Nutrition and Dry Eye
THE ROLE OF
Lipids

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Dry eye is among the most frequent complaints in a general ophthalmic practice. Approximately one in every four patients reports symptoms of dry eye[1] severe enough to reduce the sufferer's work capacity and quality of life. It is estimated that over 10 million Americans suffer from dry eye syndrome.[2]

Keratoconjunctivitis sicca was first described by the Swedish ophthalmologist Henrik S.C. Sjögren in his thesis of the 1933 as the triad that now bears his name: dry eye, dry mouth, and joint pain. Sjögren's analysis related dry eye to a reduction in the quantity of aqueous tears. We now define dry eye disease based on the understanding that the tear film has three layers: lipid, aqueous and mucin.[3] (Table 1) In addition, it has been proposed that the ocular surface epithelium and the eyelids be considered as the first and fifth layers of the tear film unit, respectively.[3] In dry eye, one or more layers can be affected, causing qualitative and quantitative changes to the tear film and ocular surface. In 1995, the National Eye Institute's Industry Workshop on Clinical Trials for Dry Eyes stratified patients with dry eye into two groups – those with abnormal tear production and those with increased evaporative loss and/or poor distribution of the tear film.[4] Other factors such as influences from sensory nerves on tear film production and surface epithelium trophism also result in dry eye disease.[5-8] For example, dry eye is the most common postoperative complication after LASIK which severs corneal nerves during flap creation.[9] Typically this condition, known as LASIK-induced neurotrophic epitheliopathy (LNE),[5-7] resolves several months after surgery, when the cornea has reinnervated. LASIK also affects ocular surface and tear dynamics, which alter tear production, stability, and clearance, and aggravates dry eye symptoms.[10,11]

Evidence is increasing that dry eye disease is accompanied by varying degrees of ocular surface inflammation, which may contribute to dry eye symptoms. Dry eye also leads to immune-inflammatory responses that aggravate the condition, creating a vicious cycle. For example, proinflammatory cytokines such as interleukin 1 (IL-1) are up-regulated in the tear fluid of patients with dry eye cause by either meibomian gland dysfunction (MGD) or Sjögren's syndrome.[12] Consequently, anti-inflammatory therapies (glucocorticosteroids and cyclosporine A) have a positive effect in treating the signs and symptoms of dry eye.

Dry eye syndrome is a complex and

Table 1. Tear Film Layers

Lipid layer -- outer layer, reduces evaporation, lubricates and waterproofs the lid margins; produced by the meibomian glands and the glands of Moll and Zeis.

Aqueous layer -- thickest layer contains lysozyme, lactoferrin, immunoglobulin, and inorganic salt; produced by the main lacrimal gland (reflex) and accessory lacrimal glands of Krause and Wolfring (basal).

Mucin layer -- contacts the microvilli of the epithelium, reduces surface tension, and allows the aqueous layer to adhere; produced by conjunctival goblet cells.

multifactorial condition. There are many presentations with different types of complaints. Typically patients report foreign body sensation, eye fatigue, fluctuation of vision, pain blurring, burning, redness, inability to form emotional tears, and, paradoxically, epiphora. It is also common to find a major disconnect between the patients' subjective complaints and the clinical findings. Clinical tests are disappointing and not very helpful in most cases. Additionally, as for any medical condition for which no definitive cure has been found, there is a vast array of therapies. Thus, despite progress in understanding tear film composition, production and ocular surface pathophysiology, the common problem of dry eye continues to plague our patients.

Table 2: Physiological Effects of 20 and 22 Carbon Omega-3 Fatty Acids 12-16

Target System	Effect	Likely Mechanism
Central Nervous System (CNS)	Improves cognitive function	Membrane composition; control of apoptosis; Neurotransmission
Immune	Immunosuppressive Anti-Inflammatory	Membrane composition; Eicosanoid synthesis; Cytokine production
Cardiovascular	Anti-arrhythmia Anti-thrombotic	Membrane composition; Intracellular signaling Decrease platelet adhesion
Liver and Systemic Lipids	Lowers triglycerides Suppresses lipogenesis Increases fatty acid oxidation Suppresses VLDL production	Intra- and intercellular signaling
Skeletal Muscle	Increases insulin sensitivity	Membrane composition; intercellular signaling

Interestingly, most dry eye patients also have other systemic problems. A recent questionnaire-based survey in a dry eye population revealed acne rosacea to be the most common. It was present in about three or four patients, along with other dermatologic conditions: eczema, chronic rash, and psoriasis.[13] Some patients had several other systemic conditions such as cardiovascular disease, allergies, chronic inflammatory conditions, gastronintestinal problems, obesity, hyperlipidemia, and psychiatric disorders. These patients were also taking medications for their specific problems. Dry mucosa was a common associated finding. Particularly in postmenopausal women. In addition, studies have demonstrated that estrogen replacement therapy without progesterone increases the risk of developing dry eye disease, possibly by affecting meibomian secretion.[14]

Several clinical studies demonstrated significant benefits of omega-3 essential fatty acids (n-3 EFA) supplementation in several systems.[15,16] (Table 2) Boerner first reported anecdotal information that n-3 EFA supplementation in the form of flaxseed oil improves 85% of dry eye patients' symptoms after two months.[17] In addition, we recently reported a preliminary, uncontrolled patient survey performed in two centers with similar results. Thus, we can hypothesize that a relative deficiency in n-3 essential fatty acids is a common factor that links several cases of dry eye to different systemic conditions. In this article, we discuss some basic aspects of essential fatty acid biochemistry and metabolism that we found important in explaining the mechanisms of action of n-3 EFA.[18]

Essential fatty acids: Biochemical background

Animal cells synthesize saturated fatty acids *de novo* from acetyl coenzyme A. Palmitic acid (16:0-16 carbon chain with no double bonds) is the end product of the fatty acids synthesis and can be enzymatically elongated to stearic acid (18:0). However, these same cells require unsaturated fatty acids for normal function16,19,20 Some organisms have specific enzymes to introduce the double bonds between carbon atoms, causing desaturation of hydrogen in the fatty acid molecule, but animal cells have limited capability for that process. Animal cells have the enzyme D^{9} desaturase, which converts stearic acid (18:0) into oleic acid (18:1n-9-18 carbon chain with 1 double bond located at omega-9 position,), introducing a double bond between the carbon atoms 9 and 10, although animal cells are unable to introduce a double bond beyond the ninth position from the methyl terminus. In other words, animal cells cannot synthesize omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFA). Therefore, these PUFA are called essential fatty acids (EFA) and are a dietary requirement for all animals – including humans.

Flora, fauna

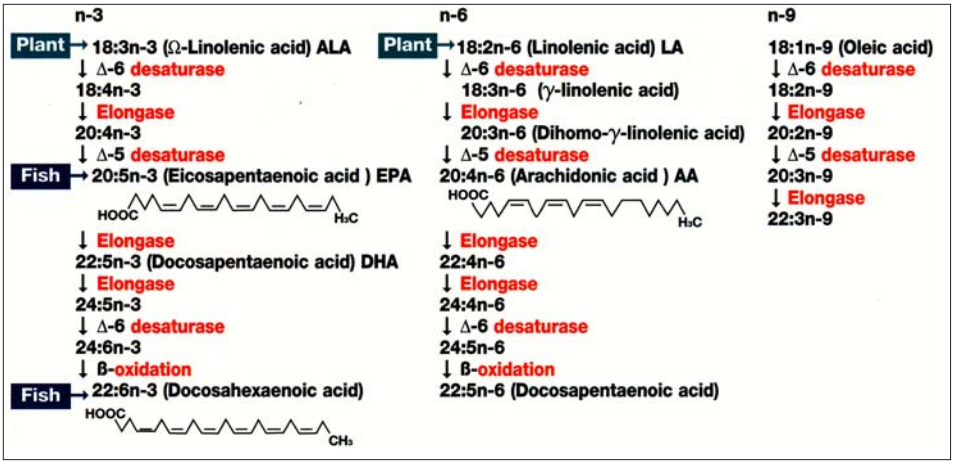
Plants, unlike animals, have the enzymatic capability to convert oleic acid (18:1n-9) to linoleic acid (LA-omega-6;18:2n-6) by D^{12} desaturase and additionally to alpha-linolenic acid (ALA-omega3;18:3n-3) by D^{15} desaturase. (Figure 1) Fish (especially cold water fish, such as salmon, mackerel, and sardines) have cells rich in unsaturated oils. Fish n-3 oils, however, differ from vegetable oils – fish oils are 20 and 22 carbon molecules (eicosapentaenoic [EPA] and docosahexaenoic [DHA]). It is not clear whether these oils result from fish's metabolism or dietary intake.

Human dietary need

Despite lacking the enzymatic ability to produce PUFA, the human body can metabolize them and produce derivatives which maintain cellular structure, fluidity, and function. Enzymes are normally present to convert ALA to EPA and DHA. Linoleic acids is converted to arachidonic acid (20:4n-6), which cascades into the chemistry of inflammation and immunologic responses.

Nutritionists have estimated that the ratio of n-3 to n-6in the American diet in the late 1700s was 1:1 and that an optimal diet might have a ratio of 1:6. The current American diet, however, has an estimated typical ratio of 1:20 to 25. The great excess of n-6 EFA results from the popularity of oils from soy, corn, safflower, peanut, and sunflower. Most n-3 oils come from leafy green vegetables, flaxseed, pine nuts, walnuts, canola, and cold water fish.

Flaxseed (*Linum usitatissimum*) is the richest source of plan-based n-3 fatty



Courtesy Sadiqa K. Stelzner, MD, and Renato Ambrósio Jr, MD

Figure 1. Elongation and desaturation of n-3, n-6, and n-9 fatty acids.

acid. It is also rich in dietary fiber known as lignan.15 Historically, flaxseed was a major dietary staple before the Industrial Revolution, but it was nearly eliminated from modern-day diet because of its limited shelf life. To decrease oxidative degradation of fatty acids and extend the shelf life of cooking oils, hydrogenated (solid fats) or trans-fatty acids were developed. The popularization of solid cooking fats along with food processing methods and fast foods has resulted in a major decrease of n-3, soluble fiber, antioxidants, and minerals in the American diet. The thinking is that this could have an impact on the incidence several diseases including cardiovascular disease, hypercholesterolemia, diabetecs, mental health problems, allergies, arthritis, dermatological problems, and cancer-not to mention dry eye.

Physiologic effects of omega-3 EFA

Several physiologic effects of omega-3 EFA have been described. For example, n-3 fatty acids are essential for normal neonatal development of the eye and brain and are highly concentrated in breast milk.[16] In the central nervous system, a deficiency of n-3 EFA can cause accelerated neuronal programmed cell death or apoptosis,[15] a process though to result in memory loss, diminished cognitive function, depression, and bipolar disease.[16,19]

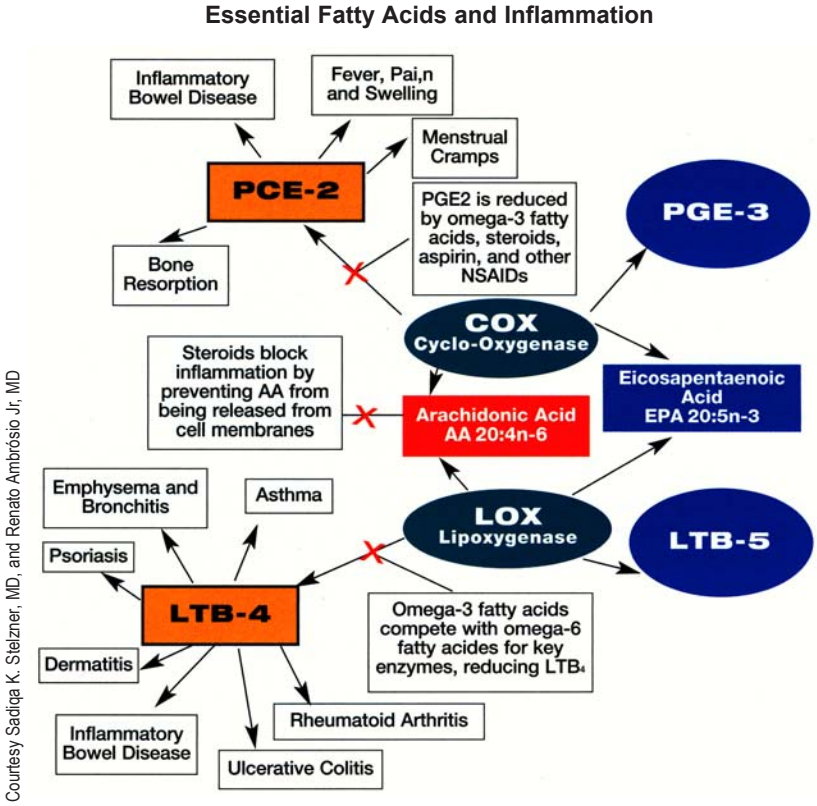
Immune reactions/ Inflammation

Omega-3 and omega-6 EFA derivatives include proinflammatory and immunoregulatory molecules, such as leukotrienes, prostaglandins, thromboxane, and prostacyclin.[16,20,21] This also has an impact on the production of cytokines, such as interleukins (IL) and tumor necrosis factor (TNF). Generally, metabolites derived from n-3 fatty metabolism are less effective for inciting and keeping inflammation and/or immune reactions, For example, PGE3 and LTB5 (resulting from n-3 EFA (eicosapentaenoic acid) metabolism) are less effective in promoting inflammation than the derivates from arachidonic acid an n-6 EFA. Thus, since the same enzymes metabolize n-3 and n-6 fatty acids, there is a competitive inhibitory effect of n-3 fatty acids on the inflammatory cascade.(Figure 2)

The term "noninflammatory diet" refers to a diet rich in omega-3 EFA.[22] In studies performed on murine peritoneal macrophages, various low-fat and n-6 rich diets increased the production of PDGE2,IL-1,IL-6, and TNF alpha, while fish oil (rich in n-3 EFA) lowered the levels of all of these cytokines.20 In addition, other studies demonstrated the modulating effects of n-3 EFA on immune cell function, proliferation, and interactions.[16,20] Interestingly, populations that consume large quantities of n-3 EFA have a very low incidence of inflammatory and autoimmune disorders, suggesting that these fatty acids might promote immunoregulatory and anti-inflammatory activities.[16,20,21]

Possible ways that omega-3 EFA can help dry eye

There are several possible ways in which n-3 fatty acids could improve dry eye symptoms. (Table 3)



Courtesy Sadiqa K. Stelzner, MD, and Renato Ambrósio Jr, MD

Figure 2. Summary of general effects of EFA in cytokine production.

Table 3: Possible Effects of Omega-3 EFA on Dry Eye

- Provide overall anti-inflammatory effect
- Increase fluidity of meiboman gland secretions
- Improve tear film quality and decrease evaporative loss
- Optimize function of goblet cells
- Improve epithelial cells microvilli expression and adhesion

Inflammation

Dry eye is accompanied by an inflammatory condition on the ocular surface.[12] Steroids and cyclosporine A have shown some success in treatment of dry eye.[23] As described, n-3 EFA has a competitive inhibitory effect on the arachidonic acid (n-6 derivate) inflammatory cascade and a modulator effect on immune cells.[20,21] This inflammation-preventing effect may, in part, explain the n-3 benefit to some patients with dry eye.

Epithelium

Omega-3 EFA supplementation has a positive impact in cell membrane structure. This could positively impact epithelium microvilli expression, which helps to stabilize the tear film. In addition, it may improve epithelium adhesion. Resolution of the symptoms related to the recurrent erosions was also observed in some patients using flaxseed oil supplementation. (Stelzner SK, Ambrósio Jr. R, McIntyre DJ, unpublished data, 2001)

Tear film quality: oil layer and mucin

Omega-3 EFA supplementation can improve meibomian gland secretion by increasing its fluidity, thereby unplugging the gland orifices. Recently, Sullivan and coworkers demonstrated that increased intake of an n-3 EFA (along with pyridoxine) improved the profile of the polar lipid fraction of meibomian secretions in patients with dry eye.[24] Improving the lipid fraction of the tear film decreases evaporative loss. Omega-3 EFA supplementation also improves dermatologic symptoms of acne rosacea.[15,17]

Other possible mechanisms include improvement in goblet cell production of mucin, which would improve tear film distribution. This could be related to the anti-inflammatory effects of n-3 EFA diet.

Clinical perspective

It is very important to note that, to date, there are only anecdotal clinical reports of the benefits of n-3 fatty acid supplementation for patients with dry eye.[17,22] Formal prospective clinical studies are necessary to determine the usefulness of omega-3 supplementation in treating dry eye and also to point out the differences between ALA (flaxseed oil) and EPA (fish oil). For example, some patients may have a better response to fish ail and EPA or DHA byproducts than to flaxseed oil because of variations in individual metabolism. Ideal dosage, side effects and limitations also require further studies. Basic science studies are needed to explore how n-3 EFA affects dry eye. In addition, combination with other nutrients such as vitamin A, calcium, and antioxidants such as vitamins C and E may be beneficial and requires further investigation.

More studies needed

Dry eye and its various associated medical conditions frustrate a large percentage of ophthalmic patients. Recent anecdotal clinical data strongly suggests a benefit from n-3 EFA dietary supplementation. The current biochemical knowledge of EFA metabolism appears to explain the mechanism of effect. Based on this information and our personal experience, we propose that while prospective studies are ongoing, patients with dry eye syndrome should be considered for therapeutic trial of n-3 EFA dietary supplementation.

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