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REVIEW

Omegas and Dry Eye: More Knowledge, More Questions

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ABSTRACT

The omega-3 (ω3) and omega-6 (ω6) essential fatty acid knowledge base has been exploding. In the last 5 years, at least 12 clinical trials on ω3 and ω6 supplementation and dry eye disease (DED) were published in the peer-reviewed literature (2010 to 2015), about double the amount published in the 5 years prior. Although there is increasing scientific evidence that supports the potential use of ω3 and ω6 supplementation for DED, there are limited randomized controlled trials to properly inform evidence-based medicine. Dry eye disease is one of the most common eye conditions that patients seek care for and cannot be disregarded as a trivial condition. The roles of ω3 and ω6 polyunsaturated fatty acids (PUFAs) in the treatment of DED are still not completely understood. There are distinct and sometimes opposite effects of ω3 and ω6 PUFAs, both of which are essential and cannot be synthesized *de novo* in the body. These fatty acids must be obtained from the diet, which varies widely by region, even within the United States. Omega-3 PUFAs have anti-inflammatory effects; a proper ratio of ω6:ω3 in the diet must be established. Objectively correlating changes in dry eye syndrome with blood levels of ω3 PUFAs has not been done in a large-scale multisite study. Just as Wilder's law of initial value states that ''the direction of response of a body function to any agent depends to a large degree on the initial level of that function,'' the baseline status needs to be taken into account. There is also no consensus on the dose, composition, length of treatment, and so on with ω3 or ω6 PUFAs. Increased quality evidence on the usefulness of over-the-counter supplements is needed to enable eye care providers to confidently outline specific treatment recommendations for using ω3 PUFAs in DED.
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Key Words: dry eye disease, omega-3, omega-6, polyunsaturated fatty acids, inflammation, anti-inflammatory, eicosanoids

In the past, using omega supplements for dry eye disease (DED) was controversial, largely because clinical studies were few and far between. The lack of evidence-based studies created a vacuum of information, which left many clinicians confused. Nonetheless, many patients as well as doctors believe that the supplements are effective. Awareness of the effects of omega-3 (ω3) and omega-6 (ω6) polyunsaturated fatty acids (PUFAs) has increased dramatically over the past few years. There has been recent interest in nutritional supplements as alternatives to pharmacological treatments.[1] The ω3/6 DED knowledge base has also exploded. Just in the last 5 years (2010 to 2015), at least 12 clinical trials were published in the peer-reviewed literature, about double the amount in the previous 5 years (2005 to 2009). These were preceded by less than a handful before 2005 (Table 1). As we become more knowledgeable, we also raise more questions. Before we look at what we still need to know, we will look at what we do know.

Dry eye disease is widely prevalent, increasing in incidence, and is a serious detriment to a patient's quality of life.[1] There is great need for the development of more effective DED treatments. Lots of attention has been paid to the use of ω3 and ω6 essential fatty acids (EFAs) for dry eye treatment. The rationale comes from the effectiveness of PUFAs for other chronic diseases and conditions. Because inflammation plays a prominent role in DED, it would seem natural to explore the use of ω3 and ω6 as a treatment.[22]

Background Information about PUFAs

The ω3 and ω6 PUFAs are derivatives of the EFAs alpha linolenic acid and linoleic acid, respectively. The ω3 PUFAs are the 18-carbon PUFAs. Both the ω3 and ω6 PUFAs are essential in the human diet because the body cannot synthesize them.[23] Once ingested, the ω3 and ω6 PUFAs are eventually desaturated and elongated to 20-carbon fatty acid, di-homo-linolenic acid (DGLA), and arachidonic acid (AA) (ω6 family), or eicosapentaenoic acid

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TABLE 1.
Summary of selected human interventional clinical trials

Author	Year	Sample size	No. sites	Study period	No. visits	Oral intervention
Oleñik[2]	2014	905	Unspecified	12 wk	2	ω3: 1050 mg DHA and 127.5 mg EPA, 90 mg DPA per day
Bhargava et al.[3]	2013	518	2	3 mo	4	ω3: 325 mg EPA, 175 mg DHA; bid
Oleñik[4]	2013	61	1	3 mo		ω3: 1050 mg DHA and 127.5 mg EPA, 90 mg DPA per day
Sheppard et al.[5]	2013	38	2	6 mo	4	ω3 and ω6 (GLA)
Kangari et al.[6]	2013	64	1	1 mo	2	ω3: 360 mg EPA and 240 mg DHA; 2 capsules per day
Pinazo-Durán et al.[7]	2013	66	1	3 mo	4	ω3: 700 mg DHA, 85 mg EPA per day
Jackson et al.[8]	2011	43	2	6 mo	4	ω3 and ω6: 1000 mg EFA and 500 mg GLA; 4 geltabs per day
Brignole-Baudouin et al.[9]	2011	106	9	3 mo	3	ω3 and ω6; 3 capsules per day
Creuzot-Garcher et al.[10]	2011	181	Unspecified	6 mo	Unspecified	ω3 and ω6; bid
Wojtowicz et al.[11]	2011	36	1	90 d	2	ω3: 450 mg of eicosapentaenoic acid, 300 mg of docosahexaenoic acid, and 1000 mg of flaxseed oil; qd
Cortina and Bazan[12]	2011	232	Unspecified	28 d	Unspecified	ω3: EPA and DHA derivatives
Larmo et al.[13]	2010	86	2	3 mo	3	ω3 and ω6: sea buckthorn oil; 2 g/d
Kokke et al.[14]	2008	76	Unspecified	6 mo	3	ω6: evening primrose oil (EPO)-omega-6
Macsai[15]	2008	38	1	1 y	5	ω3: 3.3 g/d (flaxseed oil)
Pinna et al.[16]	2007	57	1	180 d	3	ω6: linoleic acid (28.5 mg) and g-linolenic acid (15 mg); qd
Creuzot et al.[17]	2006	71	?	6 mo	4	ω3 and ω6; bid
Aragona et al.[18]	2005	40	1	1.5 mo	3	ω6: linoleic acid 112 mg, GLA 15 mg; bid
Miljanovich et al.[19]	2005	32,470 (1500 with dry eye)	Epidemiological			
Barabino et al.[20]	2003	26	1	45 d		ω6: linoleic acid 28.5 mg and GLA 15 mg; bid
Wu et al.[21]	1999	40	1	2 mo	2	Black currant seed oil (ω3 and ω6; 6 capsules per day

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TABLE 1.

(Continued)

Author	Control	Masked	Results	Notes
Oleñik[2]	None	Open label	Symptomatic improvement	
Bhargava et al.[3]	Placebo (corn oil)	Masked	Schirmer, TBUT, symptoms improvement vs. placebo	
Oleñik[4]	Placebo (sunflower oil)	Double masked	OSDI, TBUT, lid margin inflammation, MG expression, and Schirmer improvement vs. placebo	
Sheppard et al.[5]	Placebo (sunflower oil)	Double masked	OSDI, surface asymmetry index, HLA-DR and CD11 improvement vs. placebo	Postmenopausal women
Kangari et al.[6]	Placebo (medium-chain triglyceride oil)	Double masked	TBUT, OSDI, and Schirmer improvement vs. placebo	Aged 45–90 y
Pinazo-Durán et al.[7]	Normal subjects/healthy control subjects	Open label	Symptoms and IL-1β, IL-6, IL-10 lowered in both dry eye and normal subjects taking oral supplements vs. those not taking supplements	
Jackson et al.[8]	Oral supplement vs. supplement and cyclosporine bid last 3 mo of study	Open label	TBUT improved; addition of topical cyclosporine; no significant improvement in TBUT vs. supplement alone	
Brignole-Baudouin et al.[9]	Placebo (medium-chain triglycerides)	Double masked	Significant reduction in HLA-DR expression; signs and symptoms no difference vs. placebo	
Creuzot-Garcher et al.[10]	Placebo	Double masked	BUT and ocular fatigue improvement vs. placebo	
Wojtowicz et al.[11]	Placebo (wheat germ oil)	Double masked	Increased tear secretion (Schirmer and fluorophotometry) and symptomatic improvement vs. placebo	
Cortina and Bazan[12]	Placebo unspecified	Double masked	Final results not reported	Preliminary data showed dose-dependent and statistically significant improvements in DED
Larmo et al.[13]	Placebo (medium-chain triglycerides from coconut and palm kernels)	Double masked	Improved redness and burning; increased osmolarity but less than placebo	
Kokke et al.[14]	Placebo (olive oil)	Double masked	Symptoms of dryness and overall lens comfort improved, tear meniscus height increased vs. placebo	Female contact lens wearers
Macsai[15]	Placebo (olive oil)	Double masked	Decrease in red blood cell and plasma ratios, improvements in OSDI, TBUT, and meibum score; results not significant	
Pinna et al.[16]	None	Investigator masked	ω6 with eyelid hygiene improves symptom/reduces MGD eyelid margin inflammation	
Creuzot et al.[17]	Placebo	Unspecified	Reflex tearing and hyperemia improved vs. placebo	
Aragona et al.[18]	Placebo (fructose)	Double masked	PGE1 levels increased, symptoms and corneal staining improved vs. placebo	Sjogren syndrome patients
Miljanovich et al.[19]			High ω3 consumption associated with decreased dry eye, but not seen with ω6. High ω6:ω3 ratio associated with greater risk for dry eye	
Barabino et al.[20]	Tear substitute and placebo	Double masked	Signs and symptoms improved; HLA-DR expression reduced	
Wu et al.[21]	Placebo (soy bean oil)	Double masked	ω3 and ω6 reduce prostaglandin E2 production vs. placebo	

In the last 5 years (2010 to 2015), at least 12 clinical trials were published in the peer-reviewed literature, about double the amount in the previous 5 years (2005 to 2009), preceded by less than a handful (before 2005).

DPA, docosapentaenoic acid; HLA-DR, human leukocyte antigen D-related; PGE1, Prostaglandin E1.

(EPA) (ω3 family) and docosahexaenoic acid (DHA) (ω3 family).[24] All of these serve as precursors to eicosanoids. Eicosanoids formed from AA (ω6 family) (e.g., prostaglandin E2, thromboxane A2, Leukotriene 2, etc.) have the potential to increase blood pressure, inflammation, platelet aggregation, thrombosis, vasospasm, allergic reactions, and cell proliferation. Omega-6 EFAs are the precursors of eicosanoids and prostaglandins that act as natural healers but can lead to problems such as thrombosis and coronary heart problems.[24] Omega-3 eicosanoids formed from EPA (e.g., PGE3, LTB5 etc.) have opposing, anti-inflammatory effects.[25] Omega-3 eicosanoids are thought to be beneficial, whereas ω6 eicosanoids are considered to be inflammatory. However, some of the ω6 eicosanoids formed from DGLA (PGE1 and TXA1) do have anti-inflammatory effects, making the effect of ω6 PUFAs on inflammatory response complicated. A proper balance and ratio of ω6:ω3 must be established in the diet, and it is this imbalance and overabundance of ω6 that is thought to be responsible for multiple inflammatory conditions. The dietary sources, schematic metabolism of PUFAs, and inflammatory modulation effect of PUFAs are shown in Fig. 1.

Omega-3 and ω6 supplementation does have some associated precautions. Theoretically, an excess of ω3 EFAs could cause bleeding because of their antithrombotic properties. Therefore, subjects with bleeding disorders may need to seek medical advice before taking ω3 EFA supplements.[24] Also, high concentrations of ω3 in the blood have been linked to increase prostate cancer risk in a recent controversial study.[26] As mentioned before, a diet rich in ω6 EFAs has been associated with an increased risk of thrombosis and coronary heart problems.

The Effect of ω3 PUFAs on Inflammation

Omega-3 PUFAs have broad anti-inflammatory effects as shown in laboratory studies, animal feeding studies, and healthy human volunteers.[27,28] These studies have provided an understanding of

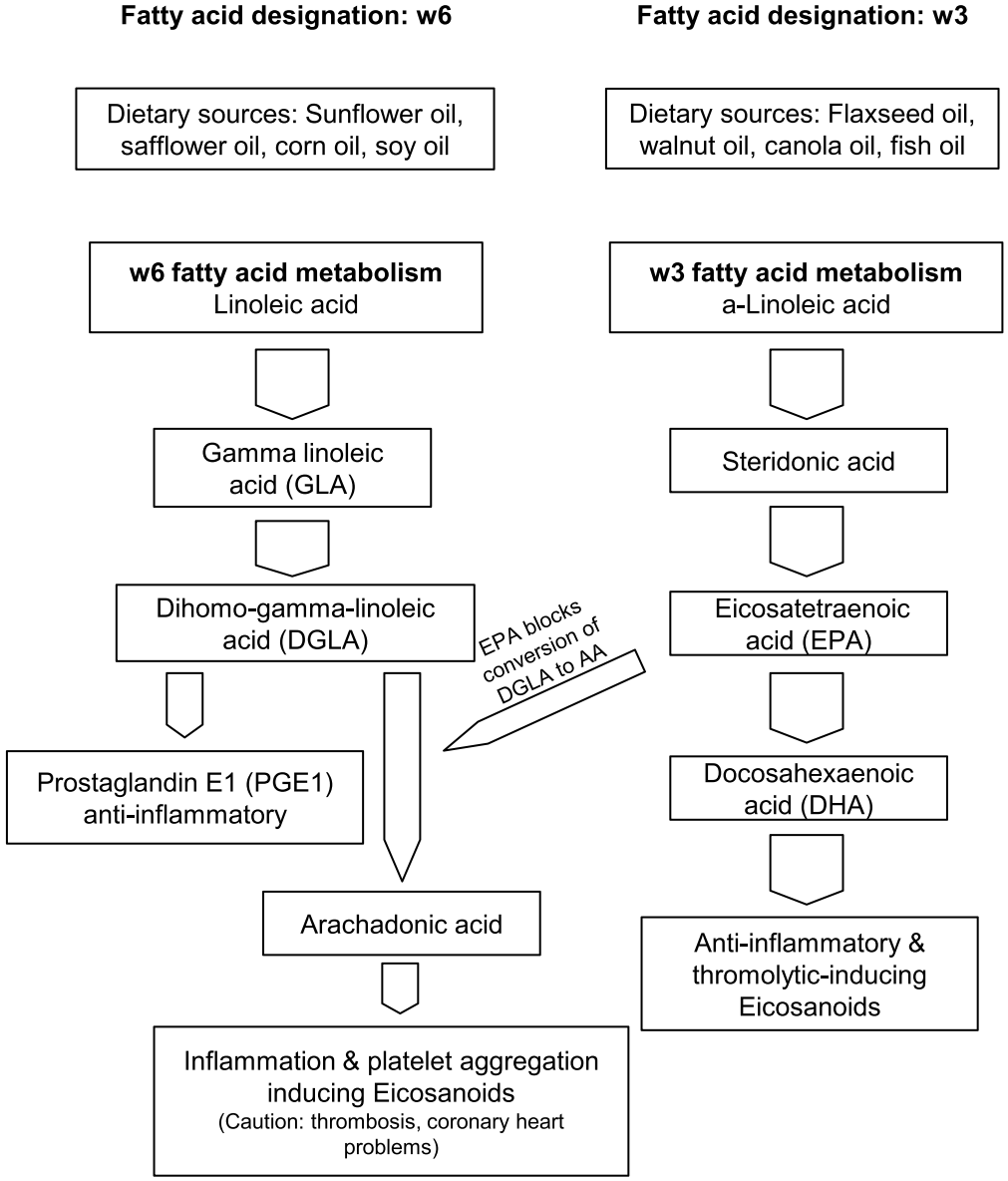

FIGURE 1.

Polyunsaturated fatty acids: dietary sources, metabolism, and inflammatory mediation/modulation (modified from Roncone et al.[24] and Macsai[15]).

the mechanism of actions of ω3 PUFAs in inflammatory diseases. Among the most widely reported effects of ω3 PUFA (EPA or DHA) on immune-cell responses is the inhibition of the production of proinflammatory cytokines interleukin (IL)-1, IL-2, and tumor necrosis factor (TNF)-α[27–32] and subsequently the proliferation of T lymphocytes.[21,30–34] Cytokines and T lymphocytes play key roles in DED.

Effectiveness of ω3 PUFAs in Inflammatory Diseases

The role of ω3 PUFAs has been evaluated in a variety of inflammatory diseases by several placebo-controlled clinical trials. Nearly all have shown that supplementation with oral ω3 PUFAs has significant benefits with regard to changes in the signs, symptoms, and pathophysiology of the disease. Polyunsaturated fatty acids also have synergistic action with other anti-inflammatory treatments. Some of the diseases that may benefit from ω3 supplementation are inflammatory diseases such as rheumatoid arthritis, Crohn disease, ulcerative colitis, psoriasis, and asthma, as well as chronic conditions like cardiovascular disease and migraine.[25,35–42]

Inflammation is now considered a part of the pathogenesis of atherosclerosis. Several studies have shown a positive effect of ω3 PUFAs in lowering the incidence of ischemic heart disease and myocardial infarction as well as the risk of atrial fibrillation. Omega-3 consumption lowers plasma triglycerides, resting heart rate, and blood pressure, and PUFAs may also improve myocardial filling and efficiency, lower inflammation, and improve vascular function. The current data provide strong concordant evidence that ω3 PUFAs are bioactive compounds that reduce risk of cardiac death.[43] The American Heart Association recommends intake of about 1 g for secondary prevention of coronary artery disease and 2 to 4 g/d for people with high triglycerides (www.americanheart.org, April 12, 2011). A meta-analysis was performed of 17 randomized controlled trials assessing the pain-relieving effects of ω3 PUFAs in patients with rheumatoid arthritis or joint pain secondary to inflammatory bowel disease and dysmenorrhea. The meta-analysis suggested that EPA/DHA supplementation reduces patient-assessed joint pain intensity, morning stiffness, number of painful and/or tender joints, and nonsteroidal ani-inflammatory drug consumption.[38] Some authors have noted that ω3 supplementation may have a beneficial effect in patients with asthma. Asthma has been associated with a disturbance of the ω3/ω6 ratio, and supplementation with ω3 may indeed reduce respiratory inflammation in asthma.[35,44] A comprehensive review on the role of ω3 PUFAs in inflammatory bowel disease noted that although clinical outcomes have been variable in different studies, some trials do report improved gut histology, decreased disease activity, decreased use of corticosteroids, and decreased relapse.[45] Besides these, ω3 supplementation has also been shown to have a positive effect in infant development, cancer, and, more recently, various mental illnesses, including depression, attention-deficit/hyperactivity disorder, and dementia.[45] Although the mechanisms of action in these are unclear, it could be partially related to the effect of ω3 PUFAs modulating the immune system.[46]

The Role of Inflammation in DED

Although the pathogenesis of DED is not fully understood, it is recognized that inflammation plays a prominent role in the development and propagation of this debilitating condition. Regardless of the etiology, DED eventually leads to inflammation of the ocular surface via various mechanisms such as tear hyperosmolarity and tear film instability. The ocular surface and the tear-secreting glands function as an integrated unit. Dysfunction of this unit may develop from aging, a decrease in supportive factors (androgen hormones), herpes simplex virus, meibomian gland dysfunction (MGD), and systemic inflammatory/autoimmune disease such as Sjögren syndrome and rheumatoid arthritis. Inflammation may, in turn, cause dysfunction or disappearance of cells responsible for tear secretion or retention, further exacerbating DED and the development of a self-perpetuating inflammatory cycle. Dysfunctional cells will lead to changes in tear composition, such as hyperosmolarity, which stimulate the production of inflammatory mediators on the ocular surface. Although DED continues to be divided into two groups (aqueous deficient and evaporative), both groups eventually enter this vicious cycle of inflammation leading to the typical symptoms of DED, chronic irritation, and pain. Clinical evidence indicates that anti-inflammatory therapies may be able to break this cycle of DED and inflammation, opening new avenues for the treatment of this complex disorder.[47–52]

Relationship of PUFA to DED

Moderate to severe DED is an inflammatory disease involving increased T-cell infiltration, tear inflammatory cytokines, ocular surface human leukocyte antigen D-related (HLA-DR) and intercellular adhesion molecule expression.[53–55] Omega-3 PUFAs have been shown to have anti-inflammatory effects. All the above inflammatory properties in DED have been reported to be inhibited by ω3 PUFAs.[25,56,57] This effect is similar to the main mechanism of action of cyclosporine in treating DED. Subjects with DED tend to have increased levels of TNF-α and IL-1α in the tear film and hence could benefit from intake of ω3 fatty acids.[24]

ω6 Alone

Essential ω6 Fatty Acids

Linoleic acid and its product gamma linolenic acid (GLA) are ω6 fatty acids. Omega-6 treatment appeared beneficial in alleviating dry eye symptoms, increasing tear production, and improving overall contact lens comfort in patients with contact lens–associated dry eye.[14] Gamma linolenic acid and linoleic acid were also found to reduce ocular surface inflammation in patients with Sjögren syndrome.[18]

Oral supplementation of linoleic acid and GLA along with eyelid hygiene has also been shown to improve symptoms and reduce eyelid margin inflammation in meibomian gland dysfunction more than either treatment alone.[16] This effect could be explained by the reduction of inflammatory AA products, where the dietary supplementation of linoleic acid and GLA results in the formation of less active prostanoids. It is also possible that these fatty acids help normalize the melting point of meibomian secretion. A closer look at the study results reveals that the ω6 effects on MGD may be marginal. For the combined treatment group of eyelid therapy and ω6, five objective tests found significance results. Similar results were also found for eyelid therapy alone in

four of the five same tests. The addition of ω6 added efficacy in one test, foam collection in the tear meniscus, over eyelid therapy alone. Despite this result, the ω6-alone group did not show significance for foam collection in the tear meniscus.[16,21]

ω3 Alone

Several trials were conducted on the effect of ω3 supplementation alone. A retrospective noninterventional cross-sectional study of 32,470 women showed that women with a higher ω3 fatty acid intake in their diets had 68% less incidence of dry eye. In the same study, the relationship between the ingestion of ω3 fatty acids, ω6:ω3 ratio, and dry eye syndrome was followed up for 4 years. The investigators found that women who ate five to six servings of tuna fish per week (which contains high levels of ω3 fatty acids) had a 66% lower incidence of DED than women who ate two or fewer servings per week.[19] A randomized pilot clinical trial investigated the effects of ω3 PUFAs (in the form of flaxseed oil) on lipid composition of meibum, aqueous tear evaporation, and tear volume in 36 dry eye patients over 90 days. The average tear production and tear volume was increased in the ω3 group as shown by the Schirmer test and fluorophotometry. There was an improvement in symptoms as measured by the Ocular Surface Disease Index (OSDI). There were no significant effects in meibum lipid composition or aqueous tear evaporation rate or clinical signs of staining.[11] Three other studies showed symptomatic improvement with ω3 dietary supplementation. A 905-patient uncontrolled study found symptomatic improvement with ω3 over 12 weeks.[2] In a 518–controlled patient study, improvements in Schirmer scores, tear breakup time (TBUT), and symptoms were found with ω3 versus placebo.[3] In a double-masked study of 61 patients, ω3 and placebo were compared in MGD patients using lid therapy. Improvements in OSDI, TBUT, lid margin inflammation, MG expression, and Schirmer scores were found.[4]

In a prospective, randomized placebo-controlled masked trial to study the effect of ω3 PUFAs in simple obstructive MGD and blepharitis, 38 patients received a dose of 3.3 g/d of ω3 PUFAs or the placebo over a period of 1 year. The clinical trial demonstrated a decrease in the red blood cell and plasma ratios of ω6:ω3 in patients taking ω3 dietary supplementation, as compared with control subjects. Improvements in their overall OSDI scores, TBUT, and meibum score were also found, but the clinical results were not significant. This was an early demonstration of an induced change in the fatty acid saturation content in meibum as a result of dietary supplementation with ω3 fatty acids.[15]

Recently, the role of newer families of anti-inflammatory mediators have been studied, specifically resolvins and protectins, both of which are derivatives of ω3 PUFAs EPA and DHA. In animal models, these ω3 derivatives have been shown to reverse corneal epithelial damage associated with dry eye, increase tear flow, promote a healthy epithelium, and decrease cyclooxygenase-2 expression and macrophage infiltration.[58] The synthetic analog of ResolvinE1 (RX-100045) is being tested in a phase 2 clinical trial for the treatment of chronic dry eye. Preliminary data from a 28-day, randomized, placebo-controlled, 232-patient trial showed dose-dependent and statistically significant improvements in dry eye patients treated with RX-100045.[12] The compound also appears to be well tolerated when applied topically.[12]

In a recent study of 66 subjects, DED subjects (n = 30) and control subjects (n = 36) were randomized to receive the placebo (−NS) or the active supplement (S+), consisting of EPA, DHA, vitamins, and antioxidants over a 3-month period. Significantly higher expressions of IL-1β, IL-6, and IL-10 and significantly lower vascular endothelial growth factor expressions were found in the DED group (DEDG) as compared with the control group (CG). However, levels of IL-1β, IL-6, and IL-10 in tears were significantly lower in the DEDG + S versus the DEDG − NS and in the CG + S versus the CG − NS. Subjective symptoms of dry eye significantly improved in the DEDG + S versus the DEDG − NS. The study concluded that supplementation with ω3 and antioxidants helps reduce inflammatory biomarkers and improve symptoms of DED.[7] In another double-blind randomized controlled trial of 64 subjects, it was shown that daily supplementation of 360 mg EPA and 240 mg DHA for 1 month led to a statistically significant improvement in TBUT, Schirmer scores, and DED symptom scores as compared with the placebo.[6]

ω6:ω3 Ratios

The anti-inflammatory properties of ω3 PUFAs, especially EPA, are attributed to competition with AA as a substrate for cyclooxygenases and 5-lipoxygenase. Polyunsaturated fatty acids derived from ω3 and ω6 compete for enzymes involved in their metabolism. Eicosapentaenoic acid (ω3) works to prevent ω6 EFAs being converted to AA, allowing DGLA to be converted to PGE1. Along with PGE3 (from ω3), PGE1 is anti-inflammatory. PGE1 inhibits TNF-α, IL-1β, and IL-6.[15,23,24] There is an overproduction of proinflammatory PGE2 and underproduction of anti-inflammatory PGE1 and PGE3 when the ω6:ω3 fatty acid ratio is high.[59] The ideal ω6:ω3 ratio in the diet is about 4:1, as is seen in the Mediterranean diet, rich in cold-water fish and natural oils. An unfortunate consequence of industrialization may be a disturbance in the ratio of ω3:ω6 fatty acids, with a higher consumption of ω6 than ω3. Studies suggest that human beings evolved with a diet that consisted of a 1:1 ratio of ω6 to ω3 fatty acids, but in current Western diets, that ratio is closer to 15:1.[60] Increasing systemic levels of ω3 fatty acids like EPA and DHA by oral supplementation would help in the lowering of the ω6:ω3 ratio and hence have an anti-inflammatory effect.[19,23,35,59,60] When the ω6:ω3 ratio is 4:1 or lower, there is competitive inhibition of the conversion of DGLA to AA resulting in more anti-inflammatory PGE1.[19] As a result, it has been suggested that ω6 and ω3 be given together, as DGLA and EPA can produce more anti-inflammatory eicosanoids.[15,18,24]

ω3 and ω6 Combinations

In a recent multicenter, randomized, controlled trial with 138 patients, it was shown that oral ω3 and ω6 for 3 months caused significant reduction in HLA-DR expression in dry eye patients as compared with placebo. However, no significant difference was found for the signs and symptoms, but there was a tendency for improvement in patients receiving the ω3 and ω6 combinations.[9] In another study comparing the effect of PUFA supplements alone to the effect of PUFA supplements with cyclosporine drops in the treatment of DED, it was shown that

supplementation with ω3 and ω6 PUFAs improved TBUT and relieved patient symptoms. The addition of topical cyclosporine did not convey any statistically significant improvement in TBUT beyond that achieved by the supplement alone.[8] In another double-masked randomized study with 181 dry eye patients, it was concluded that ω3 and ω6 PUFAs present an additional therapeutic advantage in patients experiencing ocular dryness who were already treated with lacrimal substitutes.[10] In another study, supplementation with sea buckthorn oil (*Hippophae rhamnoides*), which is high in ω3 and ω6 linoleic acid, attenuated the increase in tear film osmolarity during the cold season and reduced symptoms in patients with dry eye.[13] In a recent randomized controlled trial of 38 postmenopausal women with moderate to severe keratoconjunctivitis sicca at two centers, it was shown that a combination of GLA (ω6) with EPA and DHA (ω3) supplementation over a 6-month period led to statistically significant improvements in OSDI scores and surface asymmetry index as compared with the placebo (sunflower oil). Neither group had any improvement in TBUT, tear production, or corneal and conjunctival staining. The placebo group showed significantly increased inflammatory markers—HLA-DR and CD11—as compared with the treatment group. The potential limitations of the study included a small sample size and the effects of other ingredients in the active supplement, such as vitamins A, B_6, C, and E.[5] Another study looked into the ω3 and ω6 combination for 6 months. Seventy-one DED patients took ω3 and ω6 for 6 months. Reflex tearing and hyperemia improved compared with the placebo.[17]

What We Need to Know

Most of the studies that do exist are small studies with data recorded from a single site, offering different outcome measures and using varying combinations: ω3 or ω6 or both. Most have short study durations and contrasting results. Longitudinal assessment of DED, with respect to changes in signs, symptoms, inflammatory biomarkers, and the effect of seasonal variations, needs to be studied. There are many recent advances in minimally invasive objective metrics that may provide better methods for classifying severity and outcomes in treatment of DED. Collection of biomarkers, tear osmolarity, percent HLA DR–positive cells, and tear cytokines can contribute to our understanding of the pathology that occurs on the ocular surface with DED.[27,31] As stated earlier, the ideal ω6:ω3 ratio in the diet should be less than 4:1, but the western diets have a much higher ratio. Supplementation with ω3 would help lower this ratio. Effectiveness of nutritional supplementation, as a treatment, is difficult to determine without knowledge of a patient's blood chemistry. Only one large-scale MGD study actually recorded changes in blood levels of the PUFAs to monitor compliance and correlate treatment effect.[15] Just as Wilder's law of initial value states that "the direction of response of a body function to any agent depends to a large degree on the initial level of that function," the baseline status needs to be taken into account when assessing efficacy.[61] Objectively correlating changes in signs and symptoms with the actual levels of ω3 PUFAs in the blood has not been done in a large-scale multisite study.

Meta-analysis has shown that ω3 improves TBUT and Schirmer scores, but there is no consensus on the dose, composition, length of treatment, and so on with ω3 or ω6 PUFAs.[62,63] The Preferred Practice Pattern for Dry Eye Disease by the American Academy of Ophthalmology actually recommends the use of systemic ω3 PUFA supplements for moderate DED. However, neither the Dry Eye Workshop report nor the American Academy of Ophthalmology outlined specific treatment recommendations with respect to dosing.[64]

Many subjects already take ω3 PUFA for DED, leading to a massive expenditure of resources without strong evidence of efficacy. Evidence-based medicine describing the usefulness of over-the-counter supplements is needed to enable eye care providers to confidently outline specific treatment recommendations for using ω3 PUFAs in DED.

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