

Abstract

Purpose

Dry eye is a common complaint dealt with in optometric practice. However, it is a difficult condition to treat as clinical signs do not always explain the patient experience. Essential fatty acids (EFA), particularly omega-3 EFA, may be effective in dealing with the underlying causes.

Methods

A literature review was carried out on the Pubmed, ScienceDirect and Ovid databases. Searches included keywords such as 'dry eye', 'essential fatty acids' and 'nutrition' to find articles relating to the treatment of dry eye with omega-3 fatty acids.

Results

Omega-3 and 6 EFA need to be consumed together within a reasonable ratio to be effective. Currently, the western diet lacks omega-3 EFA which allows overexposure to omega-6. Omega-3 supplementation has an anti-inflammatory effect, inhibiting creation of omega-6 prostaglandin precursors. Omega-3 EFA also demonstrate anti-inflammatory action in the lacrimal gland preventing apoptosis of the secretory epithelial cells. Supplementation clears meibomitis, allowing a thinner, more elastic lipid layer to protect the tear film and cornea.

Conclusion

Supplementation of omega-3 EFA has already proven to be effective in coronary heart disease and arthritis. Safety is not a concern as it works synergistically with omega-6 in the body. Evidence suggests that supplementation with omega-3 EFA may be beneficial in the treatment and prevention of dry eye syndrome.

Keywords

Omega-3; alpha-linoleic acid; dry eye syndrome; essential fatty acids; linoleic acid.

Introduction

Dry eye is thought to be a product of tear film abnormality, stemming from aqueous deficiencies or evaporation of the tear film [1], although it may also arise from lid closure abnormalities or environmental conditions (e.g. air conditioning). Current treatments are centered on the management of the tear film, and temporary relief may be achieved through instillation of artificial tears, although relief does not last long because these topical treatments generally treat the symptoms and are unable to resolve the underlying cause [2]. Research has shown that up to 10% of the non-contact lens wearing population who are under the age of 60 have dry eye symptoms and these symptoms are even more common in older people and postmenopausal women [3]. Up to 25% of patients consulting eye care practitioners present with dry eye symptoms [4], as well as up to 50 % of the 35 million contact lens wearers in the US [5-7]. A survey of US practitioners showed that 12-21 % of soft contact lens patients reduced their wearing time because of dry eye symptoms, and that 6-9 % were so symptomatic that they were unable to wear lenses at all [8].

Despite its frequency, diagnosis is not always straightforward as clinical signs are not always reliable and lack the discrimination capabilities necessary to deal with such a common problem [9]. Objective tests such as fluorescein staining, rose bengal staining, tear film breakup time and Schirmer's test showed discrepancies in sensitivity and specificity when used as diagnostic tools in the clinical setting. McCarty and colleagues found the Schirmer test to be least effective and do not recommend using any of the four tests individually [9]. Tear film breakup time may be the most effective measure of dry eye because it relays directly to the optometrist the stability of the tear film.

Dry eye has been defined by the National Eye Institute as 'a disorder of the tear film due to tear deficiency or excessive tear evaporation which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort' [10]. Dry eye can be divided into two definite types: evaporative and aqueous deficient [11]. There are many factors that can lead

to dry eye syndrome (DES), and both evaporative and aqueous deficient dry eye conditions will result in increased tear osmolarity (raised concentration) [12]. Evaporative dry eye may arise due to a meibomian oil deficiency or lid inadequacies such as an incomplete blink or a low blink rate (inability to properly distribute tears) [11]. A deficiency of vitamin A, which is needed for maintaining the health of epithelial tissues, may also result in evaporative dry eye [11]. Aqueous deficient DES can be further broken down to Sjögren's and non-Sjögren dry eye. In the non-Sjögren's version, it may arise from a lacrimal gland duct obstruction [11] resulting in increased tear osmolarity [13].

Some authorities suggest that the instillation of artificial tears is the mainstay of the management of DES [14]. Over the last few years several products with a high lubricity index have become available and a recent report suggests that Systane (Alcon Laboratories) has the lowest coefficient of friction and therefore the highest lubricity index value (compared to GenTeal [Novartis Ophthalmics], Refresh Tears and Refresh Endura [Allergan] [15]. A recent study (n=40) compared Systane to Soothe (Alimera Sciences Inc., Alpharetta, GA) and found that while one drop of Systane increased lipid layer thickness by an average of 16%, the same amount of Soothe produced an average increase of 117% [16]. Ridder *et al.*, reported that Sensitive Eyes (Bausch and Lomb) low viscosity artificial tears improved contrast sensitivity and visual acuity in a group of silicon-hydrogel contact lens wearers with evaporative DES, when compared to Clerz2 (Alcon) and GenTeal (Novartis), solutions that have a higher viscosity [17]. The authors proposed that this was due to a mechanism involving aqueous supplementation and/or minimal tear layer disruption found with Sensitive Eyes.

Research has shown that dry eye and nutrition are not mutually exclusive [18], prompting interest in the use of nutritional supplementation or dietary modification for the prevention and treatment of this condition. Essential fatty acids (EFAs) may enhance the lipid layer of the tear film, thus

retarding evaporation [19]. Perhaps more importantly, EFAs have displayed anti-inflammatory properties in conditions such as rheumatoid arthritis [20]. The key to the beneficial intake of EFAs is the ratio in which they are consumed and absorbed [21, 22]. Industrialized society has led to the overconsumption of omega-6 EFAs, thus limiting the effectiveness of omega-3 EFAs. This literature review attempts to give an overview of the investigation of EFA supplementation as a treatment modality for dry eye syndrome (DES).

Methods

We identified pertinent articles on use of EFA supplementation for dry eye syndrome published in peer-reviewed journals, through a multi-staged, systematic approach. In the first stage, a computerized search of the PubMed, Science Direct and Ovid databases was performed to identify all relevant articles published between 1950 and December 2008. Terms and words used for the search included 'dry eye', 'dry eye syndrome', 'essential fatty acid' 'fatty acid', 'omega 3', 'omega 6' and 'Sjögren's syndrome'. In the second stage, copies of the entire articles were obtained, where possible. Bibliographies of the retrieved articles were manually searched with use of the same search guidelines. In the third stage, articles were reviewed and information relating to the use of essential fatty acids for dry eye syndrome was incorporated in to the manuscript. The literature search was not limited to the English language, although no translation was required

RESULTSEssential fatty acids

These fatty acids are deemed to be essential because they cannot be produced in the human body. Essential fatty acids (EFAs) are polyunsaturated and can be divided into two groups called omega-3 (ω -3) and omega-6 (ω -6); omega-9 fatty acids are not considered essential as they can be synthesised in the body from unsaturated fat. Essential fatty acids contain a carboxyl group (COOH) at one end, so are among the group of compounds known as carboxylic acids. The final position at the end of the chain opposite the carboxyl group is known as ω (omega, the final letter

of the Greek alphabet) and the terms omega-3 and omega-6 refer to the location of the first double bond in relation to the ω end of the chain.

Essential fatty acids can also be classified according to the number of carbon atoms and double bonds. For example, the lipid name for alpha-linolenic acid (ALA) is 18:3 ω -3. It contains 18 carbons and three double bonds, and the first double bond is three carbon atoms from the ω end [23].

Table 1 lists common name and lipid name of EFAs that are important in nutrition. Alpha-linolenic acid (omega-3, ALA) and linolenic acid (omega-6, LA) are short chain polyunsaturated fatty acids (SC-PUFA), while the other EFAs listed are long chain polyunsaturated fatty acids (LC-PUFA).

Insert table 1 about here.

Short chain-PUFAs (SC-PUFAs) and LC-PUFAs are available from the diet, but LC-PUFAs can also be formed within the body from the SC-PUFAs. Therefore, ALA and LA can be considered the most important as they are the starting point for the formation of other EFAs [23].

Availability

Linolenic acid (omega-6) is available in the following common oils: corn, peanut, safflower, rapeseed, sunflower, and other common sources of omega-6 EFAs are poultry, eggs, cereals and whole-grain breads [24] such that it has become almost impossible to avoid their consumption. Part of the reason for this is that early research into the benefits of omega-3 and omega-6 EFAs showed positive results, but the results for omega-3 were more subtle and omega-6 was regarded as being most important for growth and development [25]. Omega-3 EFAs are found in fish and fish oils, as well as seeds, oils, green leafy vegetables such as broccoli and spinach, nuts and beans [23]. Table 2 illustrates the fish sources of omega-3 EFAs; dark, cold water fish are best in this regard.

Insert table 2 about here.

Flaxseed is one of the best botanical sources of ALA (omega-3). The omega-3/omega-6 ratio in flaxseed is approximately 1:0.3. Table 3 compares four common nuts and seeds to show which deliver the most omega-3 EFA.

Insert table 3 about here.

Ideal ratio of essential fatty acids

It was in 1970 that studies of the Eskimos in Greenland provided an insight into the usefulness of EFAs. Despite a diet high in fat, this Eskimo population had a low incidence of cardiovascular disease and acute myocardial infarction [11]. Dietary analysis was carried out to see if solutions to common problems of the western world such as thrombosis and atherosclerosis could be found and it was noted that the Eskimos displayed low levels of low density lipoproteins and very low density lipoproteins. Eskimos were also found to have very low levels of arachidonic acid (AA, omega-6) in their blood, and high concentrations of eicosapentaenoic acid (EPA, omega-3) [11]. This is in contrast to western culture where far greater amounts of AA (omega-6) are consumed. Besides cardiovascular health, EFAs have also been found to benefit brain function [12, 25, 26], stroke [21], bipolar disorder [21] and as treatment in inflammatory problems such as joint pain [27]. However a balance needs to be struck as results are not as favourable when the omega-3/omega 6 ratio decreases [13]. Conversion of LA (omega-6) to AA (omega-6) competes with the conversion of ALA (omega-3) to EPA (omega-3) and then to docosahexaenoic acid (DHA, omega-3) [28]. In other words, consumption of excess LA (omega-6) generates excess AA (omega-6) in relation to EPA and DHA (omega-3).

Current estimates of the omega-3/omega-6 EFA ratio in the western world are as low as 1:25 with recommendations to the public that it should be much higher (ideally 1:4) [29]. Due to the

apparent inability to consume enough omega-3 EFAs through the diet there is now a large selection of oral supplements available to augment dietary intake. Table 4 lists a selection of common EFA supplements that are readily available, each with varying amounts of EPA (omega-3) and DHA (omega-3). This table highlights only on omega-3 EFA supplements.

Insert table 4 about here.

Effect of omega-6 EFA supplementation on dry eye

Before there was a clear understanding of how EFAs may help alleviate dry eye symptoms and signs, dietary supplements containing EFAs for use as a dry eye treatment became commercially available. Many of these contained omega-6 as well as omega 3 EFAs despite the fact that, as previously discussed, too much omega-6 EFA results in excess AA (omega-6) in the body which can lead to heart disease, stroke and other degenerative diseases [30].

Lipid layer

Pinna *et al* investigated the role of LA (omega-6) and GLA (omega-6) in meibomian gland dysfunction (MGD). Meibomian gland secretion is important in stabilizing the tear film and MGD is a common cause of dry eye [31].

Decreased inflammation

One intervention study that was primarily focused on improving fatigue in people with Sjögren's syndrome, found no change in eye dryness with gamma-linolenic acid (GLA omega-6) supplementation [32]. However, a review of other studies demonstrated an improvement in lacrimal function in people suffering from Sjögren's syndrome who were supplemented with GLA (omega-6) [18]. Aragona *et al.*, found the same results when using LA (omega-6) and GLA (omega-6). The group receiving treatment showed significantly higher levels of PGE₁ in their tears as well as a considerable improvement in the ocular surface and symptoms after one month

of treatment compared with the placebo group. Fifteen days after cessation, the PGE₁ levels decreased and the signs and symptoms returned. The researchers concluded that LA and GLA (omega-6) played a major role in relieving the ocular discomfort and corneal epithelial defects associated with dry eye, as well as increasing the PGE₁ levels [33].

Studies using LA (omega-6) and GLA (omega-6) as anti-inflammatory agents on the ocular surface of patients with aqueous-deficient keratoconjunctivitis sicca as well as in topical preservative-free substitute tears have also reported a reduction in dry eye symptoms. A significant decrease in conjunctival lissamine green staining as well as a decrease in symptoms and in ocular surface inflammation was found in the group of subjects receiving LA, GLA and artificial tears while no statistically significant change between the groups was found for tear break up time or Schirmer's test [34].

Increased tear secretion

Improvement in reports of dry eye and an increase in tear production has been reported after six months of omega-6 EFA treatment [35].

Effect of omega-3 EFA supplementation on dry eye

Miljanović *et al.*, confirmed the link between omega-3 EFA and dry eye, without dismissing the function of omega-6. However, for both EFA groups to perform desirably, a balance between the two must be found. A high intake ratio of dietary omega-3 to omega-6 EFA resulted in a decreased likelihood of suffering from dry eye in women [36]. It is thought that this ratio ideally should be approximately 1:4 (or as high as 1:2.3) [19], however, the ratio is typically much lower (1:10-30) in a western diet which tends to be high in meat and processed food. It was shown that women with lower than a 1:15 omega-3/omega-6 EFA ratio had a 2.5 times greater prevalence of dry eye [36]. If too much omega-6 EFA is ingested due to a diet high in processed meats and low in unprocessed oils and omega-3 EFA-containing fish, the by-product of too much pro-inflammatory prostaglandin E₂ (PGE₂) and too little anti-inflammatory PGE₁ and prostaglandin E₃

(PGE₃) may lead to dry eye [31]. It is crucial that this balance be met by not over-consuming LA and GLA through the addition of dietary supplements when enough are consumed through diet alone. Supplementary omega-3 EFA may be taken as it is often lacking in the diet. Individuals with the highest intake of omega-3 EFA show a 20 % decrease in the likelihood of suffering from dry eye as opposed to those with a low intake of omega-3 EFA. In one study, women who ate at least five servings of tuna per week compared to those eating only one were 68 times less likely to suffer from dry eye [36]. Having said this, the Food Standards Agency advise that females who are pregnant, breastfeeding, or who may one day become pregnant should limit oily fish consumption to two servings per week to avoid over consumption of pollutants [37].

Oral supplements of omega-3 have proved to be very effective, and new trials are emerging to test the use of omega-3 EFA as a topical agent. Rashid *et al.*, tested the effect of EFAs on induced dry eye in mice using three formulations (ALA (omega-3) only, LA (omega-6) only, LA/ALA combination). The LA only and LA/ALA combination proved to be insignificant and symptoms were the same as those individuals who received the placebo. However, the ALA treatment produced a considerable reduction in ocular inflammation and symptoms, a decrease in corneal staining as well as a decrease in CD11b cells. These cells occur in response to inflammation and the expression of pro-inflammatory IL-1 α and TNF- α [38]. Linolenic acid and ALA/LA combinations do not counter the already high amount of omega-6 EFA in the body. This will not offset the pro-inflammatory status already present. However, ALA (omega 3) on its own will act as an anti-inflammatory and bring about a shift in ocular condition.

Lipid layer

Omega-3 EFAs also play an important role in the synthesis of meibum, the oil secreted by meibomian glands. People with omega-3 EFA deficiency typically have a thicker meibomian gland secretion [39]. The use of omega-3 EFA supplements results in clearing and thinning of

meibomian gland secretions which in turn improves symptoms of dry eye. This finding correlates to the earlier finding by Pinna *et al.*, on the use of LA and GLA in MGD. In addition to this, it is thought that omega-3 EFA may affect the polar portion of the tear film's lipid layer by increasing the omega-3 EFA present or altering the omega-3/omega-6 ratio [40].

Decreased inflammation

Once omega-3 EFA is consumed enzymes elongate it producing PGE₃ and leukotriene B₅ (LTB₅), both of which have anti-inflammatory properties. In addition, omega-3 EFA from fish, (EPA), 'blocks the gene expression of pro-inflammatory cytokines tumour necrosis factor alpha (TNF- α), interleukin-1 α (IL-1 α), interleukin-1b (IL-1 β), proteoglycan degrading enzymes (aggrecanases) and cyclooxygenase (COX-2)' [12] as shown in figure 1. Individuals with dry eye tend to have increased levels of TNF- α and IL-1 α in the tear film [41]. The overall result when gene expression is blocked is a decrease in inflammation, which may explain why omega-3 EFA is successful in the treatment of MGD.

Insert figure 1 about here.

As previously discussed, omega-3 EFA block the gene expression of TNF- α , which is important in decreasing apoptosis. It has been shown that increased TNF- α in the lacrimal glands is responsible for lacrimal gland apoptosis, which leads to a decrease in tear production and an increase in tear film osmolarity. Increase in tear film osmolarity causes an increase in TNF- α which causes apoptosis to rise, further increasing tear film osmolarity. Furthermore, DHA (omega-3) helps to prevent lacrimal gland and ocular surface cells from apoptosis caused by TNF- α . When combined with DHA, vitamin E prevents apoptosis. DHA can also help combat dry eye by increasing synapse function which decreases with age [42]. A decrease in synapse function lends to easier inhibition of signal transduction at the synapse by pro-inflammatory cytokines leading to dry eye [12].

Increased tear secretion

Together, DHA and EPA (omega-3) work to prevent omega-6 EFA being converted into AA, allowing dihomo-gamma-linoleic acid (DGLA) to be converted to PGE₁. Along with PGE₃ (from omega-3), PGE₁ is anti-inflammatory [33]. Like PGE₃, PGE₁ is an anti-inflammatory that inhibits TNF- α , IL-1 β and IL-6 [43]. Dihomo-gamma-linoleic acid has also been shown to reduce pro-inflammatory eicosanoids such as leukotrienes B₄ and C₄ which are formed by AA [31]. When the omega-3/omega-6 ratio is 1:4 or higher, there is competitive inhibition of the conversion of DGLA to AA resulting in more PGE₁ [36]. As a result of this, it has been suggested that omega-3 and omega-6 EFA be given together [33] as more anti-inflammatory eicosanoids can be produced by DGLA and EPA with less inflammation caused by those formed by AA [36].

Discussion

Until now, the symptoms of dry eye have been treated with moderate success, but long term solutions are needed. Artificial tears are a stopgap that mask symptoms, but do not resolve underlying problems. The use of EFAs in dry eye needs to further be investigated, particularly as EFAs have already shown their usefulness in heart disease, inflammatory diseases and arthritis [20]. The key to unraveling the potential benefits of EFAs is to firstly gain a clearer understanding of their interactions and to ensure that appropriate amounts of each EFA are consumed. For example, an ideal balance of omega-3/omega-6 should be 1:2.3; this relationship needs to be reached because these two groups of EFAs perform distinct and complementary functions. 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. . An excess of omega-6 EFA, such as in the typical Western diet, allows for a disproportionate response of pro-

inflammatory prostaglandins that will not be blocked by its natural omega-3 EFA anti-inflammatory counterpart [44]. A comparison of the consumption of omega-3 and omega-6 EFA across different countries sheds light on their relationship with inflammation and heart disease. In the US, between 70-80 percent of EFA consumed within the diet is omega-6 [45, 46] and coronary heart disease rates are 200 per 100,000 [46]. On the other hand, the Japanese consumption of EFA consists of only 35-40 percent omega-6 [46, 47][35,37], and Japan has about one quarter of the heart attack rate of the USA [46]. In Greenland where omega-3 EFAs are plentiful in the diet, heart disease is almost non-existent [46]. The importance of omega-3 EFAs cannot be underestimated and in dry eye the advantages are threefold: (1) restoration of the lipid layer, (2) decreased inflammation and apoptosis, and (3) increased tear secretion. Apoptosis of the acini and epithelial cells of the lacrimal glands can lead to decreased secretory function [48]. Supplementation with anti-inflammatory omega-3 EFA counters the under-challenged pro-inflammatory omega-6 EFA, increasing the secretion from the lacrimal gland. Omega-3 EFAs also clear meibomitis allowing a thinner more fluid lipid to be secreted from the meibomian glands. This in turn will better protect the tear film and retard evaporation [19].

It is prudent to address any safety issues. Theoretically, an excess of omega-3 EFAs could cause bleeding due to their anti-thrombotic properties [19] therefore individuals that suffer from bleeding disorders should seek medical advice before taking omega-3 EFA supplements. Seen as an important element of the diet, dieticians are now encouraging the population to incorporate more omega-3 into daily routines. For example, the American Dietetic Association and the Dieticians of Canada recommend 500mg/day of EPA and DHA [49]. Individuals with dry eye often seek advice from eye care practitioners such as optometrists and therefore these professionals should familiarize themselves with EFAs, their benefits and also their potential side effects.

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