

Omega Nutrition and Dry Eye Disease

Addressing AREDS II & DREAM trial

Introduction

Dry Eye Disease is a common condition that can severely impair quality of life¹. It is a frequent cause of visits to the ophthalmic clinician due to ocular discomfort and problems with visual activities.

Inflammation is now understood to be a key process in development of dry eye disease². Essential fatty acids have been of interest in the area of dry eye disease treatment due to their anti-inflammatory properties.³ Inflammation is a part of nearly all degenerative conditions, together with ageing itself. Inflammaging is frequently used to describe how accelerated ageing occurs as a result of excess inflammation and how 'high inflammation' tends to increase as we age^{4,5}.

In this article we examine the role of nutrition on the ocular surface.

In recent years oral supplementation has become more popular with a plethora of dry eye companies now marketing Omega 3 based formulations claiming to help relieve dry eye symptoms. However, whilst many optometrists are now more confident to recommend supplements for AMD, the concept of supplements for dry eye management hasn't yet become so widely

accepted. The adoption of dry eye supplements is unlikely to be helped by the recent media headlines, following the publication of the results of AREDS II⁶ & the DREAM Trial⁷, suggesting that there is no ocular benefit to Omega 3 supplements. It is therefore timely to review this subject area and better understand the published literature supporting, as well as challenging, the nutritional benefit of fatty acids for patient's suffering with dry eye disease.

Definition of Dry Eye Disease

Dry eye disease is a result of the eye not producing enough tears, the tears not covering the surface of the eye properly or tears evaporating too quickly. This causes the eyes to become dry, red, and irritated. Symptoms include dryness, grittiness, soreness, burning and temporarily blurred vision.

There are many reasons our eyes become dry, for example, wearing contact lenses, working at a computer screen for long periods, poor diet, air conditioning and heating, inflammatory skin disease (rosacea), inflammatory eyelid disease (blepharitis) or simply growing older.

¹ Fiona Stapleton, Monica Alves, Vatinée Y. Bunya, Isabelle Jalbert, Kaevalin Lekhanont, Florence Malet, Kyung-Sun Na, Debra Schaumberg, Miki Uchino, Jelle Vehof, Eloy Viso, Susan Vitale, Lyndon Jones, TFOS DEWS II Epidemiology Report, *The Ocular Surface*, Volume 15, Issue 3, 2017, Pages 334-365, <https://doi.org/10.1016/j.jtos.2017.05.003>.

² Sayegh, Rony R. MD⁺; Yu, Yinxi MS⁺; Farrar, John T. MD, PhD⁺; Kuklinski, Eric J. BA⁺; Shtein, Roni M. MD⁺; Asbell, Penny A. MD, MBA⁺; Maguire, Maureen G. PhD⁺; for the Dry Eye Assessment and Management (DREAM) Study Research Group *Ocular Discomfort and Quality of Life Among Patients in the Dry Eye Assessment and Management Study*, *Cornea*: July 2021 - Volume 40 - Issue 7 - p 869-876 doi: 10.1097/ICO.0000000000002580

³ Deinema LA, Vingrys AJ, Wong CY, Jackson DC, Chinnery HR, Downie LE. A Randomized, Double-Masked, Placebo-Controlled Clinical Trial of Two Forms of Omega-3 Supplements for Treating Dry Eye Disease. *Ophthalmology*. 2017 Jan;124(1):43-

52. doi: 10.1016/j.ophtha.2016.09.023. Epub 2016 Nov 3. PMID: 27817918.

⁴ Deinema LA, Vingrys AJ, Wong CY, Jackson DC, Chinnery HR, Downie LE. A Randomized, Double-Masked, Placebo-Controlled Clinical Trial of Two Forms of Omega-3 Supplements for Treating Dry Eye Disease. *Ophthalmology*. 2017 Jan;124(1):43-52. doi: 10.1016/j.ophtha.2016.09.023. Epub 2016 Nov 3. PMID: 27817918.

⁵ Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci* 2014 Jun 1;69(Suppl 1):S4-9

⁶ Ferrucci L, Fabbri E. Inflammaging: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol* 2018; 15(9):505-22

⁷ National Eye Institute, *Age-related eye disease studies (AREDS/AREDS2)* [Accessed 16/06/21]

⁸ The Dry Eye Assessment and Management Study Research Group. Omega-3 fatty acid supplementation for treatment of dry eye disease. *N Engl J Med*. Published online April 13, 2018.

In 2017, over 150 Dry Eye Disease experts created a series of recommendations for the management of Dry Eye Disease.

They defined the disease as; *“Dry eye is a multifactorial disease of the ocular surface characterised by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyper- osmolarity, ocular surface inflammation and damage, and neuro- sensory abnormalities play etiological roles.”*⁸



Why is nutrition important?

There are several options to treat dry eye such as artificial tears, heating the eyelid with a warm compress and massaging the glands in the eyelids, or surgery⁹. Artificial tears are one of the most common methods of treating dry eye, however, provide temporary relief and do not address the underlying causes.¹⁰

Dietary supplementation with essential fatty acids provides an adjunctive strategy for relieving the inflammation and symptoms that dry eye disease presents.

A less invasive and more natural method to help combat dry eye disease is increasing

essential fatty acids in your diet. EPA, DHA and DPA are Omega 3 fatty acids essential for maintaining healthy mucous membranes.¹¹ They cannot be created in the body and can only be obtained from your diet or supplementation¹². These essential fatty acids are found in the most absorbable form in fish^{13, 14}. Epidemiological studies have shown a positive correlation between fish consumption and an improvement in a range of conditions such as heart disease, dementia, macular degeneration.¹⁵

Western diets tend to be deficient in Omega-3, particularly those derived from fish.¹⁶ A western diet, lacking fish, may promote the development of several chronic diseases, including dry eye.

How to increase the Fatty Acid intake

Increasing your dietary intake of essential fatty acids can be done in a number of ways. One effective method is to introduce supplements into your daily routine.

Why Omega 3?

Perhaps the main reasons the omega-3 supplements are popular is because of their role combating inflammation, and their ability to help lower or resolve inflammation.¹⁷

Increasing your intake of essential fatty acids, especially Omega 3, have been shown to improve dry eye symptoms due to their anti-inflammatory capabilities.^{18,19}

⁸ “TFOS DEWS II Definition and Classification Report” J. Craig et al. *The Ocular Surface* 15 (2017) 575 – 628.

⁹ Jones L, Downie LE, Korb D, Benitez-Del-Castillo JM, Dana R, Deng SX, Dong PN, Geerling G, Hida RY, Liu Y, Seo KY, Tauber J, Wakamatsu TH, Xu J, Wolffsohn JS, Craig JP. *TFOS DEWS II Management and Therapy Report. Ocul Surf.* 2017 Jul;15(3):575-628. doi: 10.1016/j.jtos.2017.05.006. Epub 2017 Jul 20. PMID: 28736343.

¹⁰ Rashid, et al, 2008

¹¹ 2013/02/11 - CIA - Antioxidants and Omega-3 EFAs for Patients with Dry Eye Disorders. Pinazo-Durán MD, Galbis-Estrada C, Pons-Vázquez S, et al. *Effects of a nutraceutical formulation based on the combination of antioxidants and ω-3 essential fatty acids in the expression of inflammation and immune response mediators in tears.*

¹² Bernstein B. *10 Essential Fats and Amino. Integrative Therapies for Depression: Redefining Models for Assessment, Treatment and Prevention.* 2015 Dec 1:133

¹³

¹⁴ Sprague M, Dick JR, Tocher DR. *Impact of sustainable feeds on omega-3 long-chain fatty acid levels in farmed Atlantic*

salmon, 2006-2015. Sci Rep. 2016 Feb 22;6:21892. doi:

10.1038/srep21892. PMID: 26899924; PMCID: PMC4761991.

¹⁵ Devore EE, Grødstein E, van Rooij FJ, et al. *Dietary intake of fish and omega-3 fatty acids in relation to long-term dementia risk. Am J Clin Nutr* 2009 Jul 1;90(1):170-6

¹⁶ Maria Abramova, ... Dominik Pella, in *The Role of Functional Food Security in Global Health, 2019*

¹⁷ Zhang MJ, Spite M. *Resolvins: anti-inflammatory and proresolving mediators derived from omega-3 polyunsaturated fatty acids. Annu Rev Nutr* 2012 Aug 21;32:203-27

¹⁸ “Omega-3 Fatty Acids have a Definite Role for Dry Eye Syndrome”. Bhargava R1, Kumar P2, Kumar M3, et al. *A randomized controlled trial of omega-3 fatty acids in dry eye syndrome. Int J Ophthalmol.* 2013 Dec 18;6(6):811-6.

¹⁹ Calder PC. *Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? Br J Clin Pharmacol.* 2013 Mar;75(3):645-62. doi: 10.1111/j.1365-2125.2012.04374.x. PMID: 22765297; PMCID: PMC3575932.

Oily fish contains high concentrations of Omega 3 oils, and it is these oils that are thought to offer most of these health benefits. There are many clinical papers that provide good evidence that omega-3 lowers inflammatory levels;²⁰ but when you consume oily fish it's not just omega-3 that you're ingesting.

Salmon for example contains the vitamins, minerals, lipids, and amino acids: *taurine, vitamin D, choline, phosphorus, vitamin B6, potassium, pantothenic acid, selenium, vitamin B12, potassium, biotin, and EPA, and DHA.*²¹

Omega-3 is not the only component that is responsible for the benefits we see in epidemiological studies, but we can't offer a piece of fresh fish with every eye examination. We know that omega-3 helps to lower inflammation.²²

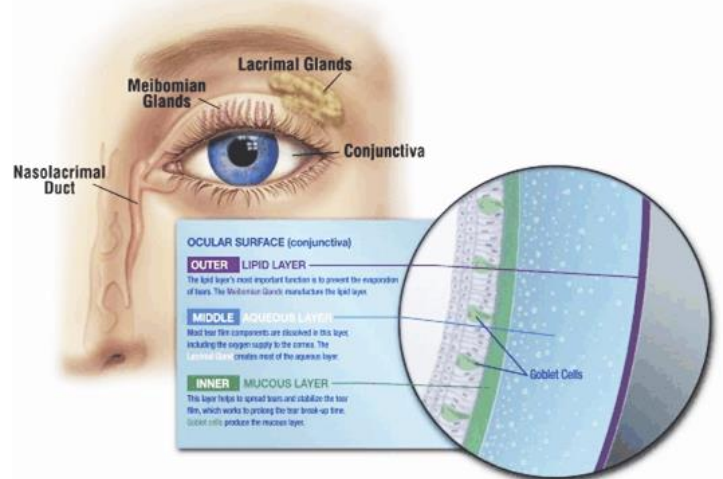
Omega 3 / Omega 6?

Omega-3 & Omega 6 are essential fatty acids, called "Essential" because our bodies need them to survive, which means that we need to obtain sufficient amounts from our diet because our bodies cannot produce their own²⁴. As the average person in the UK only eats 1/3 of a portion of fish per week, we typically don't get enough omega-3 in our diet.²⁵

We depend on our diet to get the necessary Omega-3 fatty acids into our bodies.

Omega 6 is present in most foods and our levels are considerably higher, hence there is not a widespread deficiency.²⁶

Omega-3 Fatty Acids and Omega-6 Fatty Acids are essential for normal growth and



development. Omega-3 Fatty Acids and Omega-6 Fatty Acids compete for the same enzyme to eventually be converted into anti-inflammatory prostaglandins (PGE3) and less inflammatory leukotrienes and into pro-inflammatory prostaglandins (PGE2) and more inflammatory leukotrienes, respectively^{27, 28}

Simply put, not all Omega 6 fatty acids are the same. Some produce a strong proinflammatory action and others are inherently anti-inflammatory, resembling Omega 3.²⁹ We don't have high levels of the anti-inflammatory Omega 6 compound in the western diet, but we do have plenty of the pro inflammatory Omega 6. Subsequently, there is often the general assertion that Omega 6 fatty acids are pro inflammatory, and omega-3 fatty acids are anti-inflammatory.

However, certain sources of Omega 6 have been shown to be beneficial for reducing inflammation including eye conditions associated with inflammation such as dry eye.³⁰

²⁰ Kiecolt-Glaser JK, Belury MA, Andridge R, et al. Omega-3 supplementation lowers inflammation and anxiety in medical students: a randomized controlled trial. *Brain Behav Immun* 2011 Nov 1;25(8):1725-34

²¹ Hemre GI, Lock EJ, Olsvik PA, et al. Atlantic salmon (*Salmo salar*) require increased dietary levels of B-vitamins when fed diets with high inclusion of plant based ingredients. *PeerJ*. 2016;4:e2493. Published 2016 Sep 29. doi:10.7717/peerj.2493

²² Bernstein B. 10 Essential Fats and Amino. *Integrative Therapies for Depression: Redefining Models for Assessment, Treatment and Prevention*. 2015 Dec 1:133

²⁴ Bernstein B. 10 Essential Fats and Amino. *Integrative Therapies for Depression: Redefining Models for Assessment, Treatment and Prevention*. 2015 Dec 1:133

²⁵ The BDA, Omega-3: foods fact sheet [Accessed 16/06/21]

²⁶ Neustadt J. Western diet and inflammation. *Integr Med* 2006

Aug;5(4):15

²⁷ Wada M, DeLong CJ, Hong YH, Rieke CJ, Song I, Sidhu RS, Yuan C, Warnock M, Schmaier AH, Yokoyama C, Smyth EM, Wilson SJ, FitzGerald GA, Garavito RM, Sui DX, Regan JW, Smith WL: Enzymes and receptors of prostaglandin pathways with arachidonic acid-derived versus eicosapentaenoic acid-derived substrates and products. *J Biol Chem*. 2007, 282 (31): 22254-22266. 10.1074/jbc.M703169200.

²⁸ Lands, B., Lamoreaux, E. Using 3-6 differences in essential fatty acids rather than 3/6 ratios gives useful food balance scores. *Nutr Metab (Lond)* 9, 46 (2012). <https://doi.org/10.1186/1743-7075-9-46>

²⁹ Kapoor R, Huang YS. Gamma linolenic acid: an antiinflammatory omega-6 fatty acid. *Curr Pharm Biotechnol* 2006 Dec 1;7(6):531-4

³⁰ Kokke KH, Morris JA, Lawrenson JG. Oral omega-6 essential

Inflammation is also important in long term eye conditions like age related macular degeneration (AMD).³¹ Fish consumption has long been considered protective for macular health, with some studies showing a strong correlation in a dose dependent fashion i.e. the more portions of oily fish consumed per week the lower the instance of AMD.³²

Omega-3 is associated with reduced inflammation. Inflammation is a major driver of many disease states, including dry eye disease.^{33,34}

The importance of Omega-3 EPA / DHA / DPA

EPA (Eicosapentaenoic Acid) and **DHA** (Docosahexaenoic Acid) are essential polyunsaturated fatty acids. These two fatty acids work together in human health.

EPA assists, from a physiological perspective, as an **anti-inflammatory agent** for our bodies.³⁵ Together they provide a number of important health benefits throughout our lifetime.

DHA helps with cell membrane structure and assists in normal growth and development. **DHA** Helps rebuild cell structure on ocular surface after damage due to evaporative dry eye.³⁶ This essential fatty acid is critical for cell development, growth, and maintenance, and plays in the central role in the nervous system.³⁷ The retina is also rich in DHA,

accounting for approximately 50 - 70% of fatty acid content of the photoreceptor rod outer segments.³⁸



Recently another marine oil, **DPA** (Docosapentaenoic Acid) has been discussed more frequently in the scientific community, as a new and very potent Omega-3 fatty acid. This is due to its strong anti-inflammatory properties.³⁹

All three of these polyunsaturated fats play an important role in the functioning of our bodies.

Omega 7

Omega-7 fatty acid is another polyunsaturated fatty acid that is found in some fish, including anchovy and salmon, as well as olive oil, macadamia oil and sea buckthorn oil.

fatty acid treatment in contact lens associated dry eye. Cont Lens Anterior Eye 2008 Jun 1;31(3):141-6

³¹ Kauppinen A, Paterno JJ, Blasiak J, et al. Inflammation and its role in age-related macular degeneration. *Cell Mol Life Sci* 2016 May 1;73(9):1765-86

³² Zhu W, Wu Y, Meng YF, et al. Fish consumption and age-related macular degeneration incidence: a meta-analysis and systematic review of prospective cohort studies. *Nutrients* 2016 Nov;8(11):743

³³ Wang H, Daggy BP. The Role of Fish Oil in Inflammatory Eye Diseases. *Biomed Hub*. 2017 Feb 21;2(1):1-12. doi: 10.1159/000455818. PMID: 31988905; PMCID: PMC6945974

³⁴ Calder PC. Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? *Br J Clin Pharmacol*. 2013 Mar;75(3):645-62. doi: 10.1111/j.1365-2125.2012.04374.x. PMID: 22765297; PMCID: PMC3575932.

³⁵ 1. 2013/12/15 - IJO - Omega-3 FA have a Definite Role for Dry Eye Syndrome

Bhargava R1, Kumar P2, Kumar M3, et al. A randomized controlled trial of omega-3 fatty acids in dry eye syndrome. *Int J Ophthalmol*. 2013 Dec 18;6(6):811-6.

2. 2013/08/30 - CIA - Omega-3 FA Beneficial in Treatment of Meibomian Gland Dysfunction. Oleñik A, Jiménez-Alfaro I,

Alejandre-Alba N, et al. A randomized, double-masked study to evaluate the effect of omega-3 fatty acids supplementation in meibomian gland dysfunction. *Clin Interv Aging*. 2013;8:1133-8.

3. 2013/02/11 - CIA - Antioxidants and Omega-3 EFAs for Patients with Dry Eye Disorders. Pinazo-Durán MD, Galbis-Estrada C, Pons-Vázquez S, et al. Effects of a nutraceutical formulation based on the combination of antioxidants and ω -3 essential fatty acids in the expression of inflammation and immune response mediators in tears.

³⁶ 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.

³⁷ Fighting Blindness, Can DHA save your vision [Accessed 16/06/21]

³⁸ Calder PC. Docosahexaenoic acid. *Ann Nutr Metab* 2016 69(Suppl 1):7-21

³⁹ Docosapentaenoic acid (DPA, 22:5n-3) ameliorates inflammation in an ulcerative colitis model

Crossref DOI link: <https://doi.org/10.1039/C8FO02338G>

Palmitoleic acid is one of the most common forms of Omega-7.

Emerging science on Omega-7 fatty acids is promising, specifically regarding **lipid metabolism** and the **maintenance of mucous membranes**.⁴⁰ Omega-7 can be helpful at improving lubrication throughout the body, including the ocular surface. Omega 7 helps **cells retain moisture** in the mucous membranes and so helps reduce redness, discomfort, and inflammation in dry eyes⁴¹

Vitamin D3

It's becoming common knowledge that vitamin D is important for far more than bone health. New research from the Institute of Ophthalmology at University College London revealed striking eye benefits from vitamin D3 supplementation in older mice, specifically after receiving the supplement for just six weeks.

Improvements included:

- Improved vision
- Reductions in retinal inflammation and levels of amyloid beta accumulation, which is a hallmark sign of aging,
- Significant reductions in retinal macrophage numbers and marked shifts in their morphology (macrophages are immune cells that can cause inflammatory damage).⁴²

The role of Olive oil

It is conceivable that in particular studies supplements do not measure up to their fish intake comparisons due to their absorption inside the body. When we eat fresh fish we get omega-3 along with a whole host of other compounds, many of which offer protection to the delicate nature of omega 3.

Eye Nutrients are aware of this and use natural cold pressed Olive oil as an antioxidant component to stabilise the Omega 3 and stop rancidity.

It is the olive oil lipophilic polyphenols that protect the omega-3 in the bottle and in the body. Olive oil is the same placebo used in the DREAM study.

Some of the compounds found in olive oil are potent anti-inflammatory and antioxidant agents.⁴³ As a supplement Olive oil has very high bioavailability and can help to ensure that there is no pro-oxidant effect from taking an essentially antioxidant supplement like Omega 3 fish oil.⁴⁴

Eye Nutrients combines cold pressed natural Olive oil & quality Fish oil compounds to make a stable more effective natural omega-3 supplement for ocular health.



Understanding Oxidative Stability & Rancidity of fish oil & Omega quality?

Some manufacturers will use farmed fish, however Eye Nutrient use deep sea Icelandic wild fish. Our quality fish oil contains naturally higher levels of the long chain fatty acids EPA, DHA, and DPA. Poorly sourced fish will have corresponding lower levels of EFA's.⁴⁵

⁴⁰ Solà Marsiñach M, Cuenca AP. The impact of sea buckthorn oil fatty acids on human health. *Lipids Health Dis*. 2019;18(1):145. Published 2019 Jun 22. doi:10.1186/s12944-019-1065-9

⁴¹ Oral Sea Buckthorn Oil Attenuates Tear Film Osmolarity and Symptoms in Individuals with Dry Eye. Larmo et al, June 16, 2010. *The Journal of Nutrition*

⁴² Vitamin D rejuvenates ageing eyes by reducing inflammation, clearing amyloid beta, and improving visual function.

Neurobiology of Aging 2011.12.002. V Lee, E Rekhi, JH Kam, G Jeffrey.

⁴³ Bogani P, Galli C, Villa M, et al. Postprandial anti-inflammatory, and antioxidant effects of extra virgin olive oil. *Atherosclerosis* 2007 Jan 1;190(1):181-6

⁴⁴ Clayton PR, Ladi S. From alga to omega; have we reached peak (fish) oil? *J R Soc Med* 2015 Sep;108(9):351-7

⁴⁵ Jairoun AA, Shahwan M, Zyoud SH. Fish oil supplements, oxidative status, and compliance behaviour: Regulatory

Omega 3 is a polyunsaturated fat, a very unstable oil.⁴⁶ This means the starting ingredients of fish oil supplements are paramount to **stability** in the end product, as marine Omega-3 rich oils are highly prone to **oxidation** to lipid peroxides and other secondary oxidation products, it is further susceptible to rancidity.

Oxidized oils may have altered biological activity making them **ineffective or even harmful**. To date, human clinical trials have not reported the oxidative status of the fish oil. This makes it impossible to understand the importance of oxidation to efficacy or harm. The effects of ingesting rancid fish oil are unknown; however, animal studies show that oxidized lipid products can cause harm.⁴⁷

A study highlighted some of the problems with omega-3 supplements where the researcher analysed 45 commercially available products and tested the levels of EPA and DHA along with some of the biomarkers associated with rancidity. More than half of the products contained less than 89% of the stated dose of EPA and DHA on the label and the majority tested positive for the early signs of rancidity.⁴⁸ Increasing the number of manufacturing processes introduces more opportunity for oxidation to occur and therefore, decreases the stability of many Omega 3 fish oil supplements. Most Omega 3 products are

supplied in the ethyl ester form (processed). Some contain Omega-3s in the rTG or re-esterified Triglyceride form (very processed). The most natural and most stable form of Omega fish oil is the natural tri-glyceride form.

AREDS II & DREAM trial controversy?

There has been debate surrounding the use of omega 3 supplements for eye health, along with their use in dry eye. As with most research (especially nutritional research), there are conflicting views. There have been many studies showing benefits from Omega 3 for dry eye⁴⁹ and epidemiological data suggesting its protective role in the pathogenesis of macular degeneration.⁵⁰

There have also been key papers that have found no such benefit, including some (**AREDS & AREDS II**) for AMD and a recent dry eye study (the Dry Eye Assessment and Management (**DREAM**) study), both of which found that there was no benefit over a placebo.

AREDS

The original AREDS study provided clinicians with the evidence they needed to promote several key nutrients to help slow the progression from intermediate to advanced AMD. This included beta-carotene, zinc, vitamin C, and vitamin E.

challenges and opportunities. PLoS One. 2020;15(12):e0244688. Published 2020 Dec 31. doi:10.1371/journal.pone.0244688

⁴⁶ Stephen NM, Shakila RJ, Jeyasekaran G, et al. Effect of different types of heat processing on chemical changes in tuna. *J Food Sci Technol* 2010 Mar 1;47(2):174-81

⁴⁷ Oxidation of Marine Omega-3 Supplements and Human Health. *BioMed Research International Review Article. Volume 2013 (2013) Albert et al.*

⁴⁸ Albert BB, Derraik JG, Cameron-Smith D, et al. Fish oil supplements in New Zealand are highly oxidised and do not meet label content of n-3 PUFA. *Sci Rep* 2015 Jan 21;5:7928

⁴⁹ Deinema LA, Vingrys AJ, Wong CY, et al. A randomized, double-masked, placebo-controlled clinical trial of two forms of omega-3 supplements for treating dry eye disease. *Ophthalmol* 2017 Jan 1;124(1):43-52

1 Epitropoulos AT, Donnenfeld ED, Shah ZA, et al. Effect of oral re-esterified omega-3 nutritional supplementation on dry eyes. *Cornea* 2016 Sep;35(9):1185

2 Faulkner WJ. The role of omega-3 essential fatty acids in dry eye disease. *Int J Clin Exp Ophthalmol* 2017 Dec 22;1:055-9

3 Giannaccare G, Pellegrini M, Sebastiani S, et al. Efficacy of omega-3 fatty acid supplementation for treatment of dry eye disease: a meta-analysis of randomized clinical trials. *Cornea* 2019 May 1;38(5):565-73

4 Molina-Leyva I, Molina-Leyva A, Bueno-Cavanillas A. Efficacy of nutritional supplementation with omega-3 and omega-6 fatty acids in dry eye syndrome: a systematic review of randomized clinical trials. *Acta Ophthalmol* 2017 Dec;95(8):e677-85

5 ⁵⁰ Wu J, Cho E, Giovannucci EL, et al. Dietary intakes of eicosapentaenoic acid and docosahexaenoic acid and risk of age-related macular degeneration. *Ophthalmol* 2017 May 1;124(5):634-43

6 Merle BM, Colijn JM, Coughard-Grégoire A, et al. Mediterranean diet and incidence of advanced age-related macular degeneration: The EYE-RISK Consortium. *Ophthalmol* 2019 Mar 1;126(3):381-90

7 Kang KT, Kim YC. Dietary Patterns and Age-Related Macular Degeneration in Korea: The Korea National Health and Nutrition Examination Survey 2010–2011. *Scien Rep* 2019 Jun 3;9(1):1-0

8 Montserrat-de-la Paz S, Naranjo MC, Bermúdez B, et al. Dietary fatty acids and lipoproteins on progression of age-related macular degeneration. *Grasas Y Aceites* 2017 Jun 5;68(2):187

9 van Leeuwen EM, Emri E, Merle BM, et al. A new perspective on lipid research in age-related macular degeneration. *Prog Ret Eye Res* 2018 Nov 1;67:56-86

The follow up paper, AREDS II, adjusted this formula, removing beta-carotene due to safety concerns of undue enhanced threat of lung cancer in smokers, and the addition of two ingredients creating additional benefit, lutein and zeaxanthin. One of the formulas that was tested in the AREDS II contained omega-3 and at the end of the study the authors concluded that this provided no additional benefit when added to the formula.⁵¹

There have been many criticisms of the study design, such as the use of multi-vitamins from participants before the study commenced and the higher levels of healthy nutrition (including Omega 3) pre-study from the health-conscious volunteers.⁵² If the participants already had high enough levels of Omega-3, we would see minor benefit adding more.⁵³

Post study analysis found that those who had higher levels of EPA and DHA to begin with had a lower chance of developing advanced AMD.⁵⁴ EPA and DHA, two long chain essential fatty acids, are suspected to be key to the long-term protection of the macula.

One of the roles that Omega 3 plays here is to reduce the damage caused from ultraviolet light and oxidative stress.⁵⁵ With a protective effect being found in those with higher levels pre-AREDS and the epidemiological data on fish intake.

DREAM

The DREAM trial⁵⁶, was one of the first dry eye papers that looked at Omega 3 over a comparatively long period (more than one year). The conclusion of this study was that there was no benefit from omega-3 over the placebo (olive oil) in relieving the symptoms of

dry eye disease. This has caused controversy because there was a sizeable improvement in symptoms found in both the placebo group and the treatment group from baseline.⁵⁷ Olive oil has many nutritional benefits and in fact contains Omega 7, which as discussed above, is an anti-inflammatory which can help maintain moisture in the mucous membranes, and so helps reduce the symptoms of dry eye. Olive oil should not have been used as a 'placebo'.

Olive oil is one of the components that is thought to be responsible for health promoting effects of the Mediterranean diet. Not only is this diet considered to be one of the healthiest in the world, it is also associated with good eye health. One observational study graded the level of Mediterranean foods (MDS) and correlated this data with AMD prevalence and found that those with the highest MDS scores had 50% less chance of developing neovascular AMD than those with the lowest scores.⁵⁸

Secondly, for this trial, the study participants were given ultra-concentrated Omega supplements. Most Omega 3 supplements are concentrated, i.e., esterified, or re-esterified triglyceride. As already discussed, increasing the number of manufacturing processes has a detrimental effect on the stability of fish oil and so a highly concentrated and therefore highly processed Omega 3 fish oil supplement may deleteriously impact its efficacy in dry eye disease management.

It must also be noted that both the supplement group and the placebo group had an improvement in the group's mean OSDI (Ocular Surface Disease Index) score (-13.9 points and -12.5 points respectively)⁵⁹ and it is

⁵¹ National Eye Institute, *Age-related eye disease studies (AREDS/AREDS2)* [Accessed 16/06/21]

⁵² Study TA, Group R, Papudesu C, et al. *Association of Mortality with Ocular Diseases and Visual Impairment in the Age-Related Eye Disease Study 2: Age-Related Eye Disease Study 2 Report Number 13*. *Ophthalmol* 2018 Apr 1;125(4):512-21

⁵³ Myles IA. *Fast food fever: reviewing the impacts of the Western diet on immunity*. *Nutr J* 2014 Dec;13(1):61

⁵⁴ SanGiovanni JP, Agrón E, Meleth AD, et al. *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 Dec 1;90(6):1601-7

⁵⁵ National Eye Institute, *Omega-3s from fish oil supplements no better than placebo for dry eye* [Accessed 16/06/21]

⁵⁶ The Dry Eye Assessment and Management Study Research Group. *Omega-3 fatty acid supplementation for treatment of dry eye disease*. *N Engl J Med*. Published online April 13, 2018.

⁵⁷ McDonald MB, Sheha H, Tighe S, et al. *Treatment outcomes in the dry eye amniotic membrane (DREAM) study*. *Clinical ophthalmology (Auckland, NZ)*. 2018;12:677

⁵⁸ Hogg RE, Woodside JV, McGrath A, et al. *Mediterranean diet score and its association with age-related macular degeneration: the European Eye Study*. *Ophthalmol* 2017 Jan 1;124(1):82-9

⁵⁹ McDonald MB, Sheha H, Tighe S, et al. *Treatment outcomes*

this difference between the two groups that was not statistically significant.

Importantly, the participants were free to use any combination of dry eye drops during the study which could also have influenced the results⁷.

While omega-3 was found to only have a marginally better result than the placebo, the placebo itself was also effective and this is no surprise considering its inflammation-resolving properties.

Therefore the DREAM study should be deemed more of a 'comparison study' between the two active interventions rather than a true placebo-controlled trial.

Conclusion AREDS

Epidemiological data has shown that a diet rich in an oily fish (which is a great source of Omega 3) is protective for eye health. While it could be that other components in the fish also offer protection, we know that omega-3 is an anti-inflammatory, and excess inflammation is linked to a variety of eye conditions, including AMD.

Disease associated with ageing often takes decades to develop and because of this, they are incredibly difficult to study in a controlled manner. Outside of animal models we are left with observation and data, which supports a diet rich in Omega 3.

Dry eye disease is much easier to study than AMD because of the time frame, and there are papers that have reported a benefit from supplementary omegas.

Conclusion DREAM

The DREAM conclusions suggested it does not perform any better than a placebo, but this is unreasonable:

- Considering the participants all continued with other treatments
- The choice of placebo, olive oil, a known anti-inflammatory ingredient.

- There was a huge improvement in OSDI scores in both the olive oil and omega supplementation, so it's hard to say what single component was responsible for this improvement.

Perhaps one of the key takeaways from this study was that other anti-inflammatory oils, including olive oil, are also beneficial for dry eye, and not only Omega 3.



Discussion

It is widely accepted that the best way of achieving balanced nutrition is through a balanced diet and in the case of obtaining essential fatty acids, such as Omega 3, this would be to incorporate regular portions of oily fish in the diet. The reality is that for most dry eye patients with modern busy lifestyles, who are already ingesting too much pro-inflammatory Omega 6, this means taking Omega 3 supplements in order to try to rebalance their intake to be nearer the 2:1 ratio.

However, the source and production of the supplement is particularly important in its ultimate effectiveness. Broadly speaking the closer to the natural tri-glyceride form (as found in fresh fish) the Omega 3 is, the more stable it is and the higher its nutritional content.

When discussing a dry eye product with patients it is reasonable to question the many varying qualities of different omega-3 supplements that can be bought from the supermarket, often at very low prices and of unknown quality.

in the dry eye amniotic membrane (DREAM) study. Clinical ophthalmology (Auckland, NZ). 2018;12:677

Many have wondered about the fishy smell given off by fish oils (and/or been put off taking them) given the fact that fresh fish has no odor, it only starts to smell as it degrades with aging. Similarly, fish oil supplements should be odourless. The odour often noticed is due to de-stabilized supplements degrading through oxidation, due either to over-processing during its manufacture or exposure of the product to the air and light post-manufacture.

Eye Nutrients Dry Omega is an example of a natural, stabilized, tri-glyceride Omega 3 Dry Eye supplement.

Eye Nutrients uses a unique process, blending high quality naturally sourced omega oils (triglycerides) with the natural antioxidants contained in olive oil. These **natural antioxidants** have a significantly greater effect on **maintaining the stability of the Omega 3** molecules and also impart additional benefits to health. This unique blend, Dry Omega, is available in both fish gelatine capsules and a bottled liquid form.



Conclusion

There are many nutritional Omega 3 supplements available to purchase through opticians, pharmacies, retailers and online. However, they are not equitable. The most effective and safest forms of Omega 3 are the natural tri-glyceride form, which is the least processed and most stable. Using a blend of specific oils is also more beneficial than one single oil.

Eye Nutrients' use of our unique process provides an assurance of quality. The products have been specifically designed for dry eye, to support clinicians in their management of dry eye disease. We encourage routine follow up following recommendation of Eye Nutrients to patients as part of their treatment regimen, enabling observation of patient-reported symptomatic relief and resolution of clinical signs.

Dry eye disease is a multifactorial disease, with differing levels of severity and symptoms. Treatment regimens should address the multifactorial nature and differing patient requirements.

It is not enough simply to provide artificial tears, a clinician must assess the patient's ocular surface and determine if improved nutrition, involving Omega 3 supplementation, should be used as part of a complete treatment regime.

In Dry Eye Disease, the advantages of essential fatty acids are threefold:

1. Restoration of the lipid layer,
2. Decreased inflammation and apoptosis,
3. Increased tear secretion⁶¹.

⁶¹ Essential fatty acids for dry eye: A review. Marco Roncone, Hannah Bartlett, Frank Eperjesi. *Contact Lens & Anterior Eye* 33 (2010) 49–54