Nutritional Supplements and Age-related Macular Degeneration – Focus on Omega-3 Fatty Acids

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Abstract

Age-related macular degeneration (AMD) is a leading cause of vision loss for which treatment options are limited. The socioeconomic benefits of prevention of AMD are enormous. While considerable observational evidence supports an association between dietary fats and AMD, the relation between specific types of fat and AMD has been unclear. Recent research has focused on the ω-3 polyunsaturated acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). The diets of industrialised nations contain higher levels of saturated fats, trans fatty acids and ω-6 fatty acids and less ω-3 fatty acids than they did in the past. This imbalance may have important implications for retinal health. Several observational studies have found that consumption of oily fish and high dietary intakes of DHA and EPA are associated with a reduced risk of developing AMD. Recent studies evaluating nutritional supplements containing ω-3 fatty acids for the treatment of AMD suggest a potential beneficial effect but further research in this area is warranted.

Keywords

Age-related macular degeneration, docosahexaenoic acid, eicosapentaenoic acid, omega-3, omega-6, polyunsaturated fatty acid (PUFA)

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Age-related macular degeneration (AMD) is the major cause of irreversible vision loss in adults in developed countries.[1–3] Data from the European eye study (EUREYE) indicate that the prevalence of AMD in Europeans aged 65 years and over is 3.3 %.[4] Approximately 30 % of individuals aged 75 or older have the mild or intermediate stage of the disease (age-related maculopathy [ARM]).[5] The socioeconomic burden of AMD will only increase as global life expectancy rises.[6–8] The pathogenesis of AMD is unknown but it is a multifactorial disorder, involving genetic and environmental factors. These include age, sex, diet, smoking, hypertension, genetic markers and nutritional status.[9–14]

Psychosocial and physiological changes set the stage for inadequate nutrition as the body ages.[15] Older adults who are hospitalised due to an acute illness may be at greater risk of experiencing malnutrition due to low dietary intake and/or underlying illness. Malnutrition may be present upon admission or develop during hospitalisation.[16] Among all hospitalised adult patients, prevalence of malnutrition at admission ranges between 20 and 70 % and for older patients between 12 and 72 %,[17–21] depending on the definitions used for nutritional status and the population studied.[19,21–23] Greater age in the patient population is frequently related to an increased prevalence of malnutrition, observed in trials such as those cited above.

Medical treatments for AMD are limited to neovascular AMD. Anti-vascular endothelial growth factor (VEGF) agents and other options, such as verteporfin and laser treatment, are beneficial for neovascular AMD and research in this area is active,[24–26] but no medical intervention exists to treat non-exudative or dry AMD.[27] No pharmacological treatment exists for prevention or treatment of AMD.

The identification of risk factors is of major importance for understanding the origins of AMD and for establishing strategies of prevention. Current therapeutic strategies focus on delaying or halting disease progression by modifying risk factors, such as lifestyle changes, e.g. cessation of smoking, or nutritional supplements.[28,29] Nutritional supplements are of particular interest since the nutritional quality of the diet is decreasing. Several vitamins and minerals are known to be important in eye health, with particular interest in their antioxidant efficacy, since it has been suggested that retinal damage due to oxidation may contribute towards AMD pathogenesis.[30,31] In 2001, the Age-related eye disease study (AREDS), a large-scale randomised controlled trial, found that high doses of vitamins C and E, β-carotene and zinc significantly reduced the odds of developing advanced AMD in a high-risk group.[32] A second study (AREDS2) on the effects of additional supplements on the development of AMD is on-going.

Table 1: Content of Eicosapentaenoic Acid and Docosahexaenoic Acid in Some Commonly Consumed Fish

Fish	DHA (g/100 g)	EPA (g/100 g)	DHA+EPA (g/100 g)	DHA:EPA
Tuna (bluefin)	1.141	0.363	1.504	3.1 : 1.0
Tuna (light, canned in water)	0.223	0.047	0.270	4.8 : 1.0
Tuna (albacore, canned in water)	0.629	0.233	0.862	2.7 : 1.0
Salmon (Atlantic, farmed)	1.457	0.690	2.147	2.1 : 1.0
Salmon (Atlantic, wild)	1.429	0.411	1.840	3.5 : 1.0
Salmon (Chinnook)	0.727	1.010	1.737	1.0 : 1.4
Salmon (Rockeye)	0.700	0.530	1.230	1.3 : 1.0
Mackerel (Atlantic)	0.699	0.504	1.203	1.4 : 1.0
Herring (Atlantic)	1.105	0.909	2.014	1.2 : 1.0
Trout (rainbow, farmed)	0.820	0.334	1.154	2.5 : 1.0
Trout (rainbow, wild)	0.520	0.468	0.988	1.1 : 1.0
Halibut	0.374	0.091	0.465	4.1 : 1.0
Cod	0.154	0.004	0.158	38.5 : 1.0
Haddock	0.162	0.076	0.238	2.1 : 1.0
Shrimp	0.144	0.171	0.315	1.0 : 1.2

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid.
Adapted from Lee et al., 2008.[38]

It has been hypothesised that atherosclerosis of the blood vessels that supply the retina may contribute to the risk of AMD. The link between fat intake and atherosclerosis and cardiovascular disease is well established, in particular the benefits of ω-3 fatty acids.[33–35] Interest has focused on the role of dietary fatty acids in AMD. This article will examine evidence supporting the importance of ω-3 fatty acids in AMD and their possible role in its therapeutic management.

Omega-3 Fatty Acids – A General Overview

All ω-3 polyunsaturated fatty acids (PUFAs) are considered essential dietary nutrients as they cannot be synthesised by humans *de novo*.[36] The essential ω-3 fatty acids are the short-chain α-linolenic acid and the long-chain docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). α-linolenic acid can be found in rapeseed, soybean, flax and walnut oils, whereas DHA and EPA are found in oily fish such as mackerel, tuna, herring and salmon (see *Table 1*).[37,38] EPA can also be synthesised from α-linolenic acid although there is minimal conversion *in vivo*.[39,40] EPA is itself a precursor of DHA. The cardiovascular benefits of essential ω-3 acids have been demonstrated in clinical studies. Treatment with ω-3 acids was found to reduce mortality and admission to hospital for cardiovascular reasons in patients with heart failure.[41]

The brain and eye are highly enriched with ω-3 fatty acids, which accumulate in these tissues during early neonatal life.[42] DHA is a major structural lipid in the retina, particularly the disc membranes of photoreceptor outer segments, where it accounts for over half the total fatty acyl groups, a proportion higher than is found in any other tissue.[43] Because photoreceptor outer segments are constantly being renewed, a steady supply of DHA may be necessary for correct retinal function. Marginal depletion may impair retinal function and influence the development of AMD. Although the concentration and distribution of ω-3 fatty acids suggest an important role in retinal function, their specific role is not fully understood. They have been found to exhibit cytoprotective and cytotherapeutic actions contributing to a number of antiangiogenic and neuroprotective mechanisms within the retina. The presence of a high concentration of DHA may affect photoreceptor function by altering membrane fluidity, permeability, thickness and lipid phase properties.[36]

In humans, an optimal balance between ω-3 and ω-6 fatty acids is required for normal neuronal function, and it has been suggested that the current imbalance in the ω-6:ω-3 fatty acid ratio in the diets of industrialised nations may contribute to the observed increases in many disorders.[44] Anthropological and epidemiological studies indicate that humans evolved on a diet with a ratio of ω-6:ω-3 PUFAs of approximately 1:1, whereas in Western diets the ratio is 12:1 to 18:1.[45] Alaskan Eskimos, whose diet is rich in fish and marine mammals, have a plasma ω-6:ω-3 PUFA ratio of 3.5:1.[46] The Japan Society for Lipid Nutrition recommended a dietary ω-6:ω-3 ratio of 2:1 or less for prevention of cardiovascular disease in an elderly population.[47] A recent report has concluded that the imbalance in ω-6 and ω-3 in the Western diet is inappropriate for normal growth and development and suggests a ratio of ω-6:ω-3 PUFAs of between 1:1 and 2:1.[48] However, such a ratio is hard to achieve and the French Food Safety Agency has recommended a ratio of 5:1, which is gaining widespread acceptance.[49]

The Importance of Omega-3 Fatty Acids in Age-related Macular Degeneration

Evidence supporting the association between ω-3 fatty acids and AMD is largely based on observational studies. Over the last decade, several lines of evidence have raised the possibility that a high intake of individual fatty acids, such as linoleic acid, and elevated cholesterol blood levels are related to an increased risk of AMD.[50,51] In contrast, several epidemiological studies suggest that ω-3 PUFAs could play a protective role, particularly for exudative AMD. Historically, low incidences of exudative AMD have been reported in Iceland and Japan, where fish consumption is high. However, there has been an increased incidence of exudative AMD in Japan in recent decades. This may reflect changing dietary trends such as reduced fish consumption.[52]

Nurses' Health Study and the Health Professionals Follow-up Study

The association between fat intake and development of AMD was first studied in a single-cohort study as part of the Nurses' health study and the Health professionals follow-up study, which followed 72,489 patients for 10–12 years. Among 567 patients with AMD, an inverse association was found between DHA intake and AMD (odds ratio [OR] 0.70, p=0.05). Consumption of more than four servings of fish per week compared with fewer than three servings per month was associated with a 35 % reduced risk of AMD (OR 0.65, p=0.009).[50]

The Blue Mountains Eye Study

A total of 3,654 participants were examined with a follow-up of five years. Those with the highest intake of ω-3 fatty acids had a reduced risk of incident early AMD compared with those with the lowest ω-3 fatty acid intake (OR 0.41). A 40 % reduction of incident early ARM was associated with fish consumption at least once a week (OR 0.58), whereas fish consumption at least three times per week was associated with a reduced incidence of late ARM (OR 0.25).[53] In an extension of this study (n=3,654) to 10 years, a reduced incidence of early AMD was associated with fish consumption once a week (OR 0.69), total ω-3 fatty acid intake (OR 0.63) and consumption of one or two servings of nuts per week (OR 0.65).[54]

The European Eye Study

EUREYE was a cross-sectional population-based study which investigated the dietary intake of DHA and EPA in 105 participants with neovascular AMD and 2,170 controls without AMD. DHA or EPA

consumption was associated with a reduced risk of neovascular AMD (OR 0.32, p=0.03 and OR 0.29, p=0.02, respectively). Moreover, consumption of oily fish at least once per week halved the risk of neovascular AMD compared with consumption less than once per week (OR 0.47, p=0.002).[55]

The US Twin Study of Age-related Macular Degeneration

A US comparison study of 221 twins with AMD and 459 twins with no AMD signs found that intake of ω-3 fatty acids was inversely associated with AMD (OR 0.55).[56] The reduction in the risk of AMD with a higher intake of ω-3 fatty acids was seen primarily among subjects with low levels of ω-6 fatty acids. In addition, increased fish consumption reduced the risk of AMD, particularly for two or more servings per week (OR 0.64).

Age-related Eye Disease Study

Although the AREDS nutritional supplement does not contain ω-3 fatty acids, the dietary information supplied by the AREDS population has been examined in order to determine a link between ω-3 fatty acids and AMD. Total dietary ω-3 PUFA intake was inversely associated with the incidence of neovascular AMD at baseline (OR 0.61, p<0.01) in 4,519 participants. This inverse relationship was even more significant when specifically examining the higher versus lower consumptions of DHA (OR 0.54, p<0.004). The inverse association was also observed with high fish consumption (OR 0.61, p<0.01).57 AMD progression over median follow-up greater than six years was inversely related to EPA (OR 0.44) or EPA + DHA (OR 0.45) consumption in 2,132 participants from the AREDS population.[58] Moreover, in a nested cohort study of 1,837 individuals from the AREDS population, those participants at moderate to high risk of AMD progression and with the highest intake of DHA, EPA or DHA + EPA were approximately 30 % less likely to progress over 12 years than their peers.[59,60] In a study of 2,924 participants in the AREDS trial over eight years, higher intakes of DHA and EPA were associated with a lower risk of AMD progression (OR 0.73 and 0.74, respectively), independently of consumption of the AREDS supplement.[61]

Women's Health Study

A recently published study has provided further evidence to support a role for ω-3 PUFAs in the prevention of AMD in women. Of 39,876 female health professionals enrolled in the Women's health study, 38,022 women without a diagnosis of AMD completed a detailed food-frequency questionnaire at baseline. The primary endpoint was incident AMD causing a reduction in best corrected visual acuity to 20/30 or worse, as identified by self-report and confirmed by medical record review. During the follow-up (average duration 10 years), there were 235 confirmed cases of AMD. Compared with women in the lowest tertile of DHA intake, those in the highest tertile had a reduced risk of AMD (OR 0.62). A similar finding was observed for EPA intake (OR 0.66). A reduced risk was also seen in women who consumed at least one serving of fish per week versus those who consumed less than one serving per month (OR 0.58). This lower risk appeared to be mostly attributed to consumption of canned tuna fish and dark-meat fish.[62]

Other Studies

Additional studies have examined the associations between AMD, ω-3 fatty acid intake and consumption of fish. A risk reduction in AMD was associated with the highest levels of ω-3 intake (OR 0.85, p=0.03), but not with consumption of more than two servings of fish per week, in a population of 6,734 individuals.[63]

In a US study, higher intake of specific types of fat, including vegetable, monounsaturated, PUFAs and linoleic acid, rather than total fat intake, was found to be associated with a greater risk of advanced AMD. Diets high in ω-3 fatty acids and fish were associated with a lower risk of AMD only in individuals with low intake of the ω-6 fatty acid linoleic acid.[51] In a sample of 2,520 individuals, those with advanced AMD were less likely to consume fish or shellfish high in ω-3 fatty acids (OR 0.40). There was no relationship between AMD and consumption of crab and oysters, which have high levels of zinc.[64]

The third National Health and Nutrition Examination Survey (NHANES III) found associations between fat intake and AMD in a cross-sectional study. Consumption of fish more than once a week compared with once a month or less was associated with a reduced risk of early ARM (OR 1.0) and late ARM (OR 0.04, p=0.10).[65]

The Pathologies oculaires liées à l'âge [Ocular pathologies linked to age (POLA)] study recently assessed the association of dietary fat with the risk of AMD in 832 patients. Total PUFA was not significantly associated with AMD (OR 1.02), but fish intake (more than once a month versus less than once a month) was associated with a 60 % reduction in risk of AMD (OR 0.42, p=0.01).[66]

Meta-analyses

In a meta-analysis of nine studies and 88,974 participants, high dietary intake of ω-3 fatty acids was inversely associated with the risk of late AMD (OR 0.62) (see *Table 2*).[67] Moreover, fish consumption at least twice a week was associated with a reduction in both early (OR 0.76) and late (OR 0.67) AMD (see *Table 2*).

Table 2: Pooled Odds Ratios for Age-related Macular Degeneration Comparing the Highest with the Lowest Dietary Intake of Omega-3 Fatty Acids and Fish

Conditions and studies	OR (95 % CI high vs. low intake
Omega-3 fatty acids and late AMD	
Chua et al. *Arch Ophthalmol* 2006;124:981	0.44 (0.08–2.39)
Seddon et al. *Arch Ophthalmol* 2006;124:995	0.55 (0.32–0.95)
Seddon et al. *Arch Ophthalmol* 2001;119:1191	0.75 (0.44–1.26)
AREDS *Arch Ophthalmol* 2007;125:671	0.61 (0.41–0.90)
All studies	**0.62 (0.48–0.82)**
Fish and early AMD	
Delcourt et al. Eur J Clin Nutr 2007;61:1341	0.64 (0.31–1.31)
Chua et al. *Arch Ophthalmol* 2006; 124:981	0.62 (0.38–1.02)
Amasson et al. *Am J Ophthalmol* 2006; 142:419	0.61 (0.38–0.98)
Mares-Perlman et al. *Arch Ophthalmol* 1995;113:743	0.90 (0.60–1.30)
Heuberger et al. *Arch Ophthalmol* 2001;119:1833	1.00 (0.70–1.40)
Cho et al. Am J Clin Nutr 2001;73:209	0.65 ((0.46–0.91)
All studies	**0.76 (0.64–0.90)**
Fish and late AMD	
Chua et al. *Arch Ophthalmol* 2006; 124:981	0.25 (0.06–1.02)
Mares-Perlman et al. *Arch Ophthalmol* 1995;113:743	0.80 (0.20–2.50)
Heuberger et al. *Arch Ophthalmol* 2001;119:1833	0.40 (0.20–1.20)
AREDS *Arch Ophthalmol* 2007;125:671	0.61 (0.37–1.00)
Seddon et al. *Arch Ophthalmol* 2006;124:995	0.64 (0.41–1.00)
Seddon et al. *Arch Ophthalmol* 2001;119:1191	0.86 (0.58–1.27)
All studies	**0.67 (0.53–0.85)**

AMD = age-related macular degeneration; CI = confidence interval; OR = odds ratio. Adapted from Chong et al., 2008.[67]

It can be seen that a growing body of evidence suggests an inverse association between the dietary intake of ω-3 fatty acids and AMD risk. Although more evidence is needed to support the routine recommendation of ω-3 fatty acid intake for prevention of AMD,[67,68] all studies to date have suggested a protective role of DHA for AMD, particularly for exudative AMD, despite differences in methodology and populations. There is a need for further research involving prospective cohort studies and randomised clinical trials.

Prospective Studies Evaluating Nutritional Supplements Containing Omega-3 Fatty Acids for the Treatment of Age-related Macular Degeneration

Few clinical trials have investigated the role of oral supplementation with ω-3 for the prevention of AMD. The Nutritional AMD treatment phase I (NAT-1) study evaluated the feasibility of a prospective study of oral supplementation with DHA and EPA for six months compared with placebo. Serum and red blood cell membrane levels of EPA and DHA were elevated in the treated group. No change was observed in the control group despite diet recommendations. Although no therapeutic benefit of the ω-3 fatty acid supplementation was observed over this short time period, no side effects were reported and a further study was considered feasible.[69] The further benefits of DHA supplementation are currently being evaluated in the NAT-2 study.[69]

NAT-2 is a single-centre prospective interventional randomised double-masked trial currently being conducted in France. Among its objectives is an investigation of the benefits of ω-3 supplementation for AMD. In addition, the benefits of oral supplementation with ω-3 PUFAs on the progression of AMD is being evaluated in the AREDS2 study, a multi-centre randomised placebo-controlled trial.[70] The study began in 2008, has enrolled around 4,000 participants and will run for 5–6 years. Results from AREDS2 are expected in 2013.

An Italian study investigated the benefit of supplementation with a mixture containing acetyl-L-carnitine (ALC), PUFAs, coenzyme Q10 (CoQ10) and vitamin E in patients with early AMD (n=106) over a period of 12 months. An equal number of age- and sex-matched patients were treated with vitamin E only. A slight improvement in visual function was observed in the treated group and the divergence between treated and control groups became more marked with time but was not statistically significant.[71]

The Taurine, omega-3 fatty acids, zinc, antioxidant, lutein (TOZAL) study treated 37 patients with dry AMD with a nutritional supplement containing EPA and DHA for six months. Of the patients receiving the nutritional supplement, 76.7 % showed an improvement or stabilisation in best corrected visual acuity. There was a statistically significant improvement in visual acuity compared with a placebo cohort constructed from the literature (p=0.045).[72] Increased median serum levels of ω-3 long chain fatty acids were also observed after six months following combined supplementation of EPA and DHA with lutein and zeaxanthin.[73]

Data from a study to determine the effects of lutein, a component of macular pigment, and DHA on their serum concentrations and macular pigment optical density (MPOD) suggested that DHA facilitated accumulation of lutein in the blood and macula, especially in the most central part of the fovea, suggesting a different and maybe synergistic effect of DHA + lutein on the spatial pattern of increase in MPOD.[74]

Current European Recommendations for Omega-3 Fatty Acid Intake

Several organisations have made recommendations on dietary intake of fatty acids and, although levels vary, all agree that intake of ω-6 fatty acids should be reduced and ω-3 fatty acids increased. The European Food Safety Authority (EFSA) currently states that there is insufficient evidence to derive an average requirement, lower threshold intake, population reference intake or tolerable upper intake level for α-linolenic acid.[75] It is recommended that α-linolenic represent 0.5 % of the total energy derived from fat.[75] Based on cardiovascular considerations, an adequate intake of 250 mg/day of combined EPA + DHA is recommended in healthy adults, with an additional 100–200 mg daily for pregnant or lactating individuals to compensate for the loss of DHA to the foetus/infant.[75]

In clinical studies, DHA supplementation has been found to contribute to optimal visual development in infants.[76–78] The EFSA states that "DHA contributes to the visual development of infants" and recommends an adequate intake of 100 mg/day in this age group.[75] Dietary advice for children aged 2–18 years is similar to adults, i.e. an adequate intake of ~250 mg/day combined EPA + DHA.[75] In 2010, the French Food Safety Agency[79] published its recommended intakes for fatty acids in AMD prevention: 250 mg/day of both EPA and DHA (i.e. a total of EPA + DHA 500 mg/day).[79]

Conclusions and Future Developments

The majority of evidence supporting a retinoprotective role of ω-3 fatty acids is observational. These studies show that a higher level of ω-3 fatty acid intake or the regular consumption of oily fish is associated with a 30–50 % risk reduction in the occurrence or progression of AMD. The body of evidence in support of ω-3 supplementation is growing. Recently, a high intake of ω-3 fatty acids has been shown to negate the risk of AMD posed by genetic factors.[80] The benefits of ω-3 fatty acids for the therapeutic treatment of AMD have not been demonstrated in randomised controlled trials. However, some agencies have already stated recommendations to support dietary supplementation with ω-3 fatty acids in prevention of AMD. Moreover, the on-going prospective randomised placebo-controlled trials AREDS2 and NAT-2 should address some of these concerns.

Compared with 100 years ago, current Western diets contain higher levels of saturated fats, trans fatty acids and ω-6 fatty acids, and reduced ω-3 fatty acids.[81] Redressing this imbalance may be important for general health, not just retinal health and visual function.[48,82] In terms of visual function, increasing the intake of DHA is likely to be more important than that of EPA because of the high levels and turnover of DHA in the retina.[36] However, both have antiangiogenic and anti-inflammatory properties, and EPA is a precursor to DHA, so an equal balance of both might be the best option. In the on-going AREDS2 study, the supplement is richer in EPA than DHA. Depending on the outcome of the AREDS2, this should be addressed in the design of future trials. Despite the fact that clinical trials of nutritional supplements are difficult to conduct and need large patient numbers, it is vital that studies are continued aimed at clarifying the benefits of ω-3 fatty acids. The EFSA has recommended an adequate intake of DHA and EPA. Equally important is that sustainable sources of ω-3 fatty acids continue to be developed and evaluated as alternatives to fish oils.[35,83] Recently, it has been shown that combinations of nutrients from food including vitamins, antioxidants and ω-3 are more strongly associated with a lower risk of AMD than single nutrients.[84] ■

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