Is There a Role for Nutritional Supplements in Dry Eye?
Sanjay Srinivasan,1,2 MBBS, MRCSEd, MMed (Ophthal), Chee-Chew Yip,1,3 MBBS, FRCSEd, MMed (Ophthal)

Abstract

Introduction: Dry eye syndrome is a prevalent eye condition whereby the terminology, classification and treatment are not yet clearly elucidated. Methods: Literature review was done with Pubmed search engine with key words “dry eye”, “nutritional supplements” and “treatment” for articles related to the pathogenesis of dry eye and the use of nutrients in treatment of dry eye. Results: Increased inflammatory cytokines may contribute to the pathogenesis of ocular surface and lacrimal gland inflammation. Nutritional supplementation with omega-3 fatty acids at an appropriate consumption ratio with omega-6 fatty acids was found to have a reduced incidence of dry eye due to its anti-inflammatory effects. Conclusions: The role of nutritional supplements in the treatment of dry eyes remains unknown. Omega-3 fatty acids may be considered as an adjunct therapy to conventional tear substitutes. Further research and clinical studies are necessary to validate the efficacy and safety of these nutritional supplements.

Key words: Dry eye, Nutritional supplements, Omega fatty acids

Introduction

The possible role of nutritional supplementation in preventing or halting the progression of ocular disease is of interest to healthcare professionals and patients. Nutritional supplements are available in many forms such as vitamins A, B, C and E, carotenoids (beta-carotene, lutein, and zeaxanthin), minerals such as selenium and zinc, and the herb, ginkgo biloba. Traditionally, nutritional supplements have been used in the treatment of various eye diseases including glaucoma, cataract, age-related macular degeneration (AMD) and dry eye.1

Patients with intermediate risk of AMD or advanced AMD in one eye were recommended Age-Related Eye Disease Study (AREDS) formulation which was successful in preventing the advancement of AMD by 25%. The formulation consisted of vitamins C, E, beta-carotene and zinc.2 Improvement in the visual function of patients with AMD has been noted with lutein and zeaxanthin supplementation.3 Ginkgo biloba has been reported to improve pre-existing visual field damage in some patients with normal tension glaucoma.3

Essential fatty acids such as omega-3 fatty acids are important in retinal development and in the prevention of cardiovascular diseases.3 A high ratio of omega-3 to omega-6 fatty acids and polyunsaturated fat appear to increase the risk of primary open-angle glaucoma.4 The essential omega-6 fatty acid, gamma-linolenic acid (GLA), is useful in Sjögren’s syndrome and may help in other dry eye conditions.3 It is therefore useful to review the role of nutritional supplements in the treatment of dry eye.

Literature review was done with pubmed using the key words “dry eye”, “nutritional supplements” and “treatment” for articles related to the pathogenesis of dry eye and the use of nutrients in the treatment of dry eye.

Dry Eye

Dry eye is caused by abnormalities in the quality and/or the quantity of the tear film causing ocular surface dysfunction and desquamation. The tear film serves many functions to maintain the health of the ocular surface. It acts as a lubricant to reduce friction between the eyelid and the ocular surface besides washing away debris, noxious agents and inflammatory mediators.

Sack et al5 identified over 80 chemokines, cytokines, growth factors (such as epidermal growth factor), monocyte chemoattractant protein-1, interleukin 8 (IL-8) and tissue

1 Ophthalmology and Visual Sciences, Alexandra Hospital, Singapore
2 Eye Clinic, Jurong Medical Centre, Singapore
3 Department of Ophthalmology, Tan Tock Seng Hospital, Singapore
Address for Correspondence: Dr Yip Chee Chew, Ophthalmology and Visual Sciences, 378, Alexandra Road, Alexandra Hospital, Singapore 159964.
Email: chee_chew_yip@alexhosp.com.sg
inhibitor of metalloproteinase-1 and -2 in the tears. Numerous other previously undetected tear components include angiogenin, growth factors, chemokines, gamma inducible protein-10, growth-related oncogene, epithelial neutrophil-activating protein-78, and macrophage inflammatory protein-3 alpha. Some of these, such as interleukins, function as inflammatory mediators and may contribute towards the pathogenesis of dry eyes.

A normal healthy tear film is essential for clear vision, as the tear film is the first converging lens system that light encounters as it enters the eye. The 3 layers of the tear film from outer to inner include the lipid, the aqueous and the mucin layers. Abnormalities of one or more layers of the tear film may affect the ocular surface causing dry eye symptoms.

Pathogenesis

Dry eye is highly prevalent, affecting 14% to 33% of the population worldwide depending on the study and the definition used. International specialists on dry eye used a modified, 2-round Delphi panel approach to propose an appropriate terminology, devise a classification system and develop treatment recommendations for different levels of disease severity. The panelists unanimously recommended dysfunctional tear syndrome as a more appropriate term for this disease.

On the basis of known pathophysiology, symptoms, and clinical presentation, all panelists agreed that the term dry eye did not reflect the events occurring in the eye. Specifically, all patients with this condition did not necessarily suffer from reduced tear volume but rather may have abnormalities of the tear film composition that include the presence of pro-inflammatory mediators. Patients with dry eye syndrome have been shown to possess increased concentration of interleukin1 (IL-1), interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF α) in the tear film. The balance of cytokines in the tear fluid and the conjunctival epithelium is altered in Sjögren’s syndrome/keratoconjunctivitis sicca. The severity of keratoconjunctivitis sicca increases as the tear fluid epidermal growth factor concentration decreases and the levels of inflammatory cytokines in the conjunctival epithelium increase. These findings provide new insight into the pathogenesis of keratoconjunctivitis sicca and provide potential targets for therapy. Stern et al showed that dry eye is an inflammatory disease with gradual progression to diminished tear production.

Treatment

The treatment of dry eye is challenging and the treatment algorithms are often complicated. Multiple therapeutic agents and treatment strategies are available for the treatment of different stages of same disease. To the clinician that manages dry eye patients on a daily basis, the treatment can sometimes be frustrating and unrewarding.

The conventional treatment of dry eye with artificial tears is based on the concept of volume replacement of diminished tear quantity. However, some dry eye patients do not tolerate artificial tears on a long-term basis, especially those containing preservatives such as benzalkonium.

Table 1. Treatment Recommendations for Dysfunctional Tear Syndrome (DTS) on the Basis of Level of Severity

<table>
<thead>
<tr>
<th>DTS severity</th>
<th>Patient profiles*</th>
<th>Treatment recommendations</th>
</tr>
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<tbody>
<tr>
<td>Level 1</td>
<td>Mild to moderate symptoms&lt;br&gt;and no signs&lt;br&gt;Mild to moderate conjunctival signs</td>
<td>No treatment&lt;br&gt;Preserved tears&lt;br&gt;Environmental management&lt;br&gt;Allergy drops</td>
</tr>
<tr>
<td>Level 2</td>
<td>Moderate to severe symptoms&lt;br&gt;Tear film signs&lt;br&gt;Mild corneal punctate staining&lt;br&gt;Conjunctival staining&lt;br&gt;Vesicular signs</td>
<td>Unpreserved tears&lt;br&gt;Gels&lt;br&gt;Ointments&lt;br&gt;Nutritional support (flaxseed/fatty acids)</td>
</tr>
<tr>
<td>Level 3</td>
<td>Severe symptoms&lt;br&gt;Marked corneal punctate staining&lt;br&gt;Central corneal staining&lt;br&gt;Filamentary keratitis</td>
<td>Tetracyclines&lt;br&gt;Punctal plugs</td>
</tr>
<tr>
<td>Level 4</td>
<td>Severe symptoms&lt;br&gt;Severe corneal staining erosions&lt;br&gt;Conjunctival scarring</td>
<td>Surgery&lt;br&gt;Systemic anti-inflammatory therapy&lt;br&gt;Oral cyclosporine&lt;br&gt;Moisture goggles</td>
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* Levels of severity of DTS without lid margin disease according to symptoms and signs
Omega Fatty Acids

The two best sources of omega-3 fatty acids are flaxseed and dark, cold-water fish like salmon, mackerel and tuna. Flaxseed and cold-water fish each provide a different type of omega-3 fatty acid. Flaxseed provides “short-chain” omega-3 fatty acid while cold-water fish provides “long-chain” omega-3 fatty acid. Omega-3 polyunsaturated fatty acid possesses the most potent immunomodulatory activity amongst all omega-3 fatty acids, especially those that are derived from fish oil such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The only good sources are fish, seafood and “omega-3” eggs. EPA and DHA, are more biologically potent than alpha-linolenic acid (ALA). The amounts of EPA and DHA in the diet vary greatly from person to person.

Omega-3 fatty acids act by either modulating the amount and types of eicosanoids synthesised or by eicosanoid-independent mechanisms. The latter include actions upon intracellular signaling pathways, transcription factor activity and gene expression. Simopoulos reported that dietary intake of omega-3 fatty acids at an appropriate ratio of consumption with omega-6 fatty acids (recommended ratio 2:3:1) affects the overall level of inflammatory activity in the body. In an meta analysis of the analgesic effects of omega-3 fatty acids, Goldberg and Katz suggested that omega-3 fatty acid is an attractive adjunctive treatment for joint pain associated with rheumatoid arthritis, inflammatory bowel disease, and dysmenorrhoea.

Omega 6 Fatty Acids

Linoleic acid and its derivative GLA are two omega-6 fatty acids obtained from plant source, including unprocessed, unheated oil, such as corn, sunflower seed, safflower, soy, sesame, cottonseed, black currant seed, and borage oils. Animal sources of omega-6 fatty acids, although in smaller amounts than in plants, are lean meats, organ meats and breast milk. The administration of linoleic and GLA as dietary supplements have been reported to have a beneficial effect in the treatment of chronic inflammatory disorders, such as rheumatoid arthritis.

Gamma-linolenic acid does not accumulate in significant amounts in cell membranes, even when it is provided in the diet. It is converted to dihomo-GLA (DGLA), a substrate for cyclooxygenase (that gives rise to a prostaglandin E1 series) and 15-lipoxygenase (that gives rise to 15-hydroxy-DGLA). Prostaglandin E, exerts several anti-inflammatory effects, including the inhibition of superoxide, tumour necrosis factor, interleukin-1 β (IL-1β), and IL-6. 15-hydroxy-DGLA is an inhibitor of 5-lipoxygenase and 12-lipoxygenase and thus can decrease the synthesis of some arachidonic acid (ARA)-derived mediators, such as leukotriene B4, which is a potent pro-inflammatory compound.

The administration of linoleic and GLA as dietary supplements reduces the levels of inflammatory ARA oxidation products and produces less active prostanoids. Black currant seed oil rich in both GLA and ALA, have
been shown to modulate membrane lipid composition and eicosanoid production.29

The mechanism by which omega-3 fatty acid reduces pain is not known. Evidence is equivocal for an EPA/ DHA mediated reduction in cytokine secretion in humans. Kelley et al30 reported that high-dose EPA or DHA resulted in a suppression of TNF-α or IL-1β release by monocytes, whereas Kew et al31 failed to detect any changes in cytokine release.

**The Role of Omega Fatty Acids in Age-related Macular Degeneration**

The long chain fatty acid DHA is found in high concentration in the photoreceptor outer segments and is constantly shed and turned over during the normal visual cycle. A deficiency of DHA might therefore impair retinal function and promote AMD.32 In fact, several previous epidemiologic studies and clinical trials suggested that high dietary intake of fat was associated with a higher incidence of AMD whereas high intakes of fish or omega-3 fatty acids were associated with lower rates.33,34 The US twin study of AMD provided evidence that cigarette smoking increased the risk while fish consumption and omega-3 fatty acid intake reduced the risk of AMD.35

**The Role of Omega Fatty Acids in Dry Eye**

Aqueous tear deficient dry eye syndrome is an inflammatory disorder that affects the ocular surface and the lacrimal gland. Ocular surface can become a target of the immune system and exhibit signs of inflammation in autoimmune diseases (such as Sjögren’s syndrome), organ transplantation (graft versus host disease), and ageing.36 The hallmarks of lacrimal gland inflammation are the presence of focal lymphocytic infiltrates and increased production of pro-inflammatory cytokines. The mechanisms leading to lacrimal gland dysfunction are still poorly understood. Apoptosis, the production of autoantibodies, hormonal imbalance, alterations in signaling molecules, neural dysfunction and increased levels of pro-inflammatory cytokines have been postulated mechanisms to account for the lacrimal gland insufficiency in various disease states.36

Boerner37 treated 116 patients in a open-label clinical trial with omega-3 supplements and found that 98% of dry eye patients reported an improvement in their symptoms. Miljanovic et al38 reported the relationship between dietary omega-3 and omega-6 fatty acids and clinically diagnosed dry eye syndrome and suggested that higher dietary intake of omega-3 fatty acid was associated with decreased incidence of dry eyes in women.

DGLA, ARA and EPA are omega-3 fatty acid-derived precursors of eicosanoids that function as modulators of inflammation. The omega-3 fatty acids may also have a direct effect on the polar portion of the lipid layer by increasing the amount of omega-3 fatty acid present or affecting the omega-6 to omega-3 fatty acid ratio.39 The intake of omega-3 fatty acids may decreases the endogenous oestrogen levels40 which influence the risk of developing dry eye.41 The omega-3 fatty acid deficient individuals usually have a thick meibomian gland secretion that results in evaporative tear loss.42 Pinna et al43 studied the effect of oral linoleic acid and GLA, the omega-6 essential fatty acids, on meibomian gland dysfunction. Treatment with linoleic acid and GLA tablets along with eyelid hygiene improved symptoms and reduced eyelid margin inflammation more than either omega-6 fatty acids or eyelid hygiene alone.43

**Safety of Omega Fatty Acids**

Safety concerns have been raised regarding long-term omega fatty acid supplementation. Bays44 reported a theoretical risk of bleeding (due to the antithrombotic effect of omega fatty acids), toxicity, patient intolerance (due to potential oxidation of the omega fatty acids supplements) and contamination of the fish oils with environmental toxins like mercury and dioxins. It is advisable to warn the patients of these potential risks and avoid the use of omega fatty acid supplements in individuals on anti-platelet or anti-coagulant therapy or with bleeding disorders.

**Conclusions**

Omega fatty acids are essential fatty acids present in the diet or in nutritional supplements. They may be potential therapeutic options to augment tear substitutes in the management of dry eye. Supplementation of omega fatty acids works via multiple mechanisms to relieve the symptoms of dry eye. It improves the quality of meibomian gland secretion and stimulates aqueous tear secretion via its anti-inflammatory and anti-apoptotic actions on the dysfunctional lacrimal gland. Further clinical trials are necessary to validate the risks and benefits of omega fatty acids. Eye-care practitioners should be aware of the potential side effects of these ocular nutritional supplements and to discuss them with patients before the commencement of treatment.

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