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 retinal pigment epithelium 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(45,46,47), three case-control studies(48,49,50) and three cross-sectional studies(51,52,53).

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% [(54)].

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[(55)].

The objective of **AREDS report n. 20** was to evaluate the association between lipid intake and age-related macular degeneration 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 (NV) AMD (odds ratio (OR): 0.61; 95 % confidence interval (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 NV 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 NV AMD (OR: 1.54; 95% CI: 1.04-2.29).

No statistically significant relationships were found for other lipids or groups[(56)].

More recently, in **AREDS report n. 23**, reduced likelihood of progression from bilateral drusen to CGA was observed in individuals reporting the highest EPA intakes (odds ratio (OR): 0.44; 95% confidence interval (CI): 0.23-0.87) and EPA + DHA intakes (OR: 0.45; 95% CI: 0.23-0.9).

DHA levels were associated with CGA 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 CGA[(57)]
.

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 exsudative age-related macular degeneration 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 exsudative AMD patients.

These findings confirmed the benefits of DHA supplementation in these AMD patients[(58)]
.

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[(59)].

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 vs. 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 vs. 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[(60)].

More recently, 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 CGA and NV AMD were similar; the corresponding multivariate odds ratios were 0.65 (95% CI: 0.45-0.92; p ≤ 0.02) and 0.68 (95% CI: 0.49-0.94; p ≤ 0.02)[(61)].

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