Prevention of AMD Onset

Subjects: Ophthalmology

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Age-related macular degeneration (AMD) represents the leading cause of irreversible blindness in elderly people, mostly after the age of 65. The progressive deterioration of visual function in patients affected by AMD has a significant impact on quality of life and has also high social costs. Many studies showed that a higher dietary intake of nutrients, such as lutein, zeaxanthin, beta carotene, omega-3 fatty acids and zinc, reduced the risk of early AMD. Regarding lifestyle habits, the association between smoking and AMD is currently accepted. Finally, retinal damage caused by ultraviolet rays and blue light is also worthy of attention.

Keywords: age-related macular degeneration ; prevention ; nutrients ; lifestyle

1. Introduction

Age-related macular degeneration (AMD) represents nowadays the leading cause of irreversible blindness in elderly people, mostly after the age of 65 [1]. Recent studies predict that by 2040, the number of affected individuals worldwide will be circa 288 million [2]. In addition, the progressive increase in life expectancy of the world's population and, in particular, that of developing countries, will lead to a further increase in the elderly population [3]. By 2025, it has been estimated that the geriatric population will reach the amount of circa 1.2 billion people worldwide, 70% of whom residing in developing countries [4]. This process may contribute strongly to a steady increase in the number of people suffering from AMD, even greater than that assumed by previous studies.

AMD is a retinal disease that typically affects the macula, causing progressive loss of central vision [5]. Early-stage AMD is mainly characterized by clinical signs such as drusen and alterations of the retinal pigment epithelium. Late-stage AMD can assume two different forms: neovascular, also known as wet or exudative, or non-neovascular, also named as atrophic, dry, or non-exudative. AMD progression to late stages results in loss of central vision, leading to severe and persistent visual impairment and legal blindness, thus resulting in a significant impact on the quality of life and also hindering the functional independence of affected individuals [6].

Early AMD is clinically characterized by typical disturbs, such as mild central distortion and reduced reading capacity with decreased luminance. Difficulty to clearly recognize faces and central scotoma are also additional signs that can appear. Nevertheless, in this stage, affected people are mostly asymptomatic. Late AMD may progress to a sudden and rapid deterioration in case of a neovascular form, while a slow and gradual decline of central visual function is typical of the atrophic form. The main feature of neovascular AMD (nAMD) is the presence of choroidal neovascularization and its repercussions, such as intra- and subretinal fluid, hemorrhages, pigment epithelial detachments, hard exudates and, finally, fibrotic tissue. Geographic atrophy is characterized by outer retinal thinning, and it has been evaluated that the progression rate corresponds to circa 2 mm^2/year on average [7]. It is important to point out that, according to the previous reports and classifications, what will be described regarding the prevention of AMD is relative to the "drusen-driven" AMD, without considering the spectrum of pachychoroid diseases.

Nowadays, although the use of intravitreal anti-vascular endothelial growth factor VEGFinjections has contributed considerably to improve the treatment of nAMD, no effective treatment has been yet found for both early AMD and geographic atrophy. The absence of a therapy that might at least stop the unavoidable progression of the clinical course determines a functional limitation in daily activities and, consequently, a worsening of the quality of life for the patients.

In the last years, many researchers have tried to define modifying risk factors, especially how to address retinal oxidative changes related to both onset and progression of the disease. In particular, positive behavioral modifications including smoking cessation, exercise, and healthy diet with the addition of nutritional supplements [8][9].

2. Prevalence and Incidence of AMD

The most relevant information regarding the epidemiology of AMD has been provided by three large, population-based studies: the Blue Mountains Eye Study (BMES), Beaver Dam Eye Study (BDES), and Rotterdam Study (RS), in which data were collected and analyzed, mainly related to both incidence and prevalence of AMD in white populations [10].

The above-mentioned studies have found a prevalence of late AMD of 0.2% for people aged between 55 and 64 years, while an increased prevalence (13.1%) has been observed for people over 85 years [11]. Specifically, BMES demonstrated for early AMD a 15-year incidence of 22.7% and an incidence of 6.8% for late AMD, with an overall incidence greater in women rather than men [12]. At the same time, a meta-analysis from the European Eye Epidemiology Consortium including 14 population-based cohort studies evidenced a prevalence of 13.2% for early AMD and 3.0% for late AMD for people with more than 70 years [13].

Another large meta-analysis reported a higher prevalence of early AMD in European white people when compared with Asian population (11.2% and 6.8%). Moreover, in comparison to African people, there is a major prevalence of both early and late AMD for European population, while no differences have been found between African and Asian populations. On the contrary, the prevalence of nAMD has been estimated to be similar in all ethnic groups (0.46%) [2].

Regarding the prevalence of AMD among different populations, it is noteworthy to underline that both population-based and the Age-Related Disease Eye Study AREDS studies were performed before the concept of pachychoroid spectrum diseases had been widely recognized. Specifically, the difference between pachychoroid neovasculopathy and “drusen-driven” neovascular AMD has not been exhaustively analyzed. Pachychoroid spectrum diseases are much common in Asian compared to Western populations. Asians currently constitute 60% of the world’s population and likely will contribute most greatly to the global prevalence of AMD by 2040. Before the introduction of the concept of pachychoroid spectrum diseases, pachychoroid neovasculopathy had often been diagnosed as AMD especially in Asian populations. This may partly explain why in the previous population-based studies, there was no difference in the prevalence of neovascular AMD in different ethnic groups even though early AMD is more common in Western than in Asian populations [14].

The different prevalence of non-exudative AMD among different ethnic groups may be partly explained by genetic differences. With regard to this, a genetic study has demonstrated a lower frequency of the C-risk allele of the Y402H polymorphisms in Japanese as compared with white populations [15].

3. AMD Impact on Quality of Life and Social Costs

AMD may reduce quality of life with a significant impact on the performance of normal daily activities. The burden of AMD in terms of health has been analyzed with the aim of the disability-adjusted life years (DALY), which represents an indicator that measures the loss of years of life due to AMD [16][17].

Reports exhibited increased levels of life stress and depression in patients affected by AMD compared to healthy subjects, mostly when results of treatment do not correspond to patients’ expectations [18][19]. In addition, it has been demonstrated in patients affected by AMD a greater risk of functional disability, as showed by BMES, where a two times higher risk of negative effects on daily living activity was observed [20].

An interesting paper has evaluated the correlation between AMD and the risk to develop a form of cognitive impairment, including Alzheimer’s disease, throughout the course of life. The researchers found an increased risk for AMD patients to suffer from cognitive impairment and Alzheimer’s disease, mostly in case of atrophic AMD [21].

Finally, it has been estimated by a large meta-analysis that AMD is associated with a 20% increased risk of overall mortality and, specifically, a 46% increased risk for cardiovascular disease [22].

A deepened understanding of global patterns in health burden related to AMD is fundamental to implement focused strategies of prevention. In this regard, a recent study has estimated the social costs of blindness related to AMD in 2020 in the United States. Specifically, the authors analyzed excess costs that occur because of blindness, measuring the differences in total costs between blind and non-blind individuals. They found that the annual amount of excess costs for each blind individual is about USD 5000. Translated to the whole society, it means a total societal cost of circa USD 20 billion, a value that is estimating to triple by 2050 [23].

In the last 25 years, the health burden of AMD has continuously grown without pause worldwide. Despite the introduction of anti-VEGF therapy that has radically improved the clinical history of at least exudative AMD, the DALY due to AMD has

not accordingly improved [16]. This process has been exhaustively analyzed by previous reports across countries, which estimated that the proportion of individuals affected by both visual impairment and blindness due to AMD raised by 81% and 36% between the years 1990 and 2010, respectively [24]. These observations demonstrate that the socio-economic burden related to AMD has not been relieved with the introduction of an effective therapy. For this reason, due to the challenge determined by the increase of both prevalence and burden of AMD, it may be necessary for the next years to arrange additional resources on a global scale to fight this phenomenon.

4. AREDS Studies: Interventions to Stop AMD Progression

A key role in the pathophysiology of AMD progression is played by oxidative stress. Cellular aging is mainly characterized by the production of oxygen free radicals, which eventually leads through various mechanisms to cell death. The retina has a proper defensive mechanism against oxidative processes, which consists of vitamins C and E, carotenoids, lutein, and zeaxanthin [8]. In addition, the presence of a major structural lipid, docosahexaenoic acid (DHA), at the level of cones, is involved in membrane permeability and acts against the formation of new vessels [25]. Based on these abovementioned findings, researchers have made attempts over the years to develop a therapy with nutritional supplements that can hinder an unstoppable process, such as AMD.

As early as the late 1990s, attempts have been made to evaluate the impact of adding nutrients to diet that could somehow slow or stop the progression of the disease toward blindness [26]. In 1988, Newsome et al. [27] demonstrated that a diet with zinc supplementation might reduce the visual acuity loss in patients affected by AMD. In addition, other researchers assessed the efficacy of vitamin formulations containing zinc and antioxidants for AMD, finding contrasting results [28].

The most important reports relative to the nutritional supplementation therapy have been shown by the two AREDS studies [29][30]. The AREDS study assessed the effect of high-dose vitamins C and E (500 mg and 400 IU, respectively), β-carotene (15 mg), and zinc supplementation (80 mg) on AMD progression. The patients included in the study were divided into four groups based on disease's gravity, ranging from early to advanced AMD. The study demonstrated that AREDS supplementation reduced the risk of AMD progression as compared to placebo. However, there was no significant effect on the risk of visual acuity loss. It was also recommended that nutrition supplements should only be used by people who do not smoke, because subsequent analyses of other studies has found a greater incidence of cancer in smokers or recent ex-smokers who assumed β-carotene [31].

The AREDS-2 clinical trial [30] was conducted with the aim to ameliorate the efficacy of the AREDS formulation. For this reason, a new formulation with the addition of lutein and zeaxanthin, which has the maximum concentration at the fovea, plus DHA and EPA (docosahexaenoic and eicosapentaenoic acid) was evaluated in order to find a therapy for decreasing the risk of AMD progression. Moreover, the new study also assessed the effect of the new formulation after eliminating β-carotene and adjusting the dose of zinc to only 25 mg. Therefore, it has been proved that the risk of AMD progression was not more reduced as compared to the previous AREDS study, and, in addition, it was suggested that the first formulation should have included lutein and zeaxanthin, without β-carotene supplementation. Nowadays, the recommended formulation based on AREDS-2 results for dry AMD contains vitamin E (400 IU), vitamin C (500 mg), lutein (10 mg), zeaxanthin (2 mg), copper (2 mg), and zinc (80 mg, but also available with the 25 mg formulation) (**Table 1**).

Table 1. Daily nutritional supplementation based on the results of AREDS-2 study.

AREDS-2 Formulation	
Nutritional Supplement	Recommended Daily Dose
Vitamin E	400 IU
Vitamin C	500 mg
Lutein	10 mg
Zeaxanthin	2 mg

AREDS-2 Formulation	
Nutritional Supplement	Recommended Daily Dose
Copper	2 mg
Zinc	80 mg

References

1. Jin, G.; Ding, X.; Xiao, W.; Xu, X.; Wang, L.; Han, X.; Xiao, O.; Liu, R.; Wang, W.; Yan, W.; et al. Prevalence of age-relat ed macular degeneration in rural southern China: The Yangxi eye study. Br. J. Ophthalmol. 2018, 102, 625–630.
2. Wong, W.L.; Su, X.; Li, X.; Cheung, C.M.G.; Klein, R.; Cheng, C.Y.; Wong, T.Y. Global prevalence of age-related macul ar degeneration and disease burden projection for 2020 and 2040: A systematic review and meta-analysis. Lancet Glo b. Health 2014, 2, 106–116.
3. Zimmer, Z.; Jagger, C.; Chiu, C.-T.; Ofstedal, M.B.; Rojo, F.; Saito, Y. Spirituality, religiosity, aging and health in global p erspective: A review. SSM Popul. Health 2016, 2, 373–381.
4. Mane, A.B.; Khandekar, S.; Fernandez, K. India's ageing population: Geriatric care still in infancy. J. Gerontol. Geriatr. Res. 2014, 3, 186.
5. Coleman, H.R.; Chan, C.C.; Ferris, F.L., III; Chew, E.Y. Age-related macular degeneration. Lancet 2008, 372, 1835–184 5.
6. Mitchell, P.; Liew, G.; Gopinath, B.; Wong, T.Y. Age-related macular degeneration. Lancet 2018, 392, 1147–1159.
7. Schmidt-Erfurth, U.; Klimscha, S.; Waldstein, S.M.; Bogunović, H. A view of the current and future role of optical cohere nce tomography in the management of age-related macular degeneration. Eye 2017, 31, 26–44.
8. Mukhtar, S.; Ambati, B.K. The value of nutritional supplements in treating Age-Related Macular Degeneration: A review of the literature. Int. Ophthalmol. 2019, 39, 2975–2983.
9. Chakravarthy, U.; Augood, C.; Bentham, G.; de Jong, P.; Rahu, M.; Seland, J.; Soubrane, G.; Tomazzoli, L.; Topouzis, F.; Vingerling, J.; et al. Cigarette Smoking and Age-Related Macular Degeneration in the EUREYE Study. Ophthalmolo gy 2007, 114, 1157–1163.
10. Klein, R.; Meuer, S.M.; Myers, C.E.; Buitendijk, G.H.; Rochtchina, E.; Choudhury, F.; de Jong, P.T.; McKean-Cowdin, R.; Iyengar, S.K.; Gao, X.; et al. Harmonizing the classification of age-related macular degeneration in the three-contine nt AMD consortium. Ophthalmic Epidemiol. 2014, 21, 14–23.
11. Smith, W.; Assink, J.; Klein, R.; Mitchell, P.; Klaver, C.; Klein, B.E.; Hofman, A.; Jensen, S.; Wang, J.J.; de Jong, P.T. Ri sk factors for age-related macular degeneration: Pooled findings from three continents. Ophthalmology 2001, 108, 697 –704.
12. Joachim, N.; Mitchell, P.; Burlutsky, G.; Kifley, A.; Wang, J.J. The incidence and progression of age-related macular deg eneration over 15 years: The Blue Mountains Eye Study. Ophthalmology 2015, 122, 2482–2489.
13. Colijn, J.M.; Buitendijk, G.H.; Prokofyeva, E.; Alves, D.; Cachulo, M.L.; Khawaja, A.P.; Cougnard-Gregoire, A.; Merle, B. M.; Korb, C.; Erke, M.G.; et al. Prevalence of age-related macular degeneration in Europe: The past and the future. Op hthalmology 2017, 124, 1753–1763.
14. Yamashiro, K.; Hosoda, Y.; Miyake, M.; Ooto, S.; Tsujikawa, A. Characteristics of pachychoroid diseases and age-relate d macular degeneration: Multimodal imaging and genetic backgrounds. J. Clin. Med. 2020, 9, 2034.
15. Kuo, J.Z.; Wong, T.Y.; Ong, F.S. Genetic risk, ethnic variations and pharmacogenetic biomarkers in age-related macular degeneration and polypoidal choroidal vasculopathy. Expert Rev. Ophthalmol. 2013, 8, 127–140.
16. Wang, D.; Jiang, Y.; He, M.; Scheetz, J.; Wang, W. Disparities in the Global Burden of Age-Related Macular Degenerati on: An Analysis of Trends from 1990 to 2015. Curr. Eye Res. 2019, 44, 657–663.
17. DALYs, G.; Collaborators, H.A.L.E.; Kassebaum, N.J.; Arora, M.; Barber, R.M.; Brown, J.; Carter, A.; Casey, D.C.; Charl son, F.J.; Coates, M.M.; et al. Global, regional, and national disability-adjusted life-years (dalys) for 315 diseases and in juries and healthy life expectancy (hale), 1990–2015: A systematic analysis for the global burden of disease study 201 5. Lancet. 2016, 388, 1603–1658.

18. Brody, B.L.; Gamst, A.C.; A Williams, R.; Smith, A.R.; Lau, P.W.; Dolnak, D.; Rapaport, M.H.; Kaplan, R.M.; I Brown, S. Depression, visual acuity, comorbidity, and disability associated with age-related macular degeneration. Ophthalmology 2001, 108, 1893–1901.
19. Casten, R.J.; Rovner, B.W. Update on depression and age-related macular degeneration. Curr. Opin. Ophthalmol. 201 3, 24, 239–243.
20. Gopinath, B.; Liew, G.; Burlutsky, G.; Mitchell, P. Age-related macular degeneration and 5-year incidence of impaired ac tivities of daily living. Maturitas 2014, 77, 263–266.
21. Woo, S.J.; Park, K.H.; Ahn, J.; Choe, J.Y.; Jeong, H.; Han, J.W.; Kim, T.H.; Kim, K.W. Cognitive impairment in age-relat ed macular degeneration and geographic atrophy. Ophthalmology 2012, 119, 2094–2101.
22. McGuinness, M.B.; Karahalios, A.; Finger, R.P.; Guymer, R.; Simpson, J.A. Age-Related Macular Degeneration and Mo rtality: A Systematic Review and Meta-Analysis. Ophthalmic Epidemiol. 2017, 24, 141–152.
23. Moshfeghi, A.A.; Lanitis, T.; Kropat, G.; Kuznik, A.; Gibson, A.; Feng, H.; Prenner, J. Social Cost of Blindness Due to A MD and Diabetic Retinopathy in the United States in 2020. Ophthalmic Surg. Lasers Imaging Retin. 2020, 51, S6–13.
24. Jonas, J.B.; Bourne, R.R.; White, R.A.; Flaxman, S.R.; Keeffe, J.; Leasher, J.; Naidoo, K.; Pesudovs, K.; Price, H.; Won g, T.Y.; et al. Visual Impairment and Blindness Due to Macular Diseases Globally: A Systematic Review and Meta-Analy sis. Am. J. Ophthalmol. 2014, 158, 808–815.
25. SanGiovanni, J.P.; Chew, E.Y. The role of omega-3 long-chain polyunsaturated fatty acids in health and disease of the r etina. Prog. Retin. Eye Res. 2005, 24, 87–138.
26. Rojas-Fernandez, C.H.; Tyber, K. Benefits, Potential Harms, and Optimal Use of Nutritional Supplementation for Preve nting Progression of Age-Related Macular Degeneration. Ann. Pharmacother. 2016, 51, 264–270.
27. Newsome, D.A.; Swartz, M.; Leone, N.C.; Elston, R.C.; Miller, E. Oral Zinc in Macular Degeneration. Arch. Ophthalmol. 1988, 106, 192–198.
28. Sperduto, R.D.; Ferris, F.L., III; Kurinij, N. Do we have a nutritional treatment for age-related cataract or macular degen eration? Arch. Ophthalmol. 1990, 108, 1403–1405.
29. Age Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplem entation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS r eport no. 8. Arch. Ophthalmol. 2001, 119, 1417–1436.
30. Gorusupudi, A.; Nelson, K.; Bernstein, P.S. The Age-Related Eye Disease 2 Study: Micronutrients in the Treatment of Macular Degeneration. Adv. Nutr. 2017, 8, 40–53.
31. Awh, C.C.; Hawken, S.; Zanke, B.W. Treatment response to antioxidants and zinc based on CFH and ARMS2 genetic ri sk allele number in the age-related eye disease study. Ophthalmology 2015, 122, 162–169.

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