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Current Opinion in Ophthalmology Nutritional Supplements for Dry Eye Syndrome

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Abstract

Purpose of Review—Essential Fatty Acids have been of interest in the treatment of systemic and ocular diseases, and is most recently of interest in the area of dry eye disease.

Recent Findings—Systemic and Topical Omega – 3 Fatty Acids and Omega – 6 Fatty Acids have been used recently as an adjunctive treatment for patients with dry eye disease. They appear to have efficacy against the symptoms of dry eye that many patients experience. This is postulated to secondary to the anti-inflammatory effects that have been previously described. While this effect is promising, more investigation is warranted in order to standardize indication for use, and composition and dosing for treatment.

Summary—The use of essential fatty acids as a nutritional supplement is a novel treatment for patients with dry eye syndrome.

Keywords

Dry Eye Disease; Omega – 3 Essential Fatty Acids; Omega – 6 Essential Fatty Acids; Cornea

INTRODUCTION

Patients with dry eye disease (DED) suffer from chronic ocular discomfort and variable visual disturbances. It is quite common for these symptoms to be insufficiently treated, even with the most current therapeutics and techniques in management. It will be a great benefit to many patients to find novel ways in which to alleviate these symptoms to achieve improvements in quality of life. Recently, there has been a great amount of interest generated in the arena of using essential fatty acids (EFAs) as an adjunct in the treatment of dry eye disease. In other diseases, EFAs have been shown to play a role in inflammatory processes leading to the pathologic changes that are observed, such as atherosclerotic heart disease. Since many hypothesize that the etiology of dry eye is often, by nature, inflammatory, novel methods of modifying inflammation with EFAs may prove helpful to

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patients with dry eye disease. A Limited number of studies on both topical and systemic treatments of EFAs for dry eye disease (DED) have evaluated their ability to modify manifestations of disease.

CHARACTERISTICS and METABOLISM OF ESSENTIAL FATTY ACIDS

Dietary fats are an essential part of normal human biological function and are unable to be synthesized without proper dietary intake. These fats may be classified as saturated or unsaturated. Saturated fats have no double bonds, while unsaturated fats possess at least one double bond attached to the carbon chain. Unsaturated fats may be monounsaturated or polyunsaturated, correlating with the number of double bonds that are present in the carbon chain of the fat. EFAs are polyunsaturated fats[1], which are termed “essential” and necessary for human survival..[2,3,4]

Omega – 3 and Omega – 6 EFAs are the precursors of eicosanoids, which are locally acting hormones that mediate the inflammatory processes. The four main groups of eicosanoids are prostaglandins, prostacyclins, thromboxanes, and leukotrienes. These molecules act locally and do not usually act in a remote area of the body.[1] Most research has focused on the use of Omega – 3 EFAs as anti-inflammatory mediators of disease, as well as having a tendency to be anticoagulatory in natureOmega – 3 molecules are also key promoters of the resolution of inflammation and causing a return of tissues to their previous state. One such group of molecules are the resolvins, EFAs that are present in the liver, lung, and eye[5]. These resolvins may be beneficial in the modification of pain symptoms. [6] In a mouse model, resolvins have been shown to reduce behaviors associated with inflammatory pain. [7] In a state of inflammation, these molecules may help to determine the time period and enormity of the inflammatory process. [8] It has been shown that omega – 6 EFAs, contrastingly, promote inflammation and platelet aggregation. Previous ocular studies have focused on retinal disease, suggesting that omega-3 FAs may be protective against macular degeneration, especially in the setting of low omega-6 EFA consumption. [2-4,9-10]

Omega – 3 EFA’s include alpha linoleic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) [11-12]. They are found in cold water fish, including salmon, sardines, tuna, mackerel, and herring, [13-14] and flaxseed oil [15]. Tilefish, swordfish, and other large fish may also be good sources, but may also contain higher levels of methylmercury, dioxins, and polychlorinated biphenyls, which may be more toxic than beneficial. [16-18] Omega – 6 EFAs are pro-inflammatory and pro-aggregatory and include linoleic acid (LA), gamma-linoleic acid (GLA), dihomogamma-linoleic acid (DGLA), and arachidonic acid (AA). [11-12] Sources include soybean oil, palm oil, rapeseed oil, sunflower oil, poultry, nuts, and cereals [1]. LA and ALA are the shortest chain EFAs and are converted in the liver to more complex EFA molecules. [11] It is thought that early human beings consumed a diet with an omega-6 to omega-3 ratio of close to 1:1. Shockingly, the current Western diet comprises a ratio of 15-16:1, which is contrastingly pro inflammatory by previous definitions.[19] This might possibly represent a correlation with high rates of cardiovascular diseases, autoimmune diseases, and various forms of cancer that are seen in the Western population today. [20]

CLINICAL TRIALS - OMEGA 6 SUPPLEMENTATION

The use of EFA supplementation as a standard therapy for dry eye disease is still in its early stages, as more information is necessary to correlate treatment with specific modifications of dry eye disease. Oral omega – 6 EFA supplementation has been tested in three separate trials. Barabino et al completed a double-masked, randomized controlled trial to evaluate the effect of LA and GLA on chronic ocular inflammation from keratoconjunctivits sicca. It was found that in 26 patients with keratoconjunctivitis sicca, oral supplementation with a daily

dose of 57mg LA and 30mg GLA improved HLA-DR expression as measured by impression cytology, lissamine staining, and symptoms of dry eye. Changes in Schirmer testing and fluorescein break up time (FBUT) were not seen. [21]

Aragona et al evaluated the tear film of 40 patients with Sjogren Syndrome for PGE1, a downstream product of an anti-inflammatory ecoisanoid. Patients were randomized to receiving placebo versus omega – 6 EFAs (224mg LA and 30mg GLA). Significant increases in PGE1 were seen over one month in the patients who received the omega −6 EFAs as compared to placebo. Levels declined to baseline levels when measured 15 days after cessation of therapy. A correlation was found in patient symptoms, which were most improved during therapy and worsened after cessation. Corneal fluorescein staining remained improved even after treatment was stopped. There was no measureable difference in FBUT or basal secretion. [22]

Kokke et al investigated omega – 6 supplementation in 76 patients with contact-lens-related dry eye syndrome. The patients were evaluated at baseline, three months, and six months with a symptoms questionnaire, tear meniscus height, hyperemia of the eye, staining of the cornea and conjunctiva, tear break up time, and an assessment of the meibomian glands and lipid layer. Those who received 300mg daily of GLA noticed improvement in symptoms of dry eye, and tear meniscus height. All other parameters were not statistically significant.[23]

OMEGA – 3 SUPPLEMENTATION

Macsai et al used the Ocular Surface Disease Index (OSDI) to evaluate the effect of flax seed oil (3.3g of ALA per day) on patients with blepharitis and meibomian gland dysfunction as compared to administration of olive oil placebo in similar patients. Treated patients were given 1000mg of flaxseed oil per day, split up into three doses. This totals approximately 3.3 grams of ALA per day. Outcome measures were objective, including Schirmer's testing, tear break up time, corneal and conjunctival staining, and meibomian gland assessment. In addition, blood was collected at baseline, 3 months, 6 months, and one year. Supplemented subjects showed increased omega −3 fatty acids in blood levels, and a decrease in the blood ratio of n6:n3 EFAs. There was a decrease in saturated fatty acids in the meibum of the supplanted group. They also had a significant improvement in the OSDI as compared to olive oil placebo. In addition, there was an improvement for both treatment and placebo groups in tear break up time meibum score without a statistically significant difference between groups. [24]

OMEGA – 3 and OMEGA – 6 Combined Therapy

Creuzot et al evaluated 71 patients with mild to moderate dry eye for improvements in the symptoms of ocular dryness with daily combined omega-3 and omega-6 oral supplementation over a six month period with 392mg DHA, 28mg EPA, 82mg GLA, and 126mg LA. The patients were evaluated in this randomized, double masked, placebo-controlled study with outcome measures such as symptom questionnaires, Schirmer testing, tear break up time, and staining with vital dyes including Fluorescein and Lissamine green. They were followed at baseline, and 1,3, and 6 months. The treated group had improvement in Schirmer testing, fluorescein break up time, and lissamine staining, although not significantly. There was also a noted improvement in these patients' emotional condition with treatment. [25]

Garcher et al presented data at the 2009 Association for Research in Vision and Opthalmology (ARVO). 138 patients in a multicenter trial were randomized to treatment with a daily dose of 427.5mg EPA, 285mg DHA, and 15mg GLA. These patients were followed and evaluated at six weeks, and three months time. They were evaluated by

impression cytology which was analyzed via flow cytometry for the percentage of cells expressing HLA-DR, as well as the fluorescence intensity of cells expressing this marker. Treated patients had a decreased percentage of HLA-DR in conjunctival epithelial cells measured by flow cytometry, although no significant difference in objective signs or symptoms were found between groups. [26] A trend was noted for improvement in burning, dryness and stinging, as well as corneal staining, although this was not statistically significant.

ANIMAL MODELS

Rashid et al used topical drops of ALA and LA EFAs in different formulations in a mouse model in which dry eye was both pharmacologically and environmentally induced[27] One microliter of the formulations was given daily after induction of dry eye. Extracted corneas from the mice were analyzed via immunohistochemical staining for CD11b+ cells at the periphery and center of the cornea. The CD11b+ cells are antigen presenting cells derived from bone marrow, which acquire major histocompatibility complex (MHC) Class II when they are involved in an inflammatory process. Real time PCR was used to assess pro-inflammatory cytokines. The mice induced with dry eye had increased fluorescein staining, along with increased CD11b+ antigen presenting cells and MHC Class II expression, indicating inflammation. Pro imflammatory conjunctival cytokines such as IL-1alpha, TNF-alpha, interferon gamma, IL -2, IL-6, and IL-10 also had increased expression as measured by PCR. Treatment with topical ALA reduced CD11b+ cells, as well as pro-inflammatory cytokines such as corneal IL-1alpha, TNF-alpha, and conjunctival TNF-alpha compared to other formulations. This was a noted effect when compared to the other formulations tested, including untreated, vehicle treated, LA alone, and combination LA/ALA groups.

RECOMMENDED DOSING

Flaxseed oil is about 50% ALA, but upon metabolism, only 0.1-5% can be converted to a useful anti-inflammatory compound. [16-18] There is a slightly higher rate of conversion in women. [16] Therefore, to take advantage of the benefits of high omega – 3 to omega-6 ratios, supplementation with oral compounds has become favorable. Hundreds of FDA unregulated commercial EFA supplementation exist, making it very difficult to recommend a standardized formulation or dosage for patients. Typical omega – 3 fish oil preparations contain 300mg of EPA and DHA per 1000mg capsule [12]. Prescription omega-3-acids such as Lovaza®, which are FDA approved as treatment for hypertriglyceridemia, contain approximately 840mg EPA and DHA per 1000mg capsule.

There are no formal recommendations or FDA approved formulations for dietary consumption of EFAs in the treatment of eye disease, or the promotion of eye health [3,9,11,28]. From the cardiovascular point of view, the American Heart Association recommends two servings per week of fish high in omega – 3 EFAs. It might be that these recommendations carry similar ocular benefits. For example, Miljanovic et al assessed the diets of 32,470 women in the Women's Health Study, and found that women with higher omega-3 consumption had decreased risk of dry eye. Conversely, a high n -6:n-3 ratio was associated with a greater risk for dry eye. [29] This was a survey-based study, which warrants more investigation.

Currently, there are limited randomized controlled trials as described above, which evaluate the targeted effect of various combinations of EFAs in the treatment of dry eye disease. Those that do exist tend to be small studies and contain data recorded from a single site. More specified masked randomized controlled trials using EFAs, as well as standardized outcome measures would be beneficial in the future, in order to confidently recommend this treatment to patients. Macsai's article seems to be promising, but isolated omega – 3

systemic supplementation needs to be further investigated, since this would be the most logical extrapolation of cardiovascular and autoimmune research and recommendations. [24]

CONCLUSION

It is unclear how omega-6 EFAs which are thought to be otherwise pro-inflammatory seem to have a benefit in dry eye disease, but it will be enlightening to see the outcome measures of the use of different types of EFAs compared in a standardized fashion. There is the potential to modify ophthalmic preferred practice guidelines not unlike the AREDS study has done for macular degeneration in recent times. The limited studies to date suggest that a well designed masked multicenter randomized controlled trial of EFA would be welcome and may supply the needed evidence for use of EFA, specifically Omega 3, for use as a supplement to current therapies for DED.

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BULLET POINTS

1. To provide the reader with an overview of the structure and function of various essential fatty acids, along with their potential role in ocular disease.
2. To review the current literature involving essential fatty acids in the treatment of dry eye disease and other inflammatory conditions.
3. To cite the limitations of the current research to date, and highlight the potential areas which could benefit from further investigation.