

Impact of Omega-3 Fatty Acids on Central Corneal Thickness: A Comprehensive Review

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Abstract: Central corneal thickness (CCT) is an important parameter in ophthalmology as it affects the intraocular pressure measurement and the refractive surgery outcome, and it is a possible biomarker for a number of ocular conditions. Omega-3 polyunsaturated fatty acid (PUFAs), in particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) has come into importance as modulators of ocular health for its anti-inflammatory action as well as structural components of cellular membranes. This paper reviews the relationship between omega-3 fatty acid supplementation and CCT and possible mechanisms such as modulation of inflammatory pathways, tear film stabilization and impact on corneal hydration. Current evidence for omega-3 supplementation on CCT has suggested that it may have an effect on CCT through an indirect mechanism stemming from the control of dry eye disease and maintenance of corneal surface health, but the direct causal relationship(s) need to be researched further.

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I. INTRODUCTION

➤ *Background Information on Thickness of the Central Cornea*

Central corneal thickness is the measurement of corneal thickness at a point which is the thinnest, usually the geometrical centre. Normal CCT values are somewhere between 520 and 560 micrometres but there is huge individual variation of this value between populations^[1]. CCT has taken on clinical importance for a number of reasons. First, it directly affects the accuracy of applanation tonometry measurements and thicker corneas may be overestimated and thinner corneas underestimated for intraocular pressure. Second, CCT becomes an independent risk factor for the progression of glaucoma^[2]. Third, it dictates concern for refractive surgical procedures such as LASIK and PRK^[42]. Finally, abnormal CCT values can be a sign of underlying pathology of the cornea as in keratoconus, Fuchs' endothelial dystrophy or corneal oedema.

➤ *Omega-3 Fatty Acids- Structure and Function*

Omega-3 polyunsaturated fatty acids are a group of essential fatty acids which is defined to contain a double bond three carbons from the methyl end of carb chain^[3]. Three omega-3 fatty acids, the alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the most clinically relevant omega-3 fatty acids. While ALA is found in plant sources (flaxseed, walnuts etc) EPA and DHA is mostly obtained from marine sources (fatty fish, fish oil supplements)^[4]. These fatty acids lead important structural and functional roles in the body, particularly in the

cell membranes that define fluidity and receptor function and the cellular signaling pathways^[3].

➤ *Rationale for Researching the Effects of Omega-3 On CCT*

The study of the effects of omega-3 fatty acids on CCT are based on various converging lines of evidences. Omega-3 fatty acids have well-established anti-inflammatory action and regulate the production of inflammatory mediators which have the potential to affect on the tissues of the cornea^[3,26]. In addition, supplementation with omega-3 has been shown to be efficacious in the management of dry eye disease, a condition implicated in ocular surface inflammation that potentially affects the ocular surface indirectly by affecting the cornea^[7,13,14]. The presence of DHA in high concentrations in the retinal tissues suggests the presence of important functions for omega-3 fatty acids in the entire eye^[5,17]. Furthermore, inflammatory diseases that involve the cornea would often be linked to changes in CCT, hence it appears to be possible to influence the cornea by anti-inflammatory interventions^[48,50].

II. LITERATURE REVIEW

➤ *Omega 3 Fatty Acids and Eye Health*

Extensive research has been conducted to record the beneficial effects of the omega-3 fatty acids in many areas related to eye health. Studies have shown that supplementation with omega-3 can reduce the symptoms and signs of dry eye disease and result in improvements in tear break-up time, Schirmer's test results and the subjective relief of symptoms^[8,9,10,11]. The DREAM study (Dry Eye

Assessment and Management) was a large randomised controlled trial examining the supplementation of omega-3 in dry eye disease, but results suggested that there were small benefits compared with placebo^[7,25]. Research has also suggested possible protective effects of omega-3 fatty acids against age-related macular degeneration but results are a little controversial^[19,20]. Additional studies have been done with the effect of omega-3 on retinopathy of prematurity, diabetic retinopathy, and other vascular diseases of the retina^[17,18].

➤ *Mechanisms of Action of Omega-3 in the Eye Tissues*

The effect of omega-3 fatty acids is by multiple mechanisms with some relevance to the health of the cornea. They are the precursors for the production of specialised pro-resolving mediators (SPMs) such as resolvins, protectins and maresins, which promote in a positive way the resolution of inflammation instead of its simple suppression^[6]. These fatty acids compete with the omega-6 fatty acids for incorporation into cellular membranes as well as metabolism by the cyclooxygenase and lipoxygenase enzymes that may result in reduction of the production of pro-inflammatory eicosanoids^[4,29]. In the context of ocular surface, omega-3 fatty acids may help to improve the function of the meibomian glands, improve tear film stability and decrease the expression of inflammatory cytokines in the lacrimal functional unit^[21,22,23]. They may also have an effect on the nerve function and sensitivity of the cornea which play a role in maintaining a homeostasis of the cornea^[49].

➤ *Direct Studies on Omega-3 and Thickness of Cornea*

Direct studies of the effects of omega-3 fatty acids and CCT are still limited in the scientific literature. Most studies exploring the effects of omega-3 supplementation on corneal parameters have focused mostly on dry eye symptoms, tear film quality and ocular surface inflammation and not specifically on CCT changes^[8,9,10,11,12]. Some observational studies have investigated the dietary patterns and corneal parameters and there is some evidence of associations with increased omega-3 intake and some corneal parameters, but these are usually confounded in these studies by other dietary factors as well as lifestyle factors^[15]. Clinical trials studies of supplementation of dry eye disease with omega-3 fatty acids have sometimes included CCT measurement as secondary outcome measures with generally inconsistent results^[36]. The lack of large, well-designed randomised controlled trials of CCT on the primary outcome is a large gap in the current knowledge.

➤ *Inflammatory Diseases & Difference in the Thickness of the Cornea*

Understanding the impact of inflammatory conditions upon CCT provides the context for potential effects of omega-3. Dry eye disease, in particular, has changes in corneal parameters such as corneal thickness measurements that can be subtle with a lot of inflammation associated with it^[32,47,48]. Corneal inflammation for a variety of reasons such as infectious keratitis, allergic eye disease and autoimmune diseases, commonly presents with corneal edema and corneal increased thickness. On the other hand, chronic inflammatory conditions may cause thinning of the cornea due to the

breakdown of the cornea stroma^[50]. The resolution of inflammatory episodes is usually associated with normalization of CCT and therefore, the possibility of preventing or reversing changes in thickness secondary to inflammation by anti-inflammatory intervention is suggested. Given the anti-inflammatory properties of omega-3 fatty acids, on the basis of these findings, it could be expected that omega-3 fatty acid may affect CCT through modulation of these inflammatory pathways^[26,30].

➤ *Mechanisms of Action Possible Mechanisms of Action Between Omega-3 and CCT*

• *Anti-Inflammatory Pathways*

The anti-inflammatory nature of omega 3's are the most likely mechanism whereby omega 3s may influence CCT. Corneal inflammation activates the release of matrix metalloproteinases as well as other proteolytic enzymes which can degrade corneal collagen and alter the tissue architecture^[50]. Inflammatory mediators also cause the vessels to become more leaky and promote the accumulation of fluid in the tissues and this can cause swelling of the cornea. Omega-3 through conversion to resolvins and other SPMs can effectively stimulate the process of inflammation resolution and reduction of the expression of pro-inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-alpha. By reducing chronic low-grade inflammation in the ocular surface, the supplemental anti-inflammatory effect of omega-3 might maintain the normal hydration and thickness of cornea against inflammation^[26,30].

• *Effects of Tear Film and Ocular Surface*

The tear film is an important part in maintaining cornea health and homeostasis^[46]. Omega-3 fatty acids improve tear film stability by several mechanisms such as improvement of meibomian gland secretions, decrease of tear evaporation rate, and improvement of lipid layer quality^[21,22,34,35]. A more stable tear film reduces desiccation stress on the corneal epithelium cells that may induce compensatory responses of the cornea at the cellular and stromal levels that may affect thickness measurements. Additionally, increased quality of the tear film can decrease irregularity of the cornea and increase the accuracy and reproducibility of CCT measurements^[43]. The osmolarity of the tears also plays a role in the hydration of the cornea and there is some evidence to support the use of omega 3 supplementation in normalizing the osmolarity of the tears in persons with dry eye disease^[44,45].

• *Endothelial Function (corneal function)*

The corneal endothelium act to keep the cornea de-turgor by active ion transport processes and the corneal endothelium dysfunction results in corneal edema and increased corneal thickness. While there is a limited amount of direct evidence linking omega-3 fatty acids to corneal endothelial function, the effects of omega-3 fatty acids on cellular membrane composition and function could in theory, affect endothelial pump efficiency^[31]. Additionally, oxidative stress and inflammation may impair the function of endothelial cells and the anti-oxidant and anti-inflammatory

effects of omega-3 fatty acids may confer an indirect benefit for endothelial health^[5,26]. The concentration of DHA in neural and sensory tissues allows the suggestion of functions in maintenance of specialized cellular functions including corneal endothelial cell functions^[17].

- *Extracellular Matrix of Hydration of the Cornea*

The hydration of the stroma of the cornea is the primary determinant of CCT representing the major portion of corneal volume. The composition of the extracellular matrix in particular the direction and the water content of the proteoglycans influence the water retention in stroma. Inflammatory conditions may alter synthesis and breakdown of proteoglycans and may have an effect on corneal hydration^[50]. In other tissues, an effect of omega-3 fatty acids has been demonstrated on extracellular matrix metabolism and fibroblast function^[29]. Corneal keratocytes being the resident fibroblasts of the cornea, are responsible for the homeostatic state of the stromal matrix and their function might potentially be affected by the availability of omega-3 fatty acids, as well as the inflammatory environment.

➤ *Clinical Implications*

- *Assessment and Monitoring*

For clinicians who are taking into account the possible effects of omega-3 supplementation on corneal parameters, a number of assessment considerations need to be made. Baseline CCT measurement using pachymetry should be conducted prior to the initiation of supplementation with measurements at appropriate intervals to determine if there is any change^[1]. However, clinicians need to be aware that normal diurnal variation in CCT and measurement variability may be greater than any possible effects of omega-3 supplementation. Comprehensive evaluation of the health of the ocular surface including dry eye symptom questionnaires, tear break-up time and corneal staining gives the context for interpretation of any CCT changes^[43,48]. Documentation of concomitant inflammatory and medications and other supplements that may affect the parameters of the cornea are important to proper interpretation of findings.

- *Patient Selection and Counselling*

Those patients that are most likely to see benefits from omega-3 supplementation in regards to the cornea include patients with dry eye disease, especially patients with meibomian gland dysfunction, and patients with inflammatory ocular surface diseases^[21,22,33]. Optimisation of ocular surface health prior to baseline ocular surface health measurements may benefit patients being evaluated for refractive surgery^[41,42]. However, the clinicians should counsel patients that although supplementation with omega-3 may be of help in maintaining the overall ocular surface health, dramatic changes in CCT should not be expected. Realistic expectations about time periods for possible benefits, usually taking several weeks to months of faithful supplementation should be made. Discussion of appropriate dosing, usually 1000-2000 mg combo EPA, DHA daily for ocular health, is important for ensuring adequate intake for possible benefit^[7,36].

- *Considerations for Refractive Surgery*

In the planning of refractive surgery stable and accurate CCT measurement is needed. Uncontrolled ocular surface disease can have an impact in CCT measurements, as well as in surgical planning^[41]. Optimization of ocular surface health by a number of interventions, perhaps including omega-3 supplementation may improve the accuracy and the reproducibility of preoperative measurements^[36,37]. However, surgeons should not use omega-3 supplementation exclusively to treat significant ocular surface disease and use strategies of comprehensive management. Post operative inflammation following refractive surgery may theoretically be affected by omega 3 supplementation but there is no specific evidence of effects on post-surgical CCT changes^[41].

- *Management of Factors for Glaucoma*

Given the role of CCT in the accurate measurement of intraocular pressure, as well as being an independent risk factor for glaucoma, any intervention with potential implications on CCT should be considered in the management of glaucoma^[1,2]. However, based on the current evidence, it does not seem that omega-3 supplementation leads to clinically significant changes in CCT that would have material impact on the diagnosis and decision-making regarding the management of glaucoma. Clinicians should be aware that other factors including time of day, measurement technique and corneal pathology have much greater influences on CCT than nutritional interventions. Nonetheless, the total anti-inflammatory and potentially neuroprotective actions of the omega-3 fatty acids may have broader interest in the management of glaucoma beyond the possible effects on CCT^[5,26].

➤ *Lack of Existing Evidence and Research Gaps*

- *Summary of the Evidence that is Available*

The existing evidence base of the effects of omega-3 fatty acids on CCT is restricted and indirect. Most relevant studies have been done on dry eye disease management and not corneal thickness as primary outcome^[7,8,9,10,11,12,13,14]. When CCT has been measured in omega-3 supplementation trials, there is usually very little or no significant changes. The lack of well-designed studies of CCT as a primary outcome is the major gap in existing knowledge. Observational studies that have suggested associations between consumption of dietary omega-3 and corneal parameters have been unable to demonstrate cause and effect and are subject to many confounding factors^[35]. The biological plausibility of the effects of omega-3s on CCT through the anti-inflammatory mechanisms provides reason to more thoroughly investigate in the absence of direct evidence^[3,26].

III. METHODOLOGICAL CONSIDERATIONS

Future research of the omega-3 effects on CCT will need to overcome a number of methodological difficulties. Standardization of CCT measurement techniques, including definition of instrument type, site of measurement and time of day is important for reproducibility. Adequate sample sizes need to be calculated on the basis of realistic estimates of effect sizes and an awareness of the variability of the measure.

Duration of supplementation should be sufficient to allow biological effects to take place and probably at least three to six months of consistent supplementation. Dosing needs to be standardised and validated through the measurement of biomarkers such as omega-3 index^[26]. Control of confounding factors such as concomitant medication, severity of ocular surface disease and other supplements are required^[39].

➤ Future Research Directions

There are a number of specific questions about research that are worth investigating. First is there any measurable change in CCT of patients with active ocular surface inflammation with omega 3 supplementation and if there is, what are the magnitude and time course of these changes? Second, do baseline CCT and ocular surface inflammatory status predict response to omega 3 supplementation? ^[42,48] Third, what are the relative contributions of EPA vs. DHA in the potential effects on the cornea and is the optimal contribution ratio different from the ratio used for other indications? Fourth, do the topical omega 3 formulations have different effects from the oral supplementation^[4,26]? Fifth, how do the effects of omega-3 on CCT compare to others that are anti-inflammatory, such as topical corticosteroids or cyclosporine^[37]? Additionally, investigation of possible mechanisms by analysis of corneal tissue, assessment of inflammatory biomarkers and advanced imaging techniques would increase understanding of any effects that are observed^[50].

➤ Shortcomings of Present Review

This review is limited in that there is no direct evidence that specifically examines the effects of omega-3 on CCT. Much of the discussion must necessarily be based on extrapolation from studies of the effects of omega-3s on related outcomes including dry eye disease and ocular surface inflammation^[7,13,14,25]. The heterogeneity of study designs, omega-3 formulations, dosing regimens and patient populations of existing literature prevents the potential to make firm conclusions. In addition to this, there is a possibility of publication bias with under-reporting of negative results. The complexity of the interactions between diet, inflammation and corneal physiology makes it difficult to attempt to sort out specific effects of omega-3 supplementation from other factors related to lifestyle and therapy.

IV. CONCLUSION

The interrelational relationship between the supplementation of omega-3 fatty acids and the central corneal thickness is still an area that needs to be studied further. While the biological plausibility exists for the effect of omega-3s on CCT because of their anti-inflammatory action, modulating the effect of ocular surface health and possible influences on corneal hydration, there is limited currently direct evidence for clinically significant changes^[3,26,46]. Existing studies show primarily benefit on dry eye disease symptoms and ocular surface inflammation and not on specific parameters of corneal thickness. For clinicians, the supplementation of omega-3 is an intervention

that is relatively safe and potentially beneficial to patients with inflammatory ocular surface diseases, but dramatic changes in CCT are not expected. Any changes in CCT that are observed are more likely to be resolution of pathological changes in thickness associated with inflammation and not normal corneal structures^[48,50].

Future studies with stringent techniques, adequate sample sizes, and adequate duration of supplementation are needed to characterize more appropriately the effects of omega-3 on CCT. Such research should include appropriate patient selection, the use of standardised measurement techniques and include detailed assessment of the status of the ocular surface and inflammatory status^[39,48]. Until more firm evidence becomes available, omega-3 supplementation is best considered as one part of a comprehensive ocular surface management rather than a specific one on modifying CCT. The more general benefits of omega-3 fatty acids on the ocular and systemic health provide support for consideration in the appropriate clinical context despite the questions relating to specific ocular effects on corneal thickness, which will require more complete answers^[3,17,26].

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