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Dry AMD: A new hope

High doses of omega-3 fatty acids could help, according to new data

By Dr Tassos Georgiou

Supplementation with EPA-rich omega-3 fatty acids could help battle inflammation in the macula and, therefore, improve the vision in patients with dry age-related macular degeneration (AMD), according to the findings of a new pilot study.

Dry AMD is the most common cause of vision loss in developed countries, particularly in people older than 55 years old. The projected number of people with age-related macular degeneration in 2020 is 196 million, increasing to 288 million in 2040.[1]

Inflammation and oxidative stress fundamental

Although the aetiology of AMD is unknown, inflammation and oxidative stress appear to play fundamental roles in the pathogenesis of AMD. High sensitivity CRP (hs-CRP) has been used as a marker of systemic low-level chronic inflammation. Patients with elevated hs-CRP levels (>3 mg/L) had a 31% increased risk of AMD and a nearly 2-fold increased risk of late stages AMD. Compliment factor H gene has been identified as the one gene, which significantly increases the risk of AMD by 11 times, and the LOC387715 A695 variant increases the risk of AMD by 15 times.[2] These observations suggest that low-grade chronic inflammation may play a role in the development of AMD.

The initial injury in AMD is the retinal pigment endothelium (RPE), which is the layer of cells that lies below the photoreceptors in the macula. This may possibly be due to gene mutation, oxidative stress, light damage, lipofuscin accumulation, complement-mediated injury, inflammation or a combination of the above. Regardless of the initiating factors, the result is the formation of cellular debris called drusen that accumulate between the retina and the choroid that contains the blood vessels feeding the retina. The deposition of drusen seems to be involved in the early stages as well as progression of the disease.

These observations suggest that local inflammation plays a potentially significant role in the development of AMD. Unfortunately, inflammation remains one of the most complex biological systems. This may be due in part to distinct phases of an acute inflammatory response. The first is the classic initiation phase defined by the cardinal signs of inflammation. Among the major mediators in this phase of the inflammatory response is the generation of pro-inflammatory eicosanoids generated from the omega-6 fatty acid, arachidonic acid (AA). This includes prostaglandins (such as PGE2) and leukotrienes (such as LTB4).

Still not much to offer dry AMD patients

While current anti-VEGF therapies can improve the quality of life for patients, who have neovascular AMD, we still do not have much to offer to patients with dry AMD to stop progression or improve visual acuity, who represent 90% of patients with the disease.

The AREDS study showed that daily oral supplementation with antioxidant vitamins and minerals reduced the risk of developing advanced AMD from moderate AMD by 25% at 5 years. AREDS2 study did not yield an improved formulation compared to AREDS. Addition of 1 g of EPA and DHA did not further reduce the risk of progression. However, due to, increased risk to lung cancer with β-carotene, it could be substituted with lutein and zeaxanthin.

Most human clinical fish oil studies published over the past 13 years indicates that weekly consumption of fish slows down or prevents macular degeneration. Recent studies showed significant and strong associations of neovascular AMD with red blood cell membranes EPA,[3] demonstrating that serum EPA was associated significantly with a lower risk of neovascular AMD.

Pilot study

Our initial pilot study of 40 eyes (25 patients) who had dry AMD (with a mean age of 67 years) received daily supplements of 5 g of EPA and DHA (3.4 g EPA

In short...

Dry age-related macular degeneration (AMD) is the most common cause of vision loss in developed countries. Although anti-VEGFs can be used to improve the quality of life for patients with the wet form of the disease there is still not much to offer dry AMD patients. In this article, Dr Georgiou highlights the results of his recent study looking at the value of higher doses of omega-3 fatty acids for this group of patients.

Figure 1: Number of letters gained related to AA/EPA.

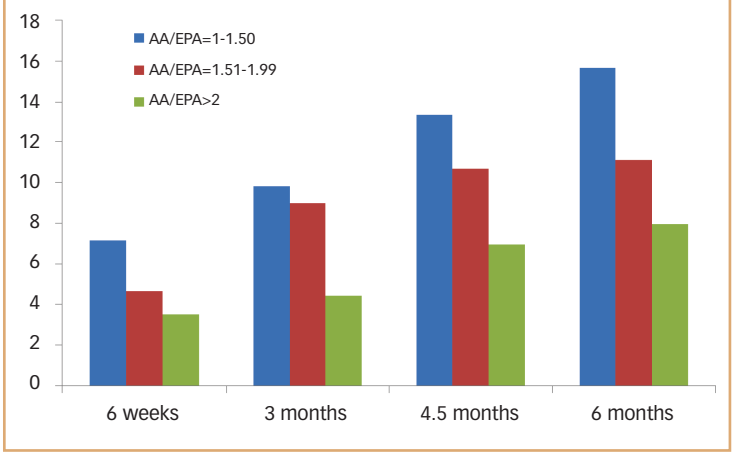
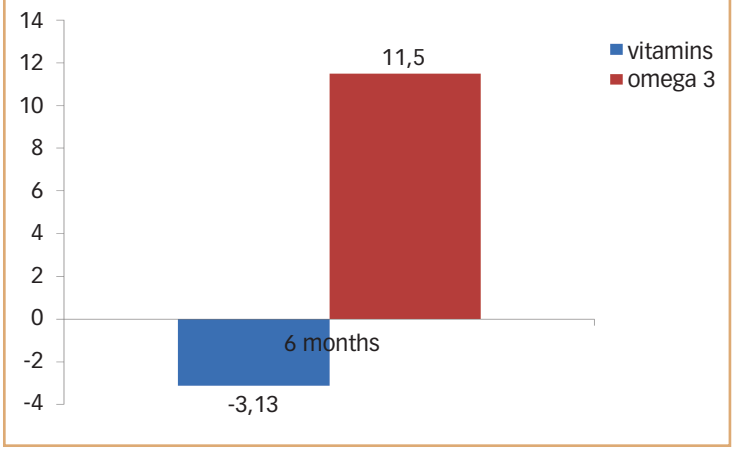


Figure 2: Shows the number of letters lost or gained during the crossover trial.



and 1.6 g DHA) for 6 months.[4] *[Led by the author and his research team at Ophthalmos Research and Educational Institute in Cyprus.]* The visual acuity ranged from 20/25 to 20/200 and was recorded according to the ETDRS electronic chart. These patients were followed up every 6 weeks for 6 months.

By the 6-month time point, the average increase in vision was 2 lines of vision or 10 letters. All eyes had improvement of visual acuity. Approximately, one-third of eyes improved by 1 line of vision (5 letters), the other third by 2 lines of vision (10 letters) and the last third by 3 lines of vision (15 letters) at the end of 6 months of the omega-3 fatty acids supplementation.

As there is no existing treatment for dry AMD, the positive clinical improvements obtained in this pilot study should be considered striking because 100% of the patients had an increase of at least one line of vision within 4.5 months after starting the omega-3 fatty acid supplementation.

Although the dose of omega-3 fatty acids used in these studies may appear high, in fact the average daily EPA and DHA dose used in the subjects reported was about one-third of those levels used in various prior studies in the treatment of severe brain trauma and ADHD.

We noted that our findings are in 'stark contrast' with other recent publications that have found no benefit for omega-3 fatty acids and AMD.[5,6]

We hypothesize the reason that our open label experiments with high-dose omega-3 fatty acids in the treatment of dry-AMD was successful is a consequence of both (a) the increased dosage and (b) the higher levels of EPA delivered with our omega-3 fatty acid formulation.

Working hypothesis

Our working hypothesis is that resolution of neuroinflammation in the macula may be mediated by E-resolvins derived from the higher daily dose of EPA. Animal studies suggest higher levels of supplementation with omega-3 fatty acids will increase local levels of both precursor EPA and the E-series resolvins in the retina.[7]

However, any increased resolvin (E, D, or neuroprotectins) production within the brain requires adequate levels of their precursors in the blood as the brain is incapable of synthesizing long-chain omega-3 fatty acids. It has been demonstrated that rate of entry of the long-chain fatty acids such as arachidonic acid (AA), DHA and EPA into the brain across the blood-brain barrier are virtually equivalent. This leads to the intriguing question as to why are the levels of EPA so low in the brain compared to other tissues in the body. This paradox appears to be a consequence of EPA becoming rapidly oxidized once it enters into the brain. Whereas, once AA and DHA enter into the brain, they are stored in neural phospholipids that have a very long half-life especially in humans. This difference in metabolism of EPA in the brain compared to DHA may explain the dramatic differences of levels of EPA and DHA in the brain

leading to an assumption that EPA has little importance in treating neurological conditions.

As EPA is an essential fatty acid that has significant anti-inflammatory properties, it initially makes no teleological sense that this particular fatty acid is chosen for rapid oxidation of EPA in the brain while being conserved in other tissues unless its oxidation serves a greater purpose. One possible explanation is that the rapid oxidation of EPA is to maintain adequate levels of anti-inflammatory resolvins in the brain to constantly protect the brain from future inflammatory damage. The rapid enzymatic conversion of EPA in the brain may provide a steady state reservoir of E-series resolvins that may serve as an anti-inflammatory, pro-resolving 'insurance policy' against future unexpected inflammatory insults to the brain and the retina. The high doses of EPA used in our supplementation may have supplied adequate levels of EPA to maintain a critical threshold of resolvins of E-series (both RvE1 and RvE2). This is also suggested by animal studies in which as the levels of EPA in the brain are significantly increased by dietary supplementation or transgenetic manipulation, are correlated with increased levels of E-series resolvins in the blood.[8]

Although the dose of omega-3 fatty acids used in these studies may appear high, in fact the average daily EPA and DHA dose used in the subjects reported was about one-third of those levels used in various prior studies in the treatment of severe brain trauma and ADHD.

Recent data

In our recent study at Ophthalmos Research and Educational Institute of 32 eyes of dry AMD and 16 eyes with macular dystrophies, we have used high doses of omega-3, 5–10 g of EPA and DHA for 6 months and the AA/EPA ratio in the blood as a clinical marker. If the AA/EPA ratio dropped below 1, then the omega-3 fatty acid dosage was reduced until the AA/EPA ratio in the blood rose about 1. Results at 6 months showed that when the blood AA/EPA ratio more than 2 then the mean gain of letters as 7.9 on the EDTRS chart. When the ratio between 1.5–2 then the gain was 11.1 letters and when the ratio was between 1–1.5 the gain was 15.7 letters (Figure 1).

Therefore at this time, we believe that maintaining an AA/EPA ratio in the blood between 1 to 1.5, provides the maximum clinical visual acuity benefit. It also provides adequate safety factor to exclude any concern about extensive bleeding while at the same time providing a clinical marker indicating whether or not the patient is obtaining a therapeutic dosage of EPA and DHA.

Geographic atrophy

Geographic atrophy (GA) is the advanced form of dry AMD. It represents the loss of photoreceptors, retinal pigment epithelium (RPE) and choriocapillaris within the macular. In the US, GA is present in 3.5% of people aged >75 years old and >22% in those >90 years old.[9]

Recently, Roche announced positive results with monthly intravitrial injection of lampalizumad for these patients. They showed 20% reduction in the area of GA at 18 months.

Our recent crossover study, at the Ophthalmos Research and Educational Institute in Cyprus, of 8 eyes with GA showed a reduction of 84% of the area of GA at 12 months. They were initially treated with vitamins for 6 months followed by 8 g/day of omega-3 fatty acids for 6 months. They all had AA/EPA ration between 1 and 1.6.

The mean initial visual acuity was 6/18. There was a mean loss of 3.13 of letters when patients treated with vitamins and 11.5 letters of gain when these patients were treated with 8 g/day of omega-3 fatty acids (Figure 2).

Conclusion

These open label studies suggest that high doses of omega-3 fatty acids, especially EPA maybe effective in treating age-related macular degeneration, which is the leading cause of blindness over the age of 50.

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Dr Georgiou had pending patents on the use of omega fatty acids and eye diseases.