmol [Internet]. 2018 Sep 14; 96(8):e926-e932.

25. Olson J, Erie J, Bakri S. Nutritional supplementation and age-related macular degeneration. Semin Ophthalmol. 2011 May 24; 26 (3):131-6.

26. Kim Ek, Kim H, Kwon O, Chang N. Associations between fruits, vegetables, vitamin A, B-carotene and flavonol dietary intake and age-related macular degeneration in elderly women in korea: The fifth korea national health and nutrition examination survey. Eur J Clin Nutr [Internet]. 2016 Sep [cited 2017 Sep 27];72, 161-167 (2018). Available from: https://pubmed.ncbi.nlm.nih.gov/28952611/ DOI: 10.1038/ejcn.2017.152

27. Chiu CJ, Klein R, Milton R, Gensler G, Taylor A. Does eating particular diets alter the risk of age-related macular degeneration in users of the age-related eye disease study supplements? Br J Ophthalmol [Internet]. 2009 Jun [cited 2011 Feb 4];93(9): 1241-1246. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3033729/ DOI: 10.1136/bjo.2008.143412