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Preventive AMD Treatments

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Introduction

A better understanding of the pathophysiological processes occurring in “retinal aging” and age-related macular degeneration (AMD) has been achieved in recent years, leading to the emergence of new treatments and consequent long-term improvements in the patients quality of life.

AMD is one of the leading causes of severe, irreversible vision impairment in developed countries, in individuals over 50 years of age.

Approximately 1.75 million people over 40 in the United States suffer from neovascular AMD or geographic atrophy; 7.3 million patients display large drusen (≥125 microns) in one or both eyes(1).

In the United States, AMD causes approximately 46% of severe visual loss cases (visual acuity of 20/200 or worse) in patients over 40(2).

Although, an estimated 80% of AMD patients display the non-neovascular form of this disease, the neovascular form is responsible for almost 90% of cases of severe visual

loss (visual acuity of 20/200 or worse) caused by AMD(3).

Data from three population-based studies – the Beaver Dam Eye Study, the Rotterdam Study and the Blue Mountains Eye Study – have led to an estimated prevalence of advanced AMD of 0-2% in patients aged 55–64, increasing to 13% in patients over 85[(4)].

Since there is no significant cure for AMD, prevention may be the first and logic approach to reduce vision loss, justifying an intensive search for some kinds of intervention able to prevent the onset of AMD or to delay its progression to more advanced and severe forms.

Age is the main risk factor for AMD; all population-based studies confirm that the prevalence of AMD increases with age in white individuals[(5,6,7)].

Belonging to the female gender may also constitute a risk factor in individuals aged over 75 years(4).

Several studies also demonstrated that effective control of modifiable risk factors, such as smoking, hypertension and body-mass index, could reduce the risk of developing AMD by half[(8)].

Since the early 90's, when "large population studies" appeared, several hypotheses have been formulated around the idea that nutritional supplements, such as antioxidants, vitamins and/or minerals may be able to reduce the risk of AMD development.

AREDS 1

Design implications and study categories

AREDS (Age-related Eye Disease Study) was a prospective, multicentric, randomised clinical trial conducted between 1992 and 2006, mainly sponsored by the National Eye Institute (NEI) of the National Institutes of Health (NIH).

This study was designed to evaluate the clinical aspects, natural course and risk factors associated with age-related cataract and AMD, as well as the effects of antioxidant vitamins and minerals on these two ocular conditions.

Eligible patients were aged 55-80 by occasion of enrolment and required to be free of any illness or condition that would make long-term follow-up or compliance with study medications unlikely or difficult.

Participants were placed in one of several AMD categories according to fundus photographs graded by a central reading centre, best corrected visual acuity and ophthalmic examination[(9):]

AREDS category 1 – (No AMD) – this was the AREDS control group, consisting of patients with no or a few small drusen (<63 microns in diameter).

AREDS category 2 – (Early AMD) – characterised by a combination of multiple small drusen, a few intermediate drusen (63 to 124 microns in diameter) or retinal pigment epithelium (RPE) abnormalities.

AREDS category 3 – (Intermediate AMD) – characterised by extensive intermediate drusen, at least one large drusen (>125 microns in diameter) or geographic atrophy not involving the centre of the fovea.

AREDS category 4 – (Advanced/Late AMD) – characterised by one or more of the following (in the absence of other causes), in one eye:

- Geographic atrophy of the RPE and choriocapillaris, including the centre of the fovea;
- Neovascular maculopathies, such as the following: choroidal neovascularization;
- Serous and/or haemorrhagic detachment of the sensory retina or the RPE;
- Hard exudates in the retina;
- Subretinal and sub-RPE fibrovascular proliferation;
- Disciform scar.

Risk factors and categories

AREDS Report no. 18 described a simplified clinical scale that defines risk categories for the development of advanced AMD(10).

The grading system described assigns one risk factor to each eye for the presence of one or more large drusen (125 microns) and one risk factor for the presence of any pigment abnormality.

If no large drusen are present, the presence of intermediate drusen in both eyes is counted as one risk factor.
Advanced AMD in one eye is counted as two risk factors; if this is observed together with large drusen and hypo/hyperpigmentary changes in the RPE, four risk factors are considered, which corresponds to the highest risk level for patients with AMD.

Risk factors are added for both eyes, leading to a 5-stage risk of developing advanced AMD in at least one eye increases as follows(10):

- Stage 0 (zero factors) – 0.5% in five years;
- Stage 1 (one factor) – 3% in five years;
- Stage 2 (two factors) – 12% in five years;
- Stage 3 (three factors) – 25% in five years;

- Stage 4 (four factors) – 50% in five years.

Results

AREDS results show an overall beneficial effect for high doses of antioxidant vitamin (vitamins C, E and beta-carotene) and zinc supplements in reducing the progression of intermediate or advanced AMD to advanced AMD in the fellow eye, corresponding to 25%.

Therefore, a formulation has been proposed[(11)]:

AREDS 1 formulation

- Antioxidant vitamins – 500 mg of vitamin C
- 400 IU of vitamin E
- 15 mg of beta-carotene
- 80 mg of zinc oxide and 2 mg of cupric oxide

This formulation has been shown to reduce the risk of developing advanced AMD and the associated visual loss by as much as 25%, over 5 years, in individuals with moderate to high risk of AMD (AREDS categories 3 and 4).

These findings were accompanied by a 19% reduction in the risk of moderate vision loss (loss of three or more lines on the visual acuity chart), at 5 years[(11)].

However, this formulation is not recommended for smokers, since beta-carotene has been shown to increase the risk of lung cancer[(12,13)].

AREDS 2

The Age-related Eye Disease Study 2 (AREDS2), initiated in 2006 enrolled 4000 patients with non-neovascular AMD consisting of large drusen in both eyes or advanced AMD in one eye and large drusen in the fellow eye (AREDS categories 3 and 4).

The aim of this study was to evaluate the effect of dietary supplements – xanthophylls (10 mg of lutein and 2 mg of zeaxanthin) and/or long-chain omega-3 polyunsaturated fatty acids (1 g of docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]) – on the progression to advanced AMD.

An additional goal of the study was to assess whether forms of the AREDS nutritional supplement with reduced zinc and/or no beta-carotene works as well as the original supplement in reducing the risk of progression to advanced AMD.

AREDS 2 formulation

- Antioxidant vitamins – 500 mg of vitamin C
- 400 IU of vitamin E
- 15 mg of beta-carotene
- 80 mg of zinc oxide and
- 2 mg of cupric oxide
- Macular pigments – xanthophylls
- 10 mg of lutein
- 2 mg of zeaxanthin
- 1 g of omega-3 fatty acids (DHA +EPA)

This study also investigated whether the current AREDS formulation might be modified by eliminating beta-carotene. As previously mentioned, beta-carotene, which is not present within the eye, constitutes a problem for smokers, due to the high incidence of lung cancer in this patient group.

A secondary randomisation in AREDS 2 evaluated the possibility of eliminating and/or lowering the amount of zinc in the AREDS formulation, since zinc levels in the current formulation are considered high and available evidence suggests that the body is only able to absorb 25 mg of zinc per day.

Results found that addition of lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation did not further reduce risk of progression to advanced AMD. However, because of potential increased incidence of lung cancer in former smokers, lutein + zeaxanthin could be an appropriate carotenoid substitute in the AREDS formulation(14).

Ocular Micronutrition

Carotenoids

Macular pigments: lutein and zeaxanthin

Over 600 carotenoids have been identified to the present date; however, only about 50 are found in normal human diets.

Vegetables are the only source of carotenoids. Macular pigments (MP) consist of two natural xanthophylls from the carotenoid family: lutein (L) and zeaxanthin (Z), as well as the products of their transformation in the body, notably meso-zeaxanthin[(15)].

These pigments are not synthesised by the human body and have been investigated for their ability to promote visual health.

Macular pigments are found in photoreceptor axons in the pigment epithelium and in the external segment.

The latter contains very high levels of polyunsaturated fatty acids, at a high risk of oxidation[(16-18)]. Macular concentrations of L and Z decrease with age, which exacerbates the harmful effects of blue light on photoreceptors.

Their protective mechanism is unknown; however, two mechanisms have been proposed: macular pigments may act as an optical filter, due to their ability to absorb blue light, and they are strong antioxidants, neutralising free radicals generated by light [(19-20)].

Several observational studies have demonstrated a correlation between plasma L and Z levels, macular pigment density and a lower risk of AMD.

Increased intake of L and Z supplements resulted in increased plasma levels, which were positively and significantly associated with the optical density of macular pigment[(21)].

Furthermore, various well-conducted population-based longitudinal studies have suggested that high dietary antioxidant levels, specifically L and Z, may have protective and beneficial effects, delaying progression to advanced AMD.

The following are some examples of observational studies investigating the relationship between dietary and/or serum antioxidant levels and the risk of AMD.

EDCCS (Eye Disease Case-Control Study): this study, published in 1993, demonstrated a high significant inverse relationship (p= 0.001) between the prevalence of AMD and serum L and Z concentrations: the risk of neovascular lesions was 70% lower in subjects with the highest serum L and Z concentrations, compared to those with the lowest levels (odds ratio (OR): 0.4; 95% confidence interval (CI): 0.2-0.6; p= 0.0001)[(22)].

In 1994, the same group concluded that the risk of developing the most severe form of macular degeneration was 43% lower in individuals who consume large amounts of fruits and vegetables rich in L and Z (6 mg/day) (OR: 0.57; 95% CI: 0.35-0.92; p= 0.02)[(23)].

Another observational study conducted in 2002 showed that average L and Z levels were 32% lower in AMD eyes than in control eyes, in elderly subjects, provided the latter were not consuming high doses of L supplements. This study demonstrated that average levels of macular pigments in patients who had begun to regularly consume supplements containing high doses of L (> 4 mg/day) after the initial diagnosis of AMD

were within the normal range and significantly higher than in AMD patients not consuming this supplementation[(24)].

In 2006, the POLA study (Pathologies Oculaires Liées a l'Age) found that high plasma L and total L and Z concentrations are associated with a reduced risk of age-related maculopathy (ARM)[(25)].

CAREDS (Carotenoids in Age-related Eye Disease Study): in this observational study, conducted in 2006, no statistically significant differences in intermediate AMD prevalence were found between subjects with high and low dietary intakes of L plus Z. However, analysis of a sub-group of women under 75 with stable L plus Z intakes revealed a reduced risk of this subtype of AMD in association with a high dietary intake of those antioxidants. A diet rich in L plus Z may protect against intermediate AMD[(26)].

In 2007, AREDS (Age-related Eye Disease Study report 22), a case-control study with 4519 participants, concluded that a high dietary intake of L and Z was independently associated with a decreased likelihood of neovascular AMD, geographic atrophy, and large and extensive drusen[(27)].

Up to the present date, seven important interventional studies have investigated the role of L supplementation in AMD patients[(28-34)].

Of the aforementioned studies, two assume major importance.

LAST (Lutein Antioxidant Supplementation Trial) was the first study to show that L supplementation improved visual function in AMD patients. Furthermore, it reinforced the notion that AMD is a nutrition-responsive disease. The results of this trial were confirmed in 2004.

In this trial, 90 AMD patients received either a daily supplement consisting of 10 mg of L, a supplement consisting of 10 mg of L and a mixed antioxidant formula (containing vitamin A, beta-carotene, vitamin C, vitamin E, vitamin B complex, copper, zinc, manganese, magnesium, selenium and other minerals), or placebo, for 12 months.

Results showed that patients receiving the L supplement displayed significant improvements in several objective visual function measures (contrast sensitivity or visual acuity) when compared to the placebo group. Slightly better results were observed in subjects consuming the combined supplement[(33)].

CARMA (Carotenoids in Age-related Maculopathy Study) was an important European intervention study, published in 2008[(34)].

This randomised, double-blind clinical trial of antioxidant supplementation versus placebo enrolled 433 patients from two centres in Ireland, with signs of early AMD of sufficient severity in at least one eye, or any level of AMD in one eye and late AMD (neovascular AMD or central geographic atrophy) in the fellow eye.

The aim of the CARMA Study was to investigate whether administration of 12 mg of L and 2 mg of Z, in combination with antioxidants (120 mg of vitamin C, 15mg of vitamin E, 20mg of zinc and 0.4 mg of copper), had a beneficial effect on visual function and/or was able to delay progression of early to late disease stages.

The primary outcome was improved or distance visual acuity was preserved at 12 months.
Although no beneficial effects were demonstrated in the primary outcome measure at the stated end point (12 months), secondary outcomes favoured the supplemented group[(34)].

In 2013, **AREDS 2** presented an exploratory analysis of the 1114 participants who received lutein/zeaxanthin added to an AREDS formulation without beta carotene versus the 1117 participants who received only beta carotene in the AREDS formulation.

This revealed that those receiving lutein/zeaxanthin without beta carotene supplement had a 18% reduction in the risk for late AMD and 22% reduction for neovascular AMD, as well as 6% reduction in the risk for geographic AMD (which yielded a P value of 0.67).

A pre-specified comparison of those receiving lutein/zeaxanthin of those who did receiving lutein/zeaxanthin revealed 10% reduction in the risk for progression to late AMD.

A second pre-specified analysis showed that those in the lowest quintile of dietary intake of lutein/zeaxanthin who received lutein/zeaxanthin along with the original AREDS formulation had a 26% reduced risk for progression to late AMD relative to participants receiving the original AREDS formulation, without lutein/zeaxanthin[(35)].

Key points

The aforementioned findings are consistent with the hypothesis that low L and Z levels in the human macula may represent a pathogenic risk factor for AMD development.

Based on the analyses from AREDS2 we recommend the patient with intermediate AMD (bilateral large drusen) or late AMD in one eye be given the AREDS2 formulation.

They also suggest that supplementation may prevent damage from oxidation and harmful wavelength of light and contribute to maintaining eye health.

Antioxidants

Vitamin and mineral supplements

Antioxidants are recommended for AMD due to oxidative stress on photoreceptors in the retina and the fact that cumulative damage caused by blue light enhances free radical production.

It has been proposed that antioxidants may prevent cellular damage in the retina by reacting with free radicals[(36)].

The substances that possess antioxidant activity are vitamins C and E, beta-carotene and some minerals, such as zinc, copper, selenium and manganese.

Some studies indicate that diets rich in antioxidants may protect against the appearance of signs of early AMD; in common perception, a diet rich in antioxidants is capable of protecting against AMD.

Randomised control trials and observational studies have been conducted in well-nourished Western populations; however, the role of dietary antioxidants in the primary prevention of AMD remains unclear.

In the 90’s, several studies reported a protective effect against AMD development for high intakes of antioxidant vitamins and minerals.

In 1993, the EDCCS (Eye Disease Case-Control Study) performed a comparison between 421 patients with neovascular AMD and 615 control subjects. The results revealed that high plasma levels of antioxidants (vitamins A, C, E, selenium and carotenoids) are associated with a lower risk of developing neovascular AMD. Additional carotenoid intakes, particularly of those present in the retina, are associated with a lower risk of developing AMD[(22)].

In 1994, the authors of the Baltimore Longitudinal Study on Aging, a study involving 976 patients, reported a protective effect against AMD for high plasma concentrations of vitamin E. The authors also found an antioxidant combination of vitamin C, vitamin E and beta-carotene to be protective[(37)].

In 1998, the Beaver Dam Eye Study, in which a cohort of 1,700 patients was subject to a 5-year follow-up eye examination, showed that a high intake of carotenoids and vitamin E is associated with a lower risk of developing large drusen. High dietary zinc intakes would be associated with a lower number of RPE anomalies[(38)].

In 2001, AREDS report no. 8, a large multicentric, randomised clinical trial, revealed that the risk of progression to advanced AMD was reduced by 28% in patients with intermediate AMD treated with high doses of antioxidant supplements (vitamins C and E, zinc and β-carotene), when compared to the placebo group (OR: 0.72; 99% CI: 0.52-0.98). This study did not specifically investigate whether antioxidant supplements were effective in the primary prevention of early AMD in individuals without signs of this

condition[(11)].

In 2004, AREDS report no. 13 evaluated mortality rates in patients with ocular disorders taking high doses of antioxidants or zinc. Results showed that mortality was lower in patients taking zinc (alone or with antioxidants) (12% reduction), when compared to those not taking this mineral (RR: 0.73; 95% CI: 0.61-0.89)[(39)].

In 2005, the Rotterdam Study, a population-based study involving 4170 participants, showed that an above-average intake of the 4 AREDS trial nutrients protected against AMD development or early AMD, as indicated by large drusen, and was associated with a 35% reduction in the risk of AMD (HR: 0.65; 95% CI: 0.46-0.92)[(40)].

In 2007, Chong and colleagues undertook a systematic review and meta-analysis of nine prospective cohort studies and three randomised clinical trials. The results from the first studies indicated that vitamin A, vitamin C, vitamin E, zinc, L, Z, alpha-carotene, beta-carotene, beta-cryptoxanthin and lycopene have little or no effect in the primary prevention of early AMD. The three randomised clinical trials failed to show that antioxidant supplements prevented early AMD[(32)].

In 2008, a systematic review and meta-analysis undertaken with the objective of examining available evidence as to whether antioxidant vitamin or mineral supplements are able to prevent AMD development or delay its progression was published online. No evidence was found that antioxidant (vitamin E or beta-carotene) supplements are able to prevent AMD (RR 1.03; 95% CI; 0.74-1.43). Some evidence was found that antioxidant (beta-carotene, vitamin C and E) and zinc supplements were able to delay progression to advanced AMD and prevent loss of visual acuity in individuals displaying signs of the disease (adjusted OR = 0.68; 95% CI: 0.53-0.57, and 0.77; 95% CI: 0.62-0.96, respectively)[(41)].

In AREDS 2, smokers were not randomized to beta-carotene, and there was a doubling of the risk of developing lung cancer in subjects randomized to beta-carotene, compared with those randomized to lutein/zeaxanthin. More than 90% of these subjects affected with lung cancer were former smokers. A large proportion of the persons affected with AMD were former or current smokers. The totality of evidence from these analysis support the substitution of lutein/zeaxanthin for beta-carotene[(35)].

Key points

According to current evidence, antioxidant vitamin supplements are unable to prevent AMD.

High-dose antioxidant supplementation may increase the risk of lung cancer in smokers (beta-carotene), heart failure in individuals with vascular disease or diabetes (vitamin E)

and hospitalisation in patients with genitourinary conditions.

The totality of evidence from all analysis supports that lutein/zeaxanthin together appeared to be a safe alternative to beta-carotene.

Dietary fatty acids

Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)

The role of fatty acids in AMD was initially investigated because of the hypothesis that AMD and cardiovascular disease may share a similar pathogenesis and fat intake has been associated with atherosclerosis and cardiovascular disease.

Fatty acids may be divided into three types:

- Saturated fat from dairy products and meat.
- Monounsaturated fatty acids (MUFA) from olive oil.
- Polyunsaturated fatty acids (PUFA), especially from fish and seafood.

Omega-3 fatty acids, also known as Long-Chain Polyunsaturated Fatty Acids (LCPUFAs), are essential to human health.

Omega-3 fatty acids include alpha-linolenic acid (a short-chain omega-3 fatty acid) and long-chain omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).

Omega-3 fatty acids, especially DHA, have morphological, functional and protective roles in the retina:

1. Morphological role – DHA is the main PUFA found within the outer segments of rods and has anti-apoptotic, anti-inflammatory and antiangiogenic functions.
2. Functional role – DHA provides an adequate environment for conformational changes in rhodopsin.
3. Protective role – DHA protects against aging of the retina and may reduce lipofuscin accumulation in the RPE and lipid deposits in Bruch’s membrane.

Several epidemiological studies have evaluated the relationship between total and specific fat intake and the risk of advanced AMD.

Results confirm that higher intakes of vegetable and animal fat are associated with a greater risk of advanced AMD. In 2008, a systematic review and meta-analysis was undertaken with the objective of evidencing the role of dietary omega-3 fatty acid and

fish intakes in the primary prevention of AMD.

This review included three randomised, controlled, prospective cohort trials(42-44), three case-control studies(45-47) and three cross-sectional studies(45,48,49).

The results of these nine studies demonstrated that high dietary omega-3 fatty acid intakes were associated with a 38% reduction in the risk of late AMD (OR: 0.62; 95 % CI: 0.48-0.82).

Eating fish at least twice a week was associated with a reduced risk of both early AMD (OR: 0.76; 95% CI: 0.64-0.90) and late AMD (OR: 0.67; 95% CI: 0.53-0.85).

Several other relevant studies evidence this fact:

A prospective study conducted by **Cho et al**. in 2001 evidenced a positive association between total fat intake and incidence of AMD. A diet rich in fat increases the risk of advanced AMD. Nevertheless, eating fish 4 or more times a week (fish is a major source of DHA) decreases the relative risk of AMD by 35%(42).

A case-control study conducted by **SanGiovanni et al.** concluded that higher omega-3 and fish intakes are associated with a decreased risk of neovascular AMD(50).

The objective of **AREDS report n. 20** was to evaluate the association between lipid intake and AMD severity at baseline.

The results of this study showed that total dietary intake of total long-chain omega-3 polyunsaturated fatty acids (LCPUFA) was inversely associated with neovascular AMD (OR: 0.61; 95 % CI: 0.41-0.90), the same occurring for docosahexaenoic acid, a retinal omega-3 LCPUFA (OR: 0.54; 95% CI: 0.36-0.80), when the highest and lowest intake quintiles were compared, after adjustment for total energy intake and covariates.

Higher fish intakes, both total and broiled/baked, were also inversely associated with neovascular AMD (OR: 0.61; 95% CI: 0.37-1.00, and OR: 0.65; 95% CI: 0.45-0.93, respectively).

Dietary intake of arachidonic acid was directly associated with the prevalence of neovascular AMD (OR: 1.54; 95% CI: 1.04-2.29).

No statistically significant relationships were found for other lipids or groups(47).

In **AREDS report n. 23**, reduced likelihood of progression from bilateral drusen to central geographic atrophy was observed in individuals reporting the highest EPA intakes (OR: 0.44; 95% CI: 0.23-0.87) and EPA + DHA intakes (OR: 0.45; 95% CI: 0.23-0.9). DHA levels were associated with central geographic atrophy in age, gender and calorie adjusted models (OR: 0.51; 95% CI: 0.36-1.00). However, this statistical relationship was not observed in multivariable models. This study suggested that dietary intake, of long-chain omega-3 polyunsaturated fatty acids, is associated with a decreased risk of

progression from bilateral drusen to central geographic atrophy[51].

European study Nat-2, performed at the University of Créteil, a double-blind, randomised, parallel, comparative study, compared oral DHA supplementation with placebo in the prevention of exudative AMD in 298 patients with any type of drusen in the study eye and wet AMD in the fellow eye. Nat-2 supplementation consisted of 10 mg of L, 2 mg of Z, 1 mg of omega-3 (DHA plus EPA), 500 mg of vitamin C, 400 IU of vitamin E, 25 mg of zinc and 2 mg of copper. Patients took no other supplements and were followed for three years (2004-2008). The first study results included in NAT-2 report no. 1, revealed high HDL and low PUFA levels in exudative AMD patients. These findings confirmed the benefits of DHA supplementation in these AMD patients[52].

Two important prospective observational studies clearly reveal that fish consumption and omega-3 fatty acid intake decrease the risk of AMD: The Blue Mountains Eye Study and the Melbourne Collaborative Cohort Study.

Blue Mountains Eye Study: The objective of this longitudinal study was to investigate the association between baseline dietary fatty acids and 10-year incidence of AMD in an elderly Australian cohort. Nutrient intakes were estimated through a semi-quantitative food frequency questionnaire.

The risk of incidence of early AMD was lower in individuals consuming 1 to 2 servings of nuts per week (RR: 0.65; 95% CI: 0.47-0.91). These results were similar to those obtained for dietary consumption of long-chain omega 3 PUFAs, which also show a lower risk of incidence of early AMD in participants eating 1 serving of fish per week (RR: 0.69; 95% CI: 0.49-0.98).
Participants consuming below-average amounts of linoleic acid contributed the most to this association (RR: 0.57; 95 % CI: 0.36-0.89).

Nut consumption was associated with a lower risk of pigmentary abnormalities in non-smokers, individuals with below-average total to high-density lipoprotein serum cholesterol ratios, and individuals with above-average beta-carotene intakes[53].

Melbourne Collaborative Cohort Study: the aim of this study, carried out in 1990-1994, was to investigate the relationship between past dietary fat intake and the ticipants aged 58-69.

The corresponding results showed that a higher dietary intake of trans unsaturated fats was associated with an increased prevalence of late AMD. Comparing the highest and lowest trans fat intake quartiles, the OR for late AMD was 1.76 (95% CI: 0.92-3.37; p = 0.02), whereas a higher intake of omega-3 fatty acids was inversely associated with early AMD (OR for highest quartile versus lowest quartile: 0.85; 95% CI: 0.71-1.02; p = 0.03). The prevalence of late AMD was lower for olive oil intakes equal to or higher than 100 mL/week versus less than 1 mL/week (OR: 0.48; 95% CI: 0.22-1.04; P = 0.03). No significant associations were found between fish, total fat, butter and margarine intakes

and AMD[(54)].

In 2009, the **SanGiovanni AREDS Group** investigated the relationship between dietary omega-3 LCPUFA intake and progression to advanced AMD in 1837 AREDS participants with a moderate risk for developing sight-threatening AMD (1211 participants in category 3a and 626 participants in category 4a).

It was observed that participants reporting the highest baseline omega-3 LCPUFA intakes were approximately 30% less likely to develop advanced AMD by the end of the 12-year follow-up period than those reporting the lowest omega-3 LC-PUFA intakes.

Results for central geographic atrophy and neovascular AMD were similar; the corresponding multivariate OR were 0.65 (95% CI: 0.45-0.92; $p \leq 0.02$) and 0.68 (95% CI: 0.49-0.94; $p \leq 0.02$)[(55)].

In 2013 based on the analysis from **AREDS2**, omega-3 LCPUFA appear to have no role and did not reduce the risk of advanced AMD, even when evaluating participants with the lowest level of dietary intake of omega-3 LCPUFA[(14,35).]

Key point

It is important to note that the observational data overwhelmingly suggest that eating fish has a favourable effect.

Response to AREDS Supplements According to Genetic Factors

The impact of nutritional supplements on rate of progression to advanced AMD for patients within specific genotype groups and the need to genotype all patients, taking the AREDS supplements, has been a subject of debate.

The first evidence of a differential treatment effect on progression according to genotype demonstrated that the odds ratio of progression for the combined antioxidant and zinc group versus the placebo group was lower for non-risk CFH (complement factor H) subjects compared with high-risk subjects. More recent publications evaluated similar relationships between treatment and genotype; however, these studies revealed conflicting results.

An initial publication by Awh et al.[(56)] reported the benefit of zinc in reducing progression to advanced AMD among 995 subjects with no risk alleles for CFH and one or

two risk alleles for ARMS2 (age-related maculopathy sensitivity 2). A more recent publication from the same group suggested a differential impact on disease progression according to the number of risk alleles for these SNPs: the detriment posed by a CFH risk allele was exacerbated and the harmful effect of the ARMS2 risk allele was alleviated in subjects receiving supplementation with zinc, both alone or as a component of the AREDS combination supplement. A survival analysis approach using the eye as the Unit of analysis, based on a larger sample of the AREDS population, concluded that the effectiveness of antioxidant and the zinc supplementation appears to differ by genotype(57).

We need more results but genetic testing is important in research and additional studies are needed.

Key point

The combination of antioxidants and zinc, as found in both the AREDS and AREDS2 supplements, remains the only proven beneficial formulation regardless of genotype, with no apparent indication for treatment with antioxidants or zinc alone.

>> References

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