# GOED OMEGA-3

#### GLOBAL ORGANIZATION FOR EPA AND DHA OMEGA-3

## **OMEGA-3 FATTY ACIDS AND EYE HEALTH**

### **Introduction**

The body's highest concentration of DHA (docosahexaenoic acid) omega-3 is found in the retina of the eye at concentrations up to 65%<sup>1,2</sup> and its presence enhances the development of photoreceptors, specialized cells in the retina necessary for vision.<sup>3</sup> High DHA concentrations are needed for rhodopsin, a pigment in the photoreceptor rod cells, to respond to light in a way that permits vision in dim light and at night.<sup>4</sup> The highly unsaturated nature of DHA has unique effects on retinal cell membranes allowing them to transmit light signals very quickly. DHA's contribution to visual development is so well established that the EU adopted two associated health claims.<sup>5</sup> Omega-3s are thought to help prevent the development of and/or attenuate the progression of age-related macular degeneration (AMD), as well as help alleviate symptoms of dry eye.

## Age-Related Macular Degeneration (AMD)

According to the National Eye Institute of the National Institutes of Health, age-related macular degeneration (AMD) is a common eye condition and a leading cause of vision loss among people age 50 and older.<sup>6</sup> It causes damage to the macula, a small spot near the center of the retina and the part of the eye needed for sharp, central vision, which lets us see objects that are straight ahead.

There are three stages of AMD that are defined, in part, by the size and number of drusen (yellow deposits under the retina).

- 1) Early AMD: This stage is defined by the presence of medium-sized drusen, which are about the width of an average human hair. People with early AMD typically do not have vision loss.
- 2) Intermediate AMD: This stage is defined by the presence of large drusen, pigment changes in the retina, or both. Intermediate AMD may cause some vision loss, but most people will not experience any symptoms.
- 3) Late AMD: This stage is defined by drusen, in addition to vision loss from damage to the macula (small spot near the center of the retina and the part of the eye needed for sharp, central vision, which lets us see objects that are straight ahead). There are two types of late AMD:
  - a. Dry AMD (aka geographic atrophy)
  - b. Wet AMD (aka neovascular AMD)

#### Omega-3s and AMD

Data from prospective studies suggesting that higher intakes of n-3 LCPUFAs and fish provide protection against AMD has been consistently positive.<sup>7-15</sup> In addition, both plasma n-3 LCPUFA and red blood cell EPA+DHA have been shown to be strongly associated with a reduced risk for late AMD.<sup>16-17</sup>

The data from intervention trials has been mixed.

• In some trials, daily supplementation with n-3 LCPUFAs (130-280 mg/day) plus one or more of the following: lutein, zeaxanthin, and antioxidants was shown to be effective in increasing the macular pigment optical density,<sup>18-20</sup> providing evidence that there is a protective effect

on the macula in individuals with AMD. In an open-label study providing EPA+DHA (5 g/day), improvement in visual acuity occurred in 100% of patients.<sup>21</sup>

- High doses of EPA+DHA (4 g/day) did not have any measurable effect on visual acuity or retinal function.<sup>22</sup>
- EPA+DHA (1110 mg/day) provided to patients with choroidal neovascularizatin (CNV eye grows new blood vessels because it needs more oxygen) showed no benefit over placebo when all subjects were included in the analysis; however, individuals achieving the highest tertile of EPA+DHA levels in red blood cells had significantly lower risk of CNV developing over three years.<sup>23</sup>
- In the largest trial to date, EPA+DHA (1 g/day) did not reduce the risk of progression to advanced AMD (Age-Related Eye Disease Study 2 Research Group).<sup>24</sup>

Given the inconsistent results, further research is necessary to support increasing intake of EPA+DHA via the diet or supplementation for the explicit purpose of preventing or slowing the progression of AMD. The strongest evidence of a potential benefit appears to be in preventing or reducing the risk of developing AMD, rather than treating it.

# Dry Eye

According to the National Eye Institute of the National Institutes of Health, dry eye is a condition that occurs when the eye does not produce tears properly, or when the tears are not of the correct consistency and evaporate too quickly.<sup>25</sup> Comparison of results between studies is difficult for a number of reasons. First, dry eye is a multifactorial disease, affecting both tears and the surface of the eye. Second, diagnostic tests (e.g. tear break-up time (TBUT), Schirmer I test, Ocular Surface Disease Index© (OSDI©), meibomian gland expression, etc...) for dry eye are not standardized. Third, some of the tests are poorly associated with subjective symptoms.

Despite these issues, results from the growing body of scientific evidence on the effect(s) of omega-3s on dry eye appear promising, albeit still inconclusive.<sup>26-29</sup> Results from two upcoming studies should provide additional insight into the benefits, or lack thereof, of omega-3s for dry eye.<sup>30-31</sup> The primary outcome measurement in both studies is OSDI©, an outcome that has been shown previously to be positively affected by omega-3s.<sup>32-33</sup>

Finally, of particular interest is a novel class of bioactive lipid mediators, enzymatically biosynthesized from EPA and DHA, termed resolvins and protectins.<sup>34-35</sup> A resolvin-based eye drop for dry eyes is under clinical development.<sup>36</sup>

# References

- 1. Bazan NG, Silvia di Fazio de Escalante M, Careaga MM, Bazan HE, Giusto NM. High content of 22:6 (docosahexaenoate) and active [2-3H]glycerol metabolism of phosphatidic acid from photoreceptor membranes. Biochim Biophys Acta 1982;712:702-6.
- 2. Fliesler SJ, Anderson RE. Chemistry and metabolism of lipids in the vertebrate retina. Prog Lipid Res 1983;22:79-131.
- **3.** SanGiovanni JP, Chew EY. The role of omega-3 long-chain polyunsaturated fatty acids in health and disease of the retina. Prog Retin Eye Res 2005;24:87-138.
- **4.** Grossfield A, Feller SE, Pitman MC. A role for direct interactions in the modulation of rhodopsin by omega-3 polyunsaturated lipids. Proc Natl Acad Sci U S A 2006;103:4888-93.

- 5. Commission Regulation (EU) No 440/2011 of 6 May 2011 on the authorisation and refusal of authorisation of certain health claims made on foods and referring to children's development and health [2011] OJ L119/4 available online at <a href="http://eur-lex.europa.eu/legal-content/EN/ALL/;jsessionid=tFTTTLRRXkT14wGd0G8z4QyqyGXgqJLZGCvFC6xXvLdn">http://eur-lex.europa.eu/legal-content/EN/ALL/;jsessionid=tFTTTLRRXkT14wGd0G8z4QyqyGXgqJLZGCvFC6xXvLdn</a> qdJ2Qdw6!-1764623831?uri=CELEX:32011R0440.
- 6. National Eye Institute Facts About Age-Related Macular Degeneration. https://www.nei.nih.gov/health/maculardegen/armd\_facts.asp.
- 7. Augood C, Chakravarthy U, Young I, Vioque J, de Jong PT, Bentham G, Rahu M, Seland J, Soubrane G, Tomazzoli L, Topouzis F, Vingerling JR, Fletcher AE. Oily fish consumption, dietary docosahexaenoic acid and eicosapentaenoic acid intakes, and associations with neovascular age-related macular degeneration. Am J Clin Nutr. 2008;88:398-406.
- 8. Cho E, Hung S, Willett WC, Spiegelman D, Rimm EB, Seddon JM, Colditz GA, Hankinson SE. Prospective study of dietary fat and the risk of age-related macular degeneration. Am J Clin Nutr 2001;73:209-18.
- **9.** Christen WG, Schaumberg DA, Glynn RJ, Buring JE. Dietary ω-3 fatty acid and fish intake and incident age-related macular degeneration in women. Arch Ophthalmol. 2011;129:921-9.
- **10.** SanGiovanni JP, Agrón E, Clemons TE, Chew EY. Omega-3 long-chain polyunsaturated fatty acid intake inversely associated with 12-year progression to advanced age-related macular degeneration. Arch Ophthalmol. 2009;127:110-2.
- 11. SanGiovanni JP, Agrón E, Meleth AD, Reed GF, Sperduto RD, Clemons TE, Chew EY; Age-Related Eye Disease Study Research Group. ω-3 Long-chain polyunsaturated fatty acid intake and 12-y incidence of neovascular age-related macular degeneration and central geographic atrophy: AREDS report 30, a prospective cohort study from the Age-Related Eye Disease Study. Am J Clin Nutr. 2009;90:1601-7.
- 12. SanGiovanni JP, Chew EY, Agrón E, Clemons TE, Ferris FL 3rd, Gensler G, Lindblad AS, Milton RC, Seddon JM, Klein R, Sperduto RD; Age-Related Eye Disease Study Research Group. The relationship of dietary omega-3 long-chain polyunsaturated fatty acid intake with incident age-related macular degeneration: AREDS report no. 23. Arch Ophthalmol. 2008;126:1274-9.
- 13. SanGiovanni JP, Chew EY, Clemons TE, Davis MD, Ferris FL 3rd, Gensler GR, Kurinij N, Lindblad AS, Milton RC, Seddon JM, Sperduto RD; Age-Related Eye Disease Study Research Group. The relationship of dietary lipid intake and age-related macular degeneration in a case-control study: AREDS Report No. 20. Arch Ophthalmol. 2007;125:671-9.
- **14.** Swenor BK, Bressler S, Caulfield L, West SK. The impact of fish and shellfish consumption on age-related macular degeneration. Ophthalmology. 2010;117:2395-401.
- **15.** Tan JS, Wang JJ, Flood V, Mitchell P. Dietary fatty acids and the 10-year incidence of agerelated macular degeneration: the Blue Mountains Eye Study. Arch Ophthalmol. 2009;127:656-65.
- **16.** Merle BM, Benlian P, Puche N, Bassols A, Declourt C, Souied E. Circulating omega-3 fatty acids and neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci. Epub ahead of print 2014 Feb 20.
- **17.** Merle BM, Delyfer MN, Korobelnik JF, Rougier MB, Malet F, Féart C, Le Goff M, Peuchant E, Letenneur L, Dartigues JF, Colin J, Barberger-Gateau P, Delcourt C. High concentrations of plasma n3 fatty acids are associated with decreased risk for late age-related macular degeneration. J Nutr. 2013;143:505-11.

- **18.** Arnold C, Winter L, Fröhlich K, Jentsch S, Dawczynski J, Jahreis G, Böhm V. Macular xanthophylls and ω-3 long-chain polyunsaturated fatty acids in age-related macular degeneration: a randomized trial. JAMA Ophthalmol 2013;131:564-72.
- **19.** Dawczynski J, Jentsch S, Schweitzer D, Hammer M, Lang GE, Strobel J. Long term effects of lutein, zeaxanthin and omega-3-LCPUFAs supplementation on optical density of macular pigment in AMD patients: the LUTEGA study. Graefes Arch Clin Exp Ophthalmol 2013;251:2711-23.
- **20.** García-Layana A, Recalde S, Alamán AS, Robredo PF. Effects of lutein and docosahexaenoic Acid supplementation on macular pigment optical density in a randomized controlled trial. Nutrients. 2013;5:543-51.
- Georgiou T, Neokleous A, Nicolaou D, Sears B. Pilot study for treating dry age-related macular degeneration (AMD) with high-dose omega-3 fatty acids. PharmaNutrition. 2014;2-8-11.
- **22.** Gerstenblith AT, Baskin DE, Shah CP, Wolfe JD, Fineman MS, Kaiser RS, Ho AC. Electroretinographic effects of omega-3 Fatty Acid supplementation on dry age-related macular degeneration. JAMA Ophthalmol. 2013;131:365-9.
- 23. Souied EH, Delcourt C, Querques G, Bassols A, Merle B, Zourdani A, Smith T, Benlian P; Nutritional AMD Treatment 2 Study Group. Oral docosahexaenoic acid in the prevention of exudative age-related macular degeneration: the Nutritional AMD Treatment 2 study. Ophthalmology. 2013;120:1619-31.
- **24.** Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA 2013;309:2005-15.
- **25.** National Eye Institute Facts About Dry Eye. <u>https://www.nei.nih.gov/health/dryeye/dryeye.asp.</u>
- **26.** Bhargava R, Kumar P, Kumar M, Mehra N, Mishra A. A randomized controlled trial of omega-3 fatty acids in dry eye syndrome. Int J Ophthalmol. 2013;6:811-6.
- **27.** Brignole-Baudouin F, Baudouin C, Aragona P, Rolando M, Labetoulle M, Pisella PJ, Barabino S, Siou-Mermet R, Creuzot-Garcher C. A multicentre, double-masked, randomized, controlled trial assessing the effect of oral supplementation of omega-3 and omega-6 fatty acids on a conjunctival inflammatory marker in dry eye patients. Acta Ophthalmol. 2011;89:e591-7.
- **28.** Kangari H, Eftekhari MH, Sardari S, Hashemi H, Salamzadeh J, Ghassemi-Broumand M, Khabazkhoob M. Short-term consumption of oral omega-3 and dry eye syndrome. Ophthalmology. 2013;120:2191-6.
- **29.** Wojtowicz JC, Butovich I, Uchiyama E, Aronowicz J, Agee S, McCulley JP. Pilot, prospective, randomized, double-masked, placebo-controlled clinical trial of an omega-3 supplement for dry eye. Cornea. 2011;30:308-14.
- **30.** ClinicalTrials.gov Dry Eye Assessment and Management Study (DREAM). http://clinicaltrials.gov/ct2/show/NCT02128763?term=omega+3+dry+eye&rank=6.
- **31.** ClinicalTrials.gov Oral Omega-3 Fatty Acids in the Treatment of Dry Eye Syndrome. http://clinicaltrials.gov/ct2/show/NCT01107964?term=omega+3+dry+eye&rank=3.
- **32.** Oleñik A, Jiménez-Alfaro I, Alejandre-Alba N, Mahillo-Fernández I. A randomized, doublemasked study to evaluate the effect of omega-3 fatty acids supplementation in meibomian gland dysfunction. Clin Interv Aging. 2013;8:1133-8.

- **33.** Mascai MS. The role of omega-3 dietary supplementation in blepharitis and meibomian gland dysfunction (an AOS thesis). Trans Am Ophthalmol Soc. 2008;106:336-56.
- **34.** Cortina MS, Bazan HE. Docosahexaenoic acid, protectins and dry eye. Curr Opin Clin Nutr Metab Care. 2011;14:132-7.
- **35.** Lee HN, Surh YJ. Therapeutic potential of resolvins in the prevention and treatment of inflammatory disorders. Biochem Pharmacol. 2012;84:1340-50.
- **36.** Lee CH. Resolvins as new fascinating drug candidates for inflammatory diseases. Arch Pharm Res. 2012;35:3-7.