



# DRY EYE SCIENCE for PRACTITIONERS

Dry-eye information to benefit patient care

## DRY EYE SCIENCE for practitioners

Dry eye trilogy

Chapter One

Chapter Two

Chapter Three

How an omega-3 supplement treats dry eye

Eyelid hygiene for pre-surgical, blepharitis, puntal plug and dry-eye patients

Research now concludes that recommending fish oil or flaxseed oil alone is not enough. The long-chain omega-3s from fish oil and the short-chain omega-3s from flaxseed oil in TheraTears Nutrition work synergistically. Together they decrease inflammation and augment the oil and water layers of the tear film, providing significantly more benefit to patients with dry eye and/or meibomitis.

**Omega-3s decrease inflammation**

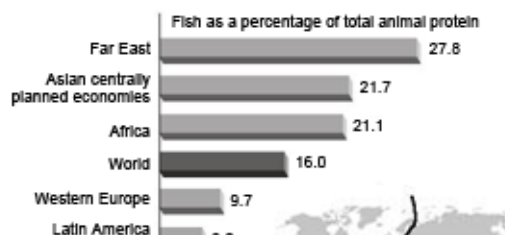
**Omega-3s decrease apoptosis**

**Omega-3s stimulate tear secretion**

**Omega-3s and the meibomian gland oils**

Omega-3s are essential fatty acids. "Essential" means that, because they cannot be produced by the body, their inclusion in the diet is essential for good health. The two best sources of omega-3s are dark, oily, cold-water fish, and flaxseed. Cold-water fish and flaxseed each provide a different type of omega-3s. Cold-water fish provide "long-chain" omega-3s while flaxseed provides "short-chain" omega-3s. Each of these omega-3s are known to have a multitude of health benefits, yet as a population, Americans are omega-3 deficient - it has been estimated that 83% of Americans are deficient in omega-3s.<sup>1,2</sup> North Americans have among the lowest dietary intake of omega-3s in the world (Figure 1).

Figure 1: Contribution of fish to human diet 1987-89



Omega-6s are another group of essential fatty acids. Americans obtain an excess of these through their consumption of beef, dairy, vegetable cooking oils, and vegetable shortenings (i.e. cookies, potato chips, snacks etc.). Unfortunately, while the recommended ratio of omega-3s to omega-6s is 1:2.3, the existing ratio of omega-3s to omega-6s consumption has

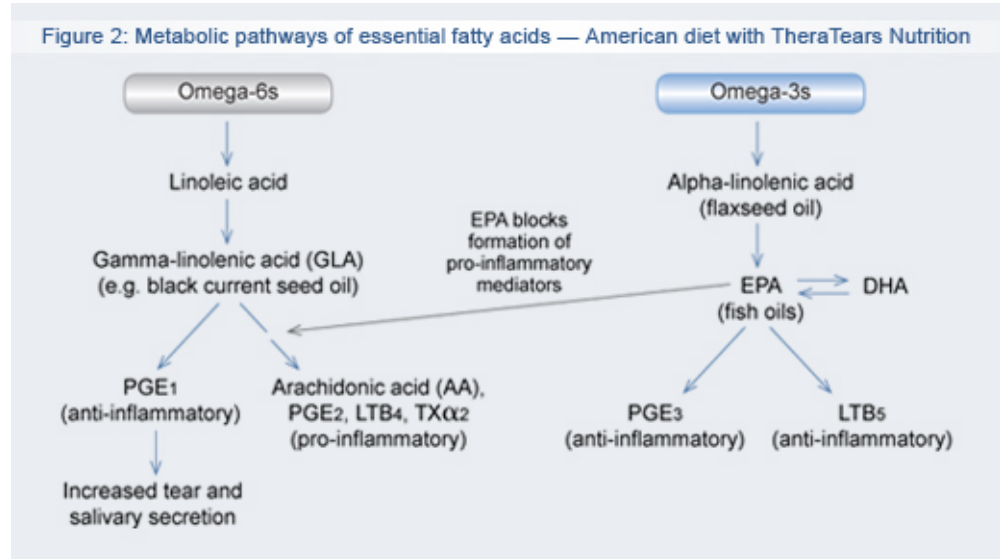


Figure 1 source: Food and Agriculture Organization of the United Nations (FAO). *Marine fisheries and the law of the sea: a decade of change*, FAO Fisheries Circular n°853 (FAO, Roma, 1993).

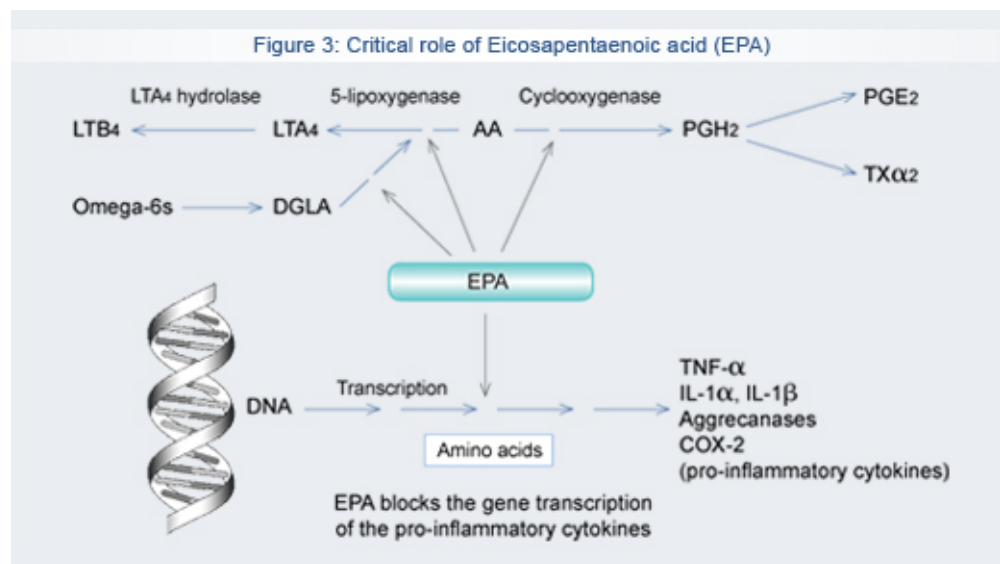
been estimated to be as low as 1:10.

## Omega-3s decrease inflammation

Once consumed, long-chain omega-3s from cold-water fish are directly elongated by enzymes to produce anti-inflammatory prostaglandin E3 (PGE3) and anti-inflammatory leukotriene B5 (LTB5) that suppress inflammation.<sup>1,2</sup> Short-chain omega-3s require several additional elongation steps, and this explains why even high-dose flaxseed supplementation has not been shown to suppress inflammation (Figure 2).<sup>3</sup>



Even more importantly, eicosapentaenoic acid (EPA), one of the long-chain omega-3s provided directly by fish oils, blocks the gene expression of the pro-inflammatory cytokines tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-1 alpha (IL-1 $\alpha$ ), interleukin-1 beta (IL-1 $\beta$ ), proteoglycan degrading enzymes (aggrecanases) and cyclooxygenase (COX-2) (Figure 3).



There is an abundance of clinical evidence that ingestion of long-chain omega-3s decreases the

inflammation seen in the joints in rheumatoid arthritis<sup>4-7</sup> and in the skin in dermatitis as well.<sup>8</sup> These anti-inflammatory effects go a long way to explain why omega-3s have been useful in helping patients with symptoms of posterior blepharitis or meibomitis. In my practice, omega-3s have been displacing my use of systemic tetracyclines as treatment for the eye irritation that my meibomitis patients experience upon awakening in the morning. But the effects of omega-3s only begin with their effects on meibomitis.

## Omega-3s decrease apoptosis

Suppressing TNF- $\alpha$  is also important because in Sjögren's syndrome and in lacrimal gland-based dry eye, increased TNF- $\alpha$  in the lacrimal glands increases lacrimal gland apoptosis (programmed cell death). Increased apoptosis contributes to the decrease in tear production, and increase in tear film osmolarity that drives dry-eye ocular surface disease.

In addition TNF- $\alpha$  induces apoptosis on the ocular surface in dry eye. Specifically, Luo and co-workers found that increasing tear film osmolarity in animal models increases the expression of TNF- $\alpha$  and the associated cell regulators that increase apoptosis on the ocular surface.<sup>9</sup> There has been a lot of interest recently in ocular surface inflammation in dry eye.<sup>10</sup> This important study shows that it is elevated tear film osmolarity that induces the increased expression of pro-inflammatory cytokines in dry eye, just as elevated tear film osmolarity has been shown to produce all the morphological ocular surface changes described in dry eye.

Restasis, a drug administered topically because it is so toxic systemically, also inhibits TNF- $\alpha$  production by monocytes. Applied topically it achieves good concentrations on the eye surface but is not thought to reach the orbital lacrimal gland in humans. TheraTears Nutrition, providing a blend of fish oil and flaxseed oil and taken by mouth, reaches the lacrimal gland by the blood supply, and, as we shall see later, the ocular surface via meibum. Restasis and TheraTears Nutrition both appear to inhibit pro-inflammatory cytokines, but differ in their ability to reach relevant target tissues.

While EPA decreases the gene expression of TNF- $\alpha$ , DHA, a long-chain omega-3 provided directly by fish oils, protects cells from TNF- $\alpha$ -induced apoptosis. Yano and co-workers have demonstrated that vitamin E works synergistically with DHA to protect cells from TNF- $\alpha$ -induced apoptosis.<sup>11</sup> So EPA and DHA work together to protect the lacrimal gland and ocular surface from apoptosis.

## Omega-3's stimulate tear secretion

The effects of suppressing pro-inflammatory cytokines don't stop here. We now know that the pro-inflammatory cytokines TNF- $\alpha$ , IL-1 $\alpha$ , and IL-1 $\beta$ , impair tear secretion in lacrimal gland disease-based dry eye by inhibiting the release of neurotransmitters from neural synapses, and interfering with the secretory response of lacrimal gland acinar cells to stimulation. This is probably the main mechanism by which tear secretion decreases in dry eye.<sup>12,13</sup>

The profound importance of this has been illustrated in recent work that shows that when TNF- $\alpha$  gene expression is blocked by gene therapy in an animal model, autoimmune lacrimal gland disease can be reversed, and tear secretion restored.<sup>14</sup> The relevance of this animal model is supported by epidemiological data that indicates that the risk for dry eye decreases with increased dietary intake of omega-3s,<sup>15</sup> as well as an additional study that finds that Sjögren's patients have a lower dietary intake of omega-3s, including EPA and DHA, than age-matched controls.<sup>16</sup>

While EPA is central in blocking the gene expression of pro-inflammatory cytokines, DHA may help in a complementary way. Neural synapses contain among the highest concentration of DHA in the body and research has shown that dietary supplementation with DHA restores neural DHA levels and improves age-related declines in synapse function.<sup>17</sup> DHA may reduce the ability of pro-inflammatory cytokines in the lacrimal gland to inhibit signal transduction at the synapse. Lending credence to this hypothesis is the finding that severity of dry eye in Sjögren's patients has been found to be inversely proportional to membrane and

serum levels of DHA.<sup>18</sup>

Omega-3s affect the lacrimal gland in another way, and here is where we begin to see the benefit of the short-chain omega-3s from flaxseed oil. EPA and DHA from fish oil and alpha-linolenic acid (ALA) from flaxseed oil work together synergistically to competitively inhibit the conversion of omega-6s to arachidonic acid (AA), with flaxseed oil blocking the elongation of short-chain omega-6s, and fish oil blocking the elongation of long-chain omega-6s. This blocks the main pathway of omega-6 metabolism that generates pro-inflammatory arachidonic acid, and forces omega-6s to take a secondary pathway that converts DGLA to prostaglandin E1 (PGE1) (Figure 2). PGE1 also has anti-inflammatory properties<sup>19,20</sup> relative to the usual products of omega-6 metabolism. Even more important for dry-eye patients, PGE1 acts on the E-prostanoid receptors EP2 and EP4 to activate adenylate cyclase, increasing cyclic AMP (cAMP),<sup>21</sup> and stimulating aqueous tear secretion.<sup>22,23,24</sup>

It is known that lacrimal and salivary gland secretion can be stimulated in similar ways. Recently, Papas and colleagues, in a prospective, randomized, double-masked, placebo-controlled clinical trial in Sjögren's patients, have shown that TheraTears Nutrition not only improves dry-eye symptoms, but also improves dry mouth symptoms by virtually doubling basal rates of salivary gland secretion (P=0.029).<sup>25</sup>

## Omega 3's and the meibomian gland oils

Meibomian glands use essential fatty acids to synthesize oil (meibum). Dietary intake of omega-3s in general have recently been shown to affect the polar lipid profiles of meibum as observed by HPLC.<sup>26</sup> Indeed, Boerner has observed the clearing and thinning of meibomian gland secretions with short-chain omega-3s provided by flaxseed oil supplementation,<sup>27</sup> and Chan and Boxer Wachler has quantified the thickening of the tear film oil layer with flaxseed oil supplementation.<sup>28</sup> Further studies are needed to determine whether these effects are sufficient to retard evaporation. To date, long-chain omega-3s from fish oil have not been shown to have these same effects on the oil layer.

There have been some attempts to treat dry eye with the omega-6 essential fatty acid gamma linolenic acid (GLA) found in black currant seed oil, evening primrose oil and borage oil. There are two published studies that concluded GLA was not effective in treating dry eye.<sup>29,30</sup> Moreover, there are risks in long-term GLA and omega-6 supplementation related to the accumulation of arachidonic acid (inflammation, thrombosis and immunosuppression).<sup>31-33</sup>

Long-chain and short-chain omega-3s each help dry eye. But as we have seen, the long-chain omega-3s from fish oil and the short-chain omega-3s from flaxseed oil in TheraTears Nutrition work together synergistically to work more effectively, consistently and across a broader range of patients than either oil alone. Together they decrease inflammation, and augment both the oil and water layers of the tear film, while providing the health benefits of a balanced spectrum of omega-3s. Additional studies are now underway with this flaxseed-fish oil-vitamin E blend to fully evaluate the magnitude of its efficacy in treating these dry-eye and meibomitis patients.

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A recent study ([JAMA 2004;29:827-835](#))\* shows that cumulative lifetime use of tetracycline for more than 50 days (just over 7 weeks) more than doubles the risk of developing breast cancer. An [Editorial](#)\* in the same issue concludes that while more research was needed " this study raises the possibility that long-term use of antibiotics may have harmful consequences, especially for patients for whom other therapeutic options are available." Now, as outlined in the article above, there is an option for those with meibomitis, blepharitis, dry eye and acne rosacea - TheraTears Nutrition, the healthy omega-3 supplement.



\*Requires Adobe Acrobat Reader.

## Footnotes

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