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Review Article

Lifestyle modification, nutritional and vitamins supplements for age-related macular degeneration

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ABSTRACT.

Purpose: **To provide a systematic review of the published studies pertaining to the lifestyle modification, dietary, nutritional and vitamins supplements for preventing occurrence or halting deterioration of age-related macular degeneration (AMD).**

Methods: **The literature searches from 1990 to December 2010 with following keywords, 'age related macular degeneration', 'nutrition', 'antioxidant', 'diet' and 'vitamins supplements' using search engines Pubmed, Google Scholar, Medline and the Cochrane Library.**

Meta-analyses, population-based cohort studies and case-controlled trials were reviewed, whereas small cases series, case reports, commentaries, abstracts in proceedings or personal observations were excluded.

Results: **Smoking and obesity are identified risk factors for AMD. High dietary intakes of omega-3 fatty acids, and macular xanthophylls lutein and zeaxanthin have been associated with a lower risk of prevalence and incidence in AMD. Vitamin B and extracts from wolfberry, *Gingko biloba* and berry anthocyanins were also subjects of intense research interests, but there has been no concluding scientific evidence yet. The Age-Related Eye Disease study (AREDS) is the only large-scale randomized controlled clinical trial to show beneficial effect of AREDS formulation of vitamins C, E, beta-carotene and zinc with copper in reducing the risk progression to advanced AMD in patients with intermediate AMD or with advanced AMD in one eye.**

Conclusion: **Quit smoking is an important advice to patients to prevent or slow the progress of AMD. There is no recommendation for routine nutritional or vitamins supplementation for primary prevention. However, patients with documented intermediate risk of AMD or advanced AMD in one eye are recommended to take AREDS-type vitamin supplements.**

Key words: age-related macular degeneration – anthocyanins – antioxidants – fatty acids, omega-3 – lutein – vitamins – zeaxanthin

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Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly of the developed countries such as United States and United Kingdom. The prevalence of AMD has been found to increase with age in all population-based studies, with reported rates of AMD among Caucasian at 1–2 per 1000 individuals in their 50s, staggering up to about 55–70 per 1000 for those 75 years of age or older. Population-based studies indicated that the disease was more prevalent in Caucasian than the people of the African lineage (Friedman et al. 1999). Two population-based studies on the prevalence of AMD in Asia were available. In the Aravind Eye Study (Nirmalan et al. 2004), early AMD was diagnosed clinically in 2.7% and late AMD in 0.6% of the 4917 Indian participants at 40 years of age or older. A 5-year cohort study in Japan reported an incidence of 8.5% for early AMD, and 0.8% for late AMD (Miyazaki et al. 2005). These observations suggest that AMD is less common in Japanese than in Caucasian (8.7% and 1.1% for early and late ARM, respectively, in Caucasian according to the Blue Mountains Eye Study (Mitchell et al. 2002)). Some investigators hypothesized the lower incidence of AMD may be related to a

higher antioxidant contents in the typical Japanese diet.

Early AMD is characterized by the presence of drusens. The intermediate form is associated with the loss of retinal pigment epithelium and progressive central chorioretinal atrophy known as geographical atrophy (Fig. 1). Clinically, patients may suffer from gradual loss of contrast sensitivity, impaired reading speed and difficult adaptation to changing light conditions. In advanced AMD, there may be severe central visual-field loss, but the peripheral visual acuity is usually preserved. Development of choroidal neovascular membranes in neovascular (wet) AMD may give rise to typical fundal appearance of exudate, subretinal fluid and haemorrhage (Fig. 2).

The pathogenesis of AMD is complex. Multiple genetic and environmental factors have been implicated. Age, smoking, hypertension and hypercholesterolaemia may be reckoned as the most well-known risk factors, among which age has been found to be the most important.

The pathogenesis of AMD is equally diverse with deranged complements inflammatory pathway, cardiovascular predisposition, localized ischaemia and oxidative stress all having been reported.

The ominous natural outcome and the difficulty in the active management of neovascular AMD by photodynamic therapies or pharmacological approaches by inhibition of the angiogenesis have instigated the pursuit for the prevention or total retardation of the progress of AMD. There are many commercially available natural products, pharmacological agents or even drugs claiming their antioxidative effects and the targeted therapeutic usefulness in preventing AMD. It is important to note that many of these agents were used without solid scientific evidence. Primary care physician need to be aware of the grounds supporting the specific indications, benefits and risks of particular supplements prior to counselling.

Role of antioxidants

Oxidative stress refers to cellular damage caused by reactive oxygen intermediates. The retina is particularly susceptible to oxidative stress because of its high consumption of oxygen, high tissue content of polyunsaturated fatty acids and exposure to visible light (Beatty et al. 2000). The formation of the reactive oxygen species causes oxidation of docosahexaenoic acid (DHA) that has been shown to be one of the major pathways for cellular damage or degeneration of the photoreceptors in AMD (Rotstein et al. 2003; Hollyfield et al. 2008). In other words, the oxidative cellular injury may be the final common pathway to incite the cascade of vascular damage, local ischaemia and the choroidal neovascularization under the interplay of many vascular growth factors like vascular endothelial growth factor (VEGF) and pigment-epithelium-derived factor (PEDF). Therefore, the mechanistic understanding of AMD may provide the theoretical basis for the therapeutic strategy by reducing oxidative damage with the measures like lifestyle modifications, dietary, nutritional or vitamins supplements. All of these preventive antioxidative measures have aroused much attention and interest from both patients and physicians in recent years. In this review, we will focus on and critically appraised the latest scientific evidences pertaining to the use of these antioxidative methods in preventing or retarding progress of AMD.

Method

The literature search to support this review was performed between 10 December 2010 and 17 December 2010. Databases included Medline, Pubmed, The Cochrane Library and Google Scholar using following keywords, 'age related macular degeneration', 'nutrition', 'antioxidant' and 'diet'. English language articles published between 1990 and 2010 were reviewed. Meta-analyses, population-based cohort studies and case-controlled trials were reviewed. Small cases series, case reports, commentaries, abstracts in proceedings or personal observations were excluded.

Lifestyle modifications

The following suggestions might be considered useful in the prevention or retarding progression of AMD:

Quit smoking;
Physical activities, avoid obesity and heavy alcohol consumption;
Dietary intake of low-index glycaemic foods, omega-3 long-chain polyunsaturated fatty acids (LCPUFA).

Cigarette smoking is an independent and avoidable risk factor for AMD (Seddon et al. 1996). There was evidence for a dose–response relationship between smoking and AMD, particularly in patients with the neovascular form of the disease (Vingerling et al. 1996). Thus, quit smoking is a very important advice.

The medical consequences of obesity are numerous, including coronary heart disease, type II diabetes mellitus, hypertension, stroke, dyslipidaemia, osteoarthritis and sleep apnoea. The relationship between obesity and AMD has been investigated in several large population-based studies. Obesity may increase systemic oxidative stress secondary to hyperleptinaemia and play an important role in the pathogenesis of AMD. There is considerable evidence indicating an association between obesity and AMD. The role of weight loss in preventing the development or slowing the progression of AMD, however, remains to be determined (Cheung & Wong 2007).

A total of 1313 participants, ranged in age from 55 to 74 years, were enroled in the Carotenoids in Age-Related Eye Disease Study (CAREDS) that focused on the modified 2005 Healthy Eating Index and food frequency questionnaire. The study showed that the requirements for a healthy daily diet included 3.5 servings of fruit and vegetables; 2.3 servings of dairy; 2.7 ounces of meat, poultry, fish, beans or eggs; and 3.5 serving of grain, including 1 wholegrain item. The results demonstrated a healthier diet, physical activities and no smoking would reduce the odds for AMD (Mares et al. 2010). In the study, women whose diets scored in the highest quintile compared with the lowest quintile on the modified 2005 Healthy Eating Index had 46% lower odds for early AMD. Women in the highest quintile compared with those in the lowest quintile for physical activity (in metabolic energy task hours per week) had 54% lower odds for early AMD, having a combination of 3 healthy behaviours (healthy diet, physical activity and not smoking) were associated with 71% lower odds

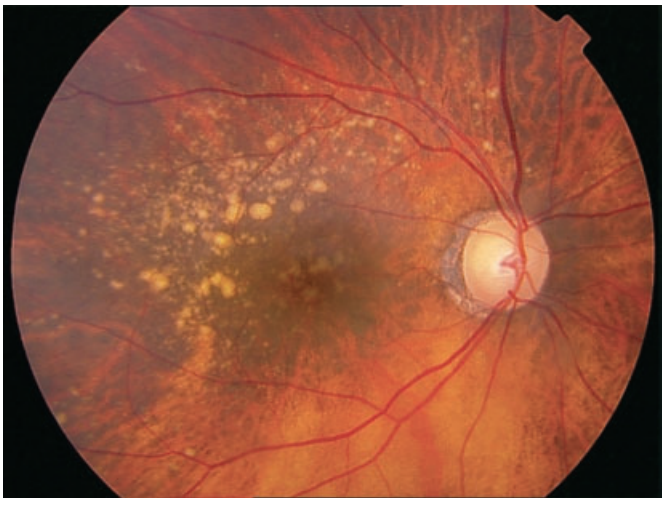

Fig. 1. Dry age-related macular degeneration (AMD) with intermediate to large drusens.

for AMD compared with having high-risk scores ($p < 0.001$).

A systemic review showed that heavy alcohol consumption (more than three standard drinks per day) was associated with an increased risk of early AMD, thus patients are advised to avoid heavy alcohol intake (Chong et al. 2008b)

Studies, including large population-based cohort study (Chiu et al. 2006; Kaushik et al. 2008) and prospective studies from the Age-Related Eye Disease Study (AREDS, Chiu et al. 2007a,b) suggested that people taking high-glycaemic-index foods have increased risk of having AMD. The glycaemic index is a measure of how fast a carbohydrate-containing food raises blood glucose in 2 hrs. Consuming less refined carbohydrates or taking more low-glycaemic-index foods, such as oatmeal, may protect against early AMD.

The effects of dietary fats and their different forms in AMD risk are the interests of many ongoing studies. Omega-3 LCPUFA include alpha-linolenic acid (ALA, short chain), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (the very long chain). Diet is the only source of these fatty acids. DHA is present in high concentrations in the outer segments of photoreceptors, which are constantly shed and turned over during the visual cycle. In a prospective cohort study of 1837 participants at moderate-to-high risk of advanced AMD from the AREDS (Age-Related Eye Disease Study Research Group 2009), those who reported the highest omega-3 LCPUFA intake (median: 0.11% of total energy intake) were 30% less likely than their peers to develop advanced AMD over 12-year period. A recent meta-analysis reviewed nine studies with a total sample of 88 974 people, including 3203 AMD cases (1847 early and 1356 late AMD cases), showed that a high dietary intake of omega-3 fatty acids was associated with a 38% reduction in the risk of advanced AMD (Chong et al. 2008a). The authors concluded that consumption of omega-3 fatty acids may be associated with a lower risk of AMD, but in the mean time, there was insufficient evidence to recommend omega-3 fatty acid supplementation for AMD prevention in the general population. Further randomized controlled trials are required to evaluate the efficacy. The Australian Blue Mountain Eye Study (Tan et al. 2009) showed that one serving of fish per week was associated with reduced risk of incidence of early AMD (relative risk, 0.69), and the EUREYE study (Augood et al. 2008) suggested that eating oily fish at least once per week compared with less than once per week was associated with a halving of the odds for neovascular AMD. Similarly, a population-based study in southern France (Delcourt et al. 2007) showed that fatty fish intake (more than once a month versus less than once a month) was associated with a 60% reduction in risk for AMD, but high total, saturated and monounsaturated fat intake were associated with increased risk for AMD.

Antioxidant supplements

AREDS-type formulations

Age-Related Eye Disease study was the first large-scale randomized controlled clinical trial to demonstrate the benefit of vitamin and mineral supplementations in preventing progression to advanced AMD.

The AREDS formulation included antioxidants of vitamin C 500 mg, vitamin E 400 IU, beta-carotene 15 mg and zinc (zinc oxide 80 mg and cupric oxide 2 mg). Copper was added to the AREDS formulations containing zinc to prevent copper deficiency anaemia, a condition associated with high levels of zinc intake. It is reminded that the level of antioxidants and zinc is considerably higher than

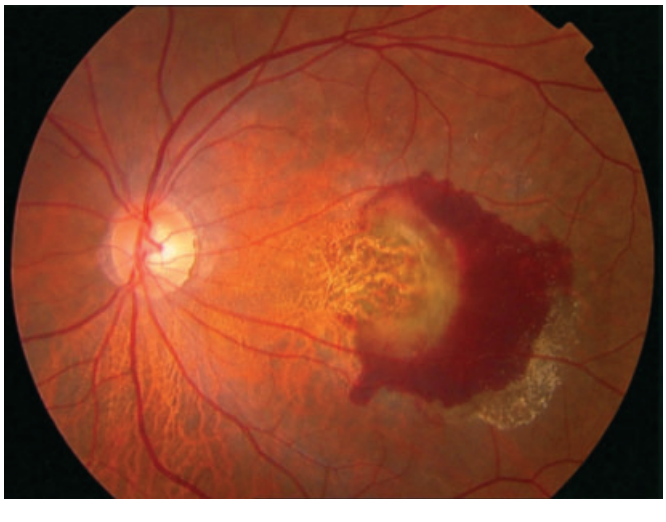

Fig. 2. A fundus photo showing neovascular age-related macular degeneration (AMD) with geographic atrophy and retinal hemorrhages.

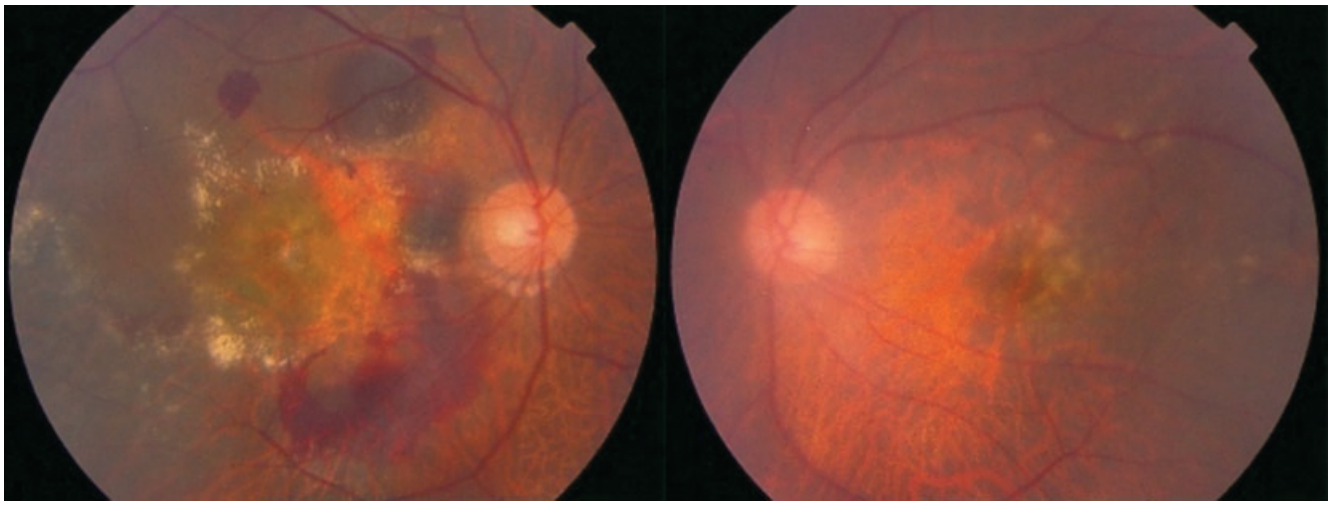

Fig. 3. The Age-Related Eye Disease Study (AREDS) formulation is indicated in patients with advanced age-related macular degeneration (AMD) or vision loss because of AMD in one eye.

the amount in any daily multivitamin and is difficult to achieve from diet alone.

Indications of AREDS formulation.

The use of AREDS formulation leads to a 25% risk reduction in progression to advanced AMD over 5 years in patients with intermediate AMD or advanced AMD in one eye (Age-Related Eye Disease Study Research Group 2001). The risk of losing vision of three or more lines also was reduced by 19% with this combination treatment. It is concluded from the study that those with extensive intermediate size drusens, at least one large drusen, noncentral geographical atrophy in one or both eyes, or advanced AMD or vision loss because of AMD in one eye (Fig. 3), and without contraindications such as smoking, should consider taking a supplement of antioxidants plus zinc like that used in the study. However, there was insufficient evidence to recommend routine supplementation with antioxidant vitamins or minerals for healthy adults to delay or prevent AMD onset, as revealed carefully by a recent Cochrane library review of the three large-scale clinical trials: Alpha-Tocopherol and Beta-Carotene study (ATBC), Physicians' Health Study (PHS I) and Vitamin E Cataract and Age-related maculopathy Trial (VECAT), a total of 23,099 patients, which investigated the efficacy of alpha-tocopherol and beta-carotene supplements (Evans & Henshaw 2008).

Potential side effects and precautions.

Studies suggested potential harmful effects of beta-carotene among smokers with increasing risks (four to five-fold) of lung cancer and cardiovascular disease (The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group 1994; Omenn et al. 1996) compared with those in nonsmokers. Thus, the ARDES formula is contraindicated in smokers. In the market, however, there have been the beta-carotene-free vitamin supplements for the smokers or ex-smokers. Potential side effects and contraindications of other medications include the following: vitamin C (kidney stones), vitamin E (fatigue, muscle weakness, decreased thyroid gland function and increased haemorrhagic stroke risk), beta-carotene (yellow skin) and zinc (anaemia, decreased high-density lipoprotein cholesterol and upset stomach).

Lutein/zeaxanthin

Besides antioxidants, such as vitamin E, C or zinc, the role of lutein and zeaxanthin has also been under constant spotlight. The central area of macula is enriched with macular pigment, which contains the carotenoids lutein and zeaxanthin. The macular pigment may protect the underlying photoreceptor cell layer from light damage by filtering off the blue light. Thus, the macular pigment optical density (MPOD) becomes a marker of eye health in many existing literature. There were studies showing that the dietary lutein and zeaxanthin intake was associated with an increase in serum lutein concentration (Rock et al. 2002), and elevated serum lutein and zeaxanthin concentration was associated with increased MPOD (Curran-Celentano et al. 2001; Johnson et al. 2008). However, the CAREDS group could not find any association between MPOD and AMD (LaRowe et al. 2008); thus, more studies are required to find out this relationship.

In 4519 AREDS participants, increased dietary lutein/zeaxanthin intake (as determined by a food frequency questionnaire at enrolment) was inversely associated with prevalent neovascular AMD, geographical atrophy, and large or extensive intermediate drusens (Age-Related Eye Disease Study Research Group 2007). In 2006, the CAREDS concluded that lutein-rich and zeaxanthin-rich diets may protect against intermediate AMD in female patients less than 75 years of age (Moeller et al. 2006).

More recently, the Blue Mountain Eye study reported that higher dietary lutein and zeaxanthin intake reduced the risk of incident early or neovascular AMD over 5 and 10 years (Tan et al. 2008).

Further evaluation of nutritional factors, specifically lutein/zeaxanthin and omega-3 fatty acids, will be tested in the ongoing multicenter controlled, randomized trial – the AREDS2. It would also refine the original AREDS formulation by eliminating beta-carotene and lowering the dose of zinc.

Vitamin B

Homocysteine is an intermediary amino acid formed during metabolism of the essential amino acid methionine.

Hyperhomocysteinaemia is thought to induce vascular endothelial dysfunction, which is implicated in neovascular AMD (Ashfield-Watt et al. 2001). Studies in the last few years suggest an association exists between elevated serum homocysteine levels and the risk of AMD (Axer-Siegel et al. 2004; Kamburoglu et al. 2006; Seddon et al. 2006; Rochtchina et al. 2007). Vitamin B12 and folate act as essential coenzymes during homocysteine metabolism. Treatment with folic acid, vitamin B6 and vitamin 12 has been shown to reduce homocysteine levels (Homocysteine Lowering Trialists' Collaboration 2005). In The Women's Antioxidant and Folic Acid Cardiovascular study, a randomized trial, although no benefit was found with treatment with vitamins B6 and B12 and folic acid in terms of cardiovascular disease reduction, the study found that they decreased the risk of developing AMD (Christen et al. 2009). However, the study is not without limitation. More randomized trials are warranted to study the role of vitamins B in AMD.

Wolfberry, Gingko biloba, black currant, blueberry

Lycium barbarum L. is a small red berry known as Fructus lycii and wolfberry in the West, Kei Tze and Gou Qi Zi in Asia. Wolfberry is rich in zeaxanthin dipalmitate and is highly valued in Chinese culture for being good for vision. A clinical trial showed that zeaxanthin in whole wolfberries does have significant bioavailability when taken orally and that intake of a modest daily amount markedly increases fasting plasma zeaxanthin levels (Cheng et al. 2005).

Gingko biloba, extracted from the leaves of the maidenhair tree, contains two constituents (flavonoids and terpenoids) that have antioxidant properties for the prevention of membrane damage caused by free radicals. It is believed that these may help to halt the progression of AMD. Two published randomized control trials using *G. biloba* extracts in AMD showed positive effects on vision; however, there trials were small and suffered from short observation period (Evans 2000). Apart from Kei Tze and *G. biloba*, well-designed and large-scaled clinical trials for the use of Chinese Herbal Medication (CHM) to prevent or retard progression of AMD are largely lacking (Manheimer et al. 2009).

Blueberry and black currant are rich food source of anthocyanins which are water-soluble flavonoid pigments that act as potent antioxidants. *In vitro* studies have demonstrated the antioxidant effects of anthocyanins (Jang et al. 2005; Durukan et al. 2006; Milbury et al. 2007). Furthermore, one study showed accumulation of anthocyanins in the brain, liver and eye tissues in animals after 4-week diets supplemented with blueberries, illustrating the potential ocular protective benefits from oral intakes of anthocyanins (Kalt et al. 2008).

The roles of wolfberry, berry anthocyanins and their extracts seem promising for reversing oxidative stress and possibly improving AMD. However, physicians should be aware that convincing evidence of their dosage and efficacy in AMD, in relation to safety, tolerability, pharmacokinetics and pharmacodynamics, is still lacking.

Conclusions

There are reversible environmental and modifiable factors, and quit smoking and healthier diet are useful for preventing or slowing the progress of AMD. In the mean time, there is no recommendation for routine nutritional supplementation as primary prevention of AMD in healthy individuals. However, patients with intermediate risk of AMD or advanced AMD in one eye are recommended to take AREDS-type supplements based on the best available scientific evidence. Many observational studies have suggested benefit from increased dietary intake of additional nutrients such as carotenoids, omega-3 fatty acids and vitamin B. However, more clinical trials are required for concrete recommendations on their use, particularly the clinically effective daily portion, which also preempt any enthusiastic recommendation for products with extracts of wolfberry, *G. biloba* and berry anthocyanins.

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