

# The ONIT Study–Ocular Nutrition Impact on Tear Film

**Research Article**

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**\*Corresponding author:** Sean P Mulqueeny, Mulqueeny Eye Centers, 612 N New Ballas Road, Saint Louis, MO 63141, Tel: 314-542-3600; Email: smulqueeny@mulqueenyeye.com**Received:** January 27, 2015 | **Published:** March 26, 2015**Abstract**

**Purpose:** To better understand the role of a proprietary dietary supplement formulated to contain Omega 3 and seven other anti-inflammatories plays in patients with established clinical findings consistent with dry eye disease. Secondly, this evaluation will attempt to discover if any of the diagnostic markers are predictive to the therapeutic approach of omega 3 anti-inflammatory dietary supplements.

**Design:** Clinical-based, multi-center cohort study.

**Methods:** This eight-week feasibility study was to determine if subjects presenting with dry eye confirmed by diagnostic markers and symptoms responded to nutritional therapy via an oral nutritional supplement (EyePromise EZ Tears™). Analyses were completed on a subgroup of subjects with 4 of 7 possible diagnostic criteria.

**Results:** A total of 67 patients were enrolled between 18-79 years of age inclusive. At the conclusion of the study, improvement from baseline was demonstrated in OSDI decreasing scores by 38%. Improved tear breakup time and phenol red thread scores were seen and was reduced conjunctival staining. There was also a decrease noted in lid inflammation. Osmolarity scores were variable and inconclusive.

**Conclusion:** Supplementation with this Omega-3 anti-inflammatory product in dry eye showed significant improvement in OSDI, TBUT, conjunctival staining lid inflammation and phenol red tear meniscus and corneal staining scores. This decrease in patient symptoms could be an indication of decreasing ocular surface inflammation and possible stabilization of the lipid layer. The change from baseline for these signs appears to be rapid, as differences were shown as early as one-week post-supplementation.

**Keywords:** Dry eye; Omega 3; Meibomian gland dysfunction; Tear osmolarity; Supplementation

**Abbreviations:** TFD: Tear Film Dysfunction; ONIT: Oral Nutrition Impact on Tear Film; OSDI: Ocular Surface Disease Index; GLA: Gamma-linoleic Acid

## Introduction

Dry eye disease is one of the most frequently encountered conditions observed in clinical practice. Its proper diagnosis and management can be challenging [1]. Developing practical and effective therapeutic strategies is often elusive and frequently must be customized to the individual patient. The ocular surface is one of the most challenging aspects of the ocular anatomy to study because it is affected by so many exogenous factors. Studies have indicated that short-term consumption of oral omega-3 fatty acid can positively impact dry eye syndrome [2].

The 1995 report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eye defined dry eye, or keratoconjunctivitis sicca, as a disorder of the pre-corneal tear film caused by tear deficiency or excessive tear evaporation that results in damage to the inter-palpebral ocular surface and is associated with ocular discomfort [3]. The etiological classification of the disease has defined two main subtypes, aqueous deficient and evaporative dry eye, which relates to disorders of the lacrimal and meibomian glands, respectively [4].

The DEWS Report is one of the most important summary publications regarding ocular surface disease. In 2007, the

International Dry Eye Workshop redefined dry eye as “a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.” Clinically diagnosing direct causality of each of these subtypes is problematic; in reality, ocular surface disease is likely to be a combination of several alterations of the tear film [5]. In 1997, Tseng and Tsubota [6] reported that the ocular surface and tear film interact to such an extent that individual layers do not have separate functions but rather, they are inextricably intertwined to maintain a healthy ocular surface.

Aqueous tear film deficiency may result from T-cell mediated inflammation of the main and accessory lacrimal glands, or may occur secondary to medications that reduce secretion by these glands. A deficient aqueous layer may contribute to, or cause the disruption of tear production [7]. Patients with evaporative dry eye typically have lid disease which may include blepharitis and/or meibomian gland dysfunction. Decreased lipid production results in increased evaporation of tears and contributes to tear film instability. In most patients, the effects of dry eye of either subtype are manifested as blurriness, stickiness, burning, stinging, foreign-body sensation, grittiness, dryness, photophobia and itching [4]. Also, there are often accompanying signs of corneal and conjunctival inflammation. In more severe cases, the consequences of chronic dry-eye disease can include poor

lubrication, altered barrier function, sterile melting, and bacterial keratitis.

In 2006, the International Task Force Delphi panel on dry eye developed treatment recommendations. The panel noted that disease severity is the most important factor to consider in treatment decision-making. The group categorized disease severity into four levels based on symptom severity and frequency; including visual symptoms; conjunctival injection; conjunctival staining; corneal staining; corneal/tear signs; lid/meibomian gland dysfunction; tear-film breakup; and Schirmer score [8].

Each layer of the tear film has contributory anatomical components that can lead to “Tear Film Dysfunction” (TFD). The meibomian glands producing the lipid layer, the lacrimal glands as the source for aqueous tear and vital proteins, and the goblet cells producing the mucin layer are all critical and interact with each other in maintaining a healthy tear film, corneal and conjunctival anatomy [9]. Clinically when we observe a deficient tear film layer, the underlying mechanisms of the disease cannot be observed because changes in environmental stress, androgen secretions, inflammatory components, and lipid components have a role in the initiation and progression of the disease [10-13].

The International Workshop on Meibomian Gland Dysfunction: Executive Summary was the first to define meibomian gland dysfunction as a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretions [9]. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease. It is the pathology of the gland that defines the disease.

In this study, we will measure the baseline tear film to see if there is a change in the diagnostic parameters over a two-month period through the ingestion of a dietary supplement that is unique due to seven anti-inflammatory phyto-nutrients and a highly-purified and concentrated fish oil. This is a non-significant risk, prospective, multiple clinical site investigation using dry eye measurements, including osmolarity, tear break up time, tear meniscus height, phenol red thread test, corneal conjunctival staining and lid margin scoring. Patients will also be assessed using subjective questionnaires (OSDI) to document the change of comfort and vision with the addition to their diet omega-3 supplements.

## Methods

Data for the Oral Nutrition Impact on Tear Film (ONIT) Study were obtained from a prospective, multicenter clinical study with four sites in Saint Louis, MO; Chicago, IL; Amarillo, TX; and Lexington, KY. A total of 67 patients ranging in age from 18-79 were enrolled. The patients were from the general practice patient population who met criteria on four of the seven diagnostic markers. The investigators selected potential candidates without any requirements as to gender, or racial/ethnic and religious backgrounds. The inclusion criteria in the study were based on a global clinical assessment by the attending investigator, patient complaint of dry eye symptoms as confirmed by the OSDI, and dry eye testing results.

Patients were excluded from the study if there was a diagnosis of clinically significant eyelid deformity or eyelid movement

disorder; previous ocular disease leaving sequelae or requiring current topical eye therapy other than for DED; active ocular or nasal allergy; LASIK or PRK surgery that was performed within one year of Visit 1 or at any time during the study; ophthalmic drop use within 2 hours of any study visits; pregnancy or lactation at any time during the study by history; abnormality of nasolacrimal drainage (by history); punctal cauterization or current punctal plug placement or within 30 days of punctal plug removal; use prohibited medications such as cyclosporine; any topical ocular prescription medication (i.e., steroids, NSAIDs, etc); glaucoma medications; oral tetracyclines or topical macrolides; oral nutraceuticals (flax, fish, black currant seed oils, etc...) within 3 weeks of baseline; having started or changed the dose of chronic systemic medication known to affect tear production within 30 days of Visit 1.

## Study enrollment

This study was conducted in accordance with the guidelines provided by the Declaration of Helsinki, approved by an Institutional Review Board (Oaklawn IRB# 1940) and in adherence to the guidelines of the respective sites conducting this study. The clinicaltrial.gov identifier was NCT01561040. All patients who voluntarily provided written informed consent and were capable of complying with the study visit schedule were enrolled.

## Examination procedures

The following procedures were performed and information recorded at the Baseline/Screening Visit and at all follow-up visits. Patients were examined for eligibility at the baseline examination following informed consent. Patient's demographics and medical history were recorded. The following examination procedures were performed for both eyes at all visits. Slit-lamp examination included assessments of corneal edema, bulbar conjunctival injection, cornea staining, chemosis, inflammatory cell, and flare. The ocular surface was examined by assessing the entire bulbar conjunctiva. The patient's eyes were evaluated under the slit-lamp biomicroscope using a cobalt blue filter transmitting 330 to 400 nm and a beam approximately 4 mm wide and 10 mm high. Corneal staining was observed in the central, inferior, nasal, temporal and superior regions on a scale of 0 to 3 based on the Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eye. A total grade of greater than 3 out of 15 for the five corneal regions is considered significant for dry eye staining. Conjunctival staining was observed in the six regions on a scale of 0 to 3 based on the Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eye. Using this method, a total grade of greater than 3 out of 18 for the six conjunctival regions was considered significant for dry eye staining (Table 1).

The Phenol Red Thread Test was chosen to measure the tear volume because it is reproducible, does not produce corneal staining, and induces less reflex tearing compared to Schirmer testing. Three mm of thread was inserted into lateral 1/3 conjunctival fornix and after 15 seconds was measured for the length of thread changing color from orange to red. Any value less than 10mm suggests a tear volume deficiency. The tear film break-up time was defined as the interval between the last complete blink and the first appearance of a dry spot, or disruption in the tear film. Fluorescein dye was instilled in each eye. A break up time less than or equal to 10 seconds was considered abnormal (inclusion less than or equal to 10 seconds) (Table 2).

**Table 1:** Dry eye diagnostic criteria used for the ONIT Study.

Must demonstrate 4 abnormal categories out of 7 (excluding Slit Lamp)	
Test	Inclusion in the study
Tear Breakup Time	Less than 10 seconds
Osmolarity	Greater than 310
Corneal Staining	Greater than 3 out of 15
Conjunctival Staining	Greater than 3 out of 18
Tear Meniscus Height	Less than .3 mm
Phenol Red thread test	Less than 10 seconds
OSDI	More than 23
Slit Lamp Score	Scores greater than 2

**Table 2:** Percent change from baseline by visit for outcomes of interest among patients with 3 or more diagnostic signs of dry eye.

Variable	% Change at 1 week (± sd)	% Change at 4 weeks (± sd)	% Change at 8 weeks (± sd)
OSDI	-11.7 ± 113.1	-39.4 ± 36.8	-37.5 ± 45.1
Osmolarity OD	-0.7 ± 5.6	0.2 ± 5.4	-0.1 ± 5.9
Osmolarity OS	-0.8 ± 4.9	-0.5 ± 5.2	-0.3 ± 5.9
Tear break-up time OD	28.2 ± 63.6	26.1 ± 59.9	45.5 ± 73.2
Tear break-up time OS	26.8 ± 64.9	28.7 ± 70.5	44.6 ± 69.0
Phenol red OD	23.6 ± 101.9	24.4 ± 66.9	14.9 ± 61.0
Phenol red OS	41.0 ± 78.0	51.2 ± 106.7	43.0 ± 78.2
Tear meniscus height OD	24.6 ± 57.6	26.6 ± 56.0	37.7 ± 65.0
Tear meniscus height OS	37.8 ± 69.4	36.6 ± 67.8	55.4 ± 86.1
Corneal staining OD	-26.1 ± 52.6	-41.0 ± 63.1	-34.1 ± 75.3
Corneal staining OS	-27.4 ± 52.7	-41.2 ± 59.7	-34.1 ± 75.0
Conjunctival staining OD	-4.6 ± 130.4	-29.4 ± 84.0	-46.8 ± 56.8
Conjunctival staining OS	-10.5 ± 78.5	-28.2 ± 81.8	-50.5 ± 44.7
Lid inflammation OD	-17.8 ± 62.2	-53.6 ± 47.2	-42.9 ± 59.0
Lid inflammation OS	-11.3 ± 49.9	-33.3 ± 39.4	-38.3 ± 57.6

Tear meniscus height was measured with the graduated scale on the slit lamp beam affixed to the slit lamp biomicroscope, while the patient focused at a distance target. The tear meniscus height was measured vertically at the region of the center of the lower lid of the right eye to the tiny black line that marked the top tear prism level, where the tear meniscus meets the cornea. The tiny black line at the top, where the tear meniscus meets the cornea, represents localized thinning of tears, observed with cobalt blue filter. Tear osmolarity was measured with The TearLab™ Osmolarity System (TearLab™ Corp., San Diego, CA) which uses a 50 nL tear sample in order to measure the osmolarity of the tear film. Osmolarity readings were taken prior to instillation of drops or stains.

The Ocular Surface Disease Index (OSDI) is a 12-item questionnaire designed to provide a rapid assessment of the symptoms of ocular irritation consistent with dry eye disease and their impact on vision-related functioning. OSDI is a valid and reliable instrument for measuring the severity of dry eye disease and it possesses the necessary psychometric properties to be used as an end point in clinical trials [14]. The questionnaire

was evaluated using these cut points: normal ocular surface (0-12 points); mild (13-22 points); moderate (23-32 points); or severe (33-100 points) ocular surface disease.

We had considered incorporating additional testing procedures, such as interferometry and fluorophotometry into the protocol. While these techniques have value, neither has been established as the standard of care for dry eye assessment. In addition, both of these tests have limitations [15-17]. For example, the literature points out difficulties in securing reliable data in fluorophotometry. This is due to several factors, including excessive lacrimation upon instillation of fluorescein, blinking and eye squeezing to name a few. In addition, the device is unable to distinguish the tear film from the cornea. There is also fluorescein uptake into the cornea and conjunctiva, making accurate measurements difficult. These uncontrolled issues would impact outcomes. Additionally, these instruments were not universally available in our four-site, private practice clinical investigation and would require significant financial support. As mentioned, tolerance of the fluorophotometry procedure is an impediment, making it difficult to secure reliable data.

At the completion of the baseline examination, patients were dispensed study supplements and dosing instructions. They were asked to refrain from taking a new supplement for the duration of the study. At the dispensing visit the number of bottles and pills were documented on the Supplement Tracking Form. At each follow-up visits, the above examination procedure was followed. Additionally, the patient returned all bottles dispensed and the remaining pills were counted and documented. The number of pills ingested between visits was tracked to determine if the correct therapy was maintained.

### Statistical analysis

The primary analysis evaluates changes from baseline in osmolarity and other diagnostic signs for dry eye. Basic means and standard deviations were computed by visit for the variables of interest. Frequency was used for any categorical data. Due to the potential for inter-eye variability given a dry eye diagnosis, the decision was made not to average the eyes together, but assess each separately. In order to assess whether these variables differed across visit, a mixed model analysis was done. This analysis accounts for the repeated visits across person, taking into account the correlated nature of the visits. The ability for the model to adjust for correlations within a patient also allowed for the inclusion of both eyes in the model, as well. If there was a significant effect of time (visit), Tukey’s post-hoc analyses

were used in order to determine which visits were significantly different from each other. Percent change from the baseline visit was calculated for each visit as well, to control for the magnitude at baseline and attempt to present a standardized picture. Patients used in these analyses were selected to meet at least four of the seven diagnostic criteria for dry eye in order to have a pool of patients likely to have dry eye.

### Results

Sixty-seven patients were enrolled that met inclusion criteria and 134 eyes were included in our analysis. Of these 84.1% were female, and a similar percentage were Caucasian. The mean age of participants was 55.4 years ( $\pm 15.1$ , range 21-79 years). Twenty percent of the patients were contact lens wearers and two-thirds of the females were post-menopausal. These analyses included participants who had four or more of the dry eye criteria referenced in the methods (n=47).

The means for each variable are presented by visit and eye (Figures 1-8, p-values indicate the effect of visit (time)). OSDI at the first visit was  $41.0 \pm 22.0$  (Figure 1). The score decreased over each visit (p-value from mixed model,  $p < 0.0001$ ), and was  $24.4 \pm 19.2$  at the eight-week visit. This represented a 38% decrease in OSDI over two months (Table 2). A significant decrease was seen as early as the one-week visit in OSDI as well (p-value  $< 0.0001$ ).

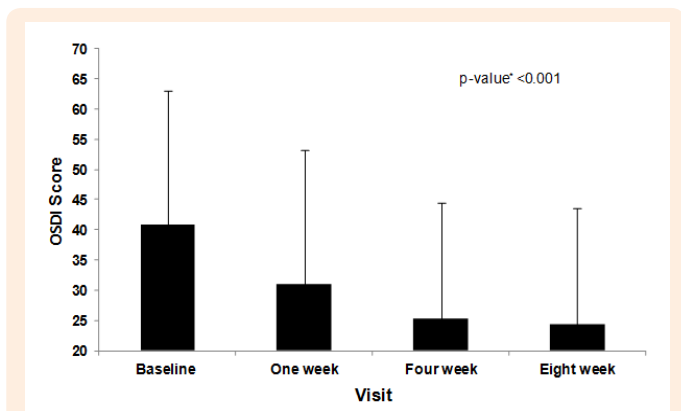


Figure 1: Mean OSDI ( $\pm$  sd) by visit (y-axis abbreviated) (p-value for effect of visit).

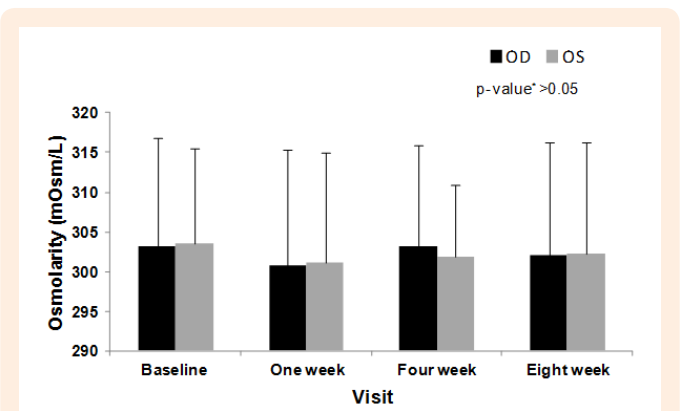


Figure 2: Mean osmolarity ( $\pm$  sd) by visit (y-axis abbreviated) (p-value for effect of visit).

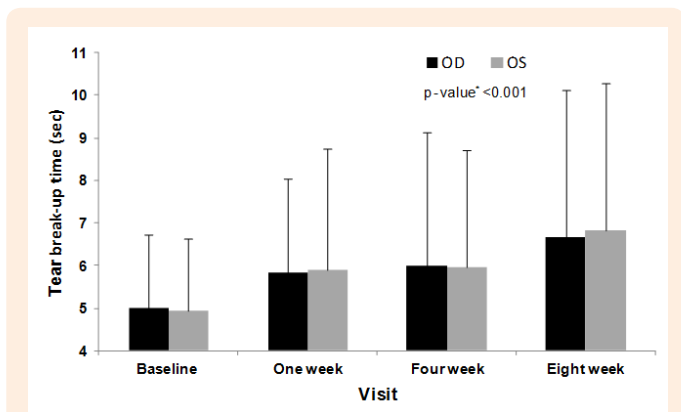


Figure 3: Mean tear break-up time ( $\pm$  sd) (y-axis abbreviated) (p-value for effect of visit).

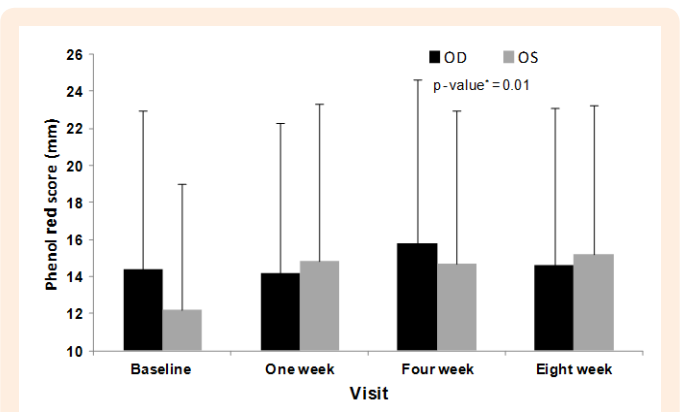
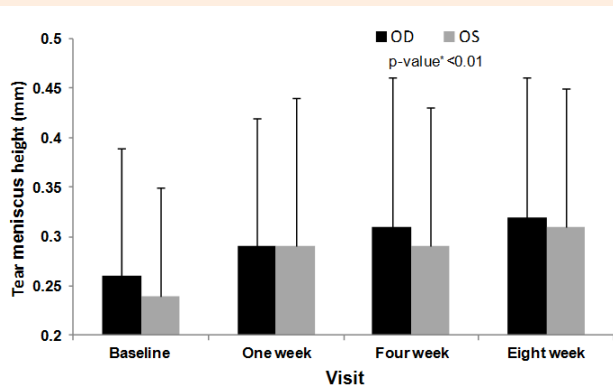
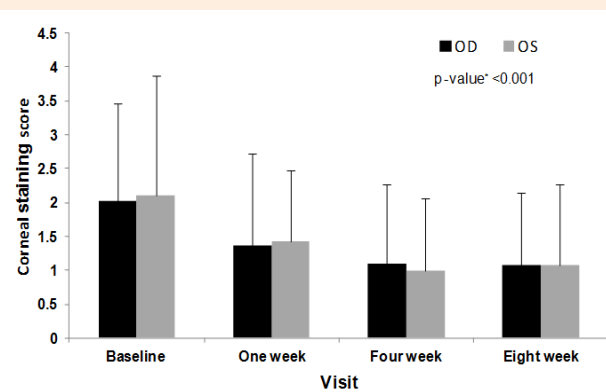


Figure 4: Mean phenol red score ( $\pm$  sd) (y-axis abbreviated) (p-value for effect of visit).

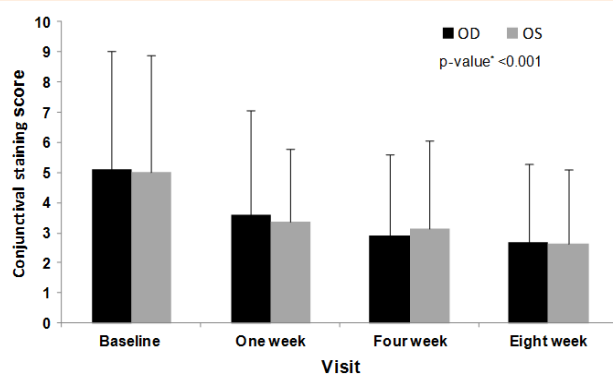




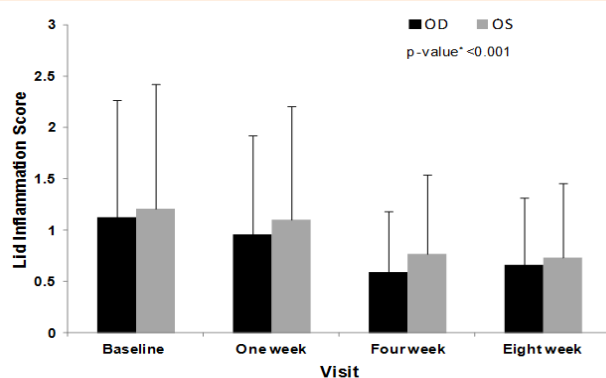
**Figure 5:** Mean tear meniscus height ( $\pm$  sd) (y-axis abbreviated) (p-value for effect of visit).



**Figure 6:** Mean corneal staining score ( $\pm$  sd) (p-value for effect of visit).



**Figure 7:** Mean conjunctival staining score ( $\pm$  sd) (p-value for effect of visit).



**Figure 8:** Mean lid inflammation score ( $\pm$  sd) (p-value for effect of visit).

Osmolarity was similar across visits as well as between eyes (Figure 2, both p-values  $> 0.05$ ). The osmolarity at the first visit was 303 mOsm/l, and 302 mOsm/l at the eight-week visit. The percent change from baseline across eyes was less than 1%.

There was not a statistically significant difference between eyes for tear break-up time ( $p > 0.05$ ). There was a statistically significant effect of time, with the four-week and eight-week visits showing a significant increase from baseline (Figure 3, p-values  $< 0.05$ ). Average baseline tear break-up time was roughly 5 sec, while by week 8 the average time was about 6.8 sec, about a 45% increase from baseline (Table 2). There was roughly a 27% percent increase in tear break-up time from baseline to 1 week, with a similar increase at four weeks.

Phenol red did not demonstrate a statistically significant difference between eyes, ( $p = 0.22$ ) but the mean phenol red values did differ across time (Figure 4,  $p < 0.05$ ). Post-hoc testing indicated that the difference between baseline and four weeks was statistically significant. The difference at eight weeks was not statistically significant ( $p = 0.06$ ). Table 2 shows that the percent change from baseline across the two eyes, with more change occurring in the left eye.

There was a significant difference between the eyes for tear meniscus height that was controlled for in the analysis ( $p = 0.04$ ). Meniscus height showed a statistically significant increase across

visits ( $p = 0.004$ ), from 0.25 mm to 0.32 mm (Figure 5). Post-hoc testing indicated that the four-week visit and the eight-week visit were statistically significantly different than baseline. A large proportion of the percent increase happened by one week (Table 2, between 25 and 38%). By week eight there was roughly 38 and 55% increase from the initial visit.

Corneal and conjunctival staining had similar results (Figures 6 and 7, respectively). The two eyes were similar for both kinds of staining ( $p > 0.05$ ), and there was a statistically significant difference between staining across the visits ( $p < 0.001$ ), with the initial values higher than each of the subsequent visits. The corneal staining score began at just over 2.0 at the first visit and decreased to about 1.0 by the eight-week visit. There were negative percent changes from baseline at all visits, starting with a decrease of about 26% by one week and ending up with a percent decrease of about 33% (Table 2). Conjunctival staining was about 5.0 at the first visit and dropped to 2.6 at the eight week visit. Percent decrease from baseline to week one was between 5 and 10%. There was a 50% decrease in conjunctival staining by eight weeks.

Lid inflammation scores were statistically significantly different between eyes ( $p = 0.001$ ), remaining a little higher in the left eye than the right eye. There was also a significant difference across visits in the lid inflammation score ( $p < 0.001$ ). Scores were

about 1.2 at baseline and decreased to 0.7 by the eight-week visit (Figure 8). At the one-week visit, there was no statistically significant decrease from baseline ( $p > 0.05$ ), but it was seen at the four- and eight-week visit ( $p < 0.0001$ ). By week eight, the percent decrease from baseline was about 40% (Table 2).

## Discussion

Dry eye disease is a multifactorial disease of the ocular surface and tears film which results in ocular discomfort, visual disturbances, and tear instability with potential damage to the cornea and conjunctiva. Patient subjective discomfort arises from the corneal and conjunctival disruption caused by a dysfunctional tear film. OSDI reflects the corneal and conjunctival disruption caused by a deficient tear film. It is the lack of lubrication on the corneal surface that causes the subjective complaint of dry eye.

We have found that an aggregate of dry eye measures may better predict a given patient's dry eye status at a given point in time, but these measures taken individually may not be predictive at all [8]. It is more the ocular surface-tear film interaction that was of primary interest in this study. We were able to show that the nutritional supplement not only improved signs of dry eye among individuals suffering more signs of dry eye (i.e., moderate dry eye), but also symptoms as measured by the OSDI survey as well. Analyses indicated improvement even in those presenting with fewer signs of dry eye. Nearly 66% of patients were post-menopausal white females. These demographics may limit broader relevance to the general population. We found variable osmolarity results and recent studies have indicated that this linking can be difficult to establish. A recent paper concluded that changes in tear osmolarity do not correlate significantly with changes in patient symptoms or corneal fluorescein staining in dry eye disease [18].

Omega-3 fatty acid supplementation has long been associated with reducing the signs of dry eye and conversely, high Omega-6 to Omega-3 ratio in the diet increases the risk of Dry Eye Syndrome [19]. The study supplement strategically included Omega three and Turmeric Extract (curcumin) mediating the conversion of Omega-6 fatty acids to pro-inflammatory prostaglandin. One of the most surprising findings from this study was the rapid onset of action of supplementation. OSDI, TBUT, Phenol Red Thread Test, Tear Meniscus, Conjunctival Staining, Corneal Staining and Lid Inflammation scores began to improve just after one week of supplemental therapy. We attribute this rapid onset to the study supplement's formulation; primarily that it contains anti-inflammatory components that specifically target inflammation of the ocular surface. An example of this is the incorporation of evening primrose oil, which as far back as 1980 was shown to reduce symptoms of dry eye in Sjogren's patients [20]. Evening primrose oil contains gamma-linoleic acid (GLA) which has been shown to favorably affect dry eye symptoms, probably by affecting conversion of Omega-6 fatty acids to pro-inflammatory molecules [21].

The other anti-inflammatory components in the study supplement formulation include Vitamin A (as retinyl palmitate), which is a fat soluble vitamin essential for corneal surface health, as well as mucosal, conjunctival, meibomian and lacrimal gland health. It is needed by genes/cells that express mucin (a polysaccharide) of major importance in one of the three major

tear layers. Vitamin D<sub>3</sub>, a fat soluble vitamin that is generally deficient in the American diet, is also incorporated [22]. Numerous clinical studies have elucidated the health benefits of vitamin D and many are likely explained by its master effects on immunity and systemic inflammation [23]. Vitamin E, alpha-tocopherol fat soluble vitamins and their related compounds are fat-soluble vitamins and are essential for reduction of systemic and ocular inflammation [24-25]. These compounds are found in a healthy American diet and also important in stabilizing Omega-3 fatty acids. Turmeric Extract (curcumin) has a number of systemic and ocular anti-inflammatory mechanisms including COX-2 mediated conversion of Omega-6 fatty acids to pro-inflammatory prostaglandins and inhibition of other pro-inflammatory signals on the ocular surface. (Interleukins MMP-9, MAPK, TNF-alpha, p38, JNK and NF-Kappa B) [26].

Another unique component of the study supplement is green tea extract, which contains ECGG; a component found helpful in treatment of connective tissue disorders and dry eye. Green Tea Extract (50mg containing 95% polyphenols and 40% ECGG)-has both antioxidant and multi-modes of action on anti-inflammatory pathways in systemic and ocular tissues [27]. An intriguing observation is that ECGG and curcumin are natural inhibitors of MMP-9, a central mediator of ocular surface pro-inflammatory cytokines, a major contributor of dry eye.

The study supplement's Omega-3 Fatty Acids (1000mg DHA/EPA) are derived from fish oil that has been purified and enriched until it contains nearly 70% (by weight) of the two compounds DHA and EPA. These two compounds have been identified as important compounds responsible for the many beneficial effects of fish oil on human health [2, 28-30].

Conflicting signs are a hallmark of dry eye disease. Some of the dry eye markers used in this study also lacked agreement with patient symptoms. Recently, more has been written about this perplexing feature in the diagnosis and treatment of dry eye [1, 31-34]. Better terminology is needed to reflect the ways in which the lacrimal/meibomian/corneal lacrimal functional unit can become compromised [34].

Our findings showed improvement in corneal and conjunctival staining scores, OSDI, tear breakup time, phenol red scores, tear meniscus and lid inflammation. The rapid onset of action, both subjectively as measured by OSDI and objectively was notable. Osmolarity scores were variable and inconclusive. However, the association between dry eye and elevated tear film osmolarity has been evaluated and confirmed by numerous studies; Gilbard et al. [35] reported this association as early as 1978. Lemp et al. [36] reported that tear film osmolarity is the best single means of diagnosing and classifying dry eye disease. His group used a recently-introduced impedance-based system osmometer that uses nanometric volumes of fluid to evaluate tear film osmolarity (TearLab San Diego, CA, USA). Versura et al. [37] also reported that tear film osmolarity is the best single test for predicting dry eye disease. In the present study, which extended over a period of eight weeks, we found minimal correlation between the ingestion of the study supplement and changes in tear film osmolarity. This is not entirely surprising; Szalai et al. [38] reported that while hyperosmolarity is a key factor in dry eye, his group found that other diagnostic tests such as Schirmer I test, tear film break-up time, and corneal staining did not correlate well with tear film

osmolarity.

There are relatively few studies addressing the use of systemic supplementation, specifically with omega essential fatty acids, for the treatment of dry eye. Rand and Asbell [39] reported the benefits for omega-3 essential fatty acids, a primary component of the study supplement, in managing dry eye. Larmo et al. [40] evaluated the effect of sea buckthorn oil, a source of both omega-3 and omega-6 essential fatty acids on tear film osmolarity in individuals with dry eye. They found that over the course of the study, subjects taking the omega essential fatty acids groups showed lower tear film osmolarity compared to controls. One plausible explanation for the discrepancy in our study between conventional dry eye tests and tear film osmolarity is relatively brief length of the study. In future trials, extending the length of the study might result in better correlation between osmolarity and other tests. An additional explanation of the results may reflect that osmolarity is a response to an improved tear film layer, whereas the other diagnostic tests are a direct measurement of specific layers of the tear film.

A limitation to this study was that it was not a randomized trial and there was no control group. The investigators considered during the design of this clinical trial the use of a placebo. The definition of a placebo is a “simulated or otherwise medically ineffectual treatment for a disease intended to deceive the recipient”. The use of active lipids like Omega-3 fatty acids in a soft gel make the design of an appropriate “neutral” soft gel technically difficult. The use of an Omega-6 fatty acid as a substitute cannot be considered as neutral as they are often pro-inflammatory. Stable mono-unsaturated fatty acids (like olive oil) were once used as placebos for lipid studies until it was discovered that it contains a powerful antioxidant. Mineral Oil is another choice but it is known to deplete the body of fat soluble nutrients. The informed clinician has poor choices in trying to deceive the recipient in lipid soft gel based trials. For these reasons, the investigators chose not to attempt a placebo arm for the study. By not using a placebo makes it impossible to say for certain that the changes seen here are directly related to the administration of the supplement to these patients. By analyzing changes from baseline, it would seem to indicate that there really are true improvements in the signs associated with dry eye, particularly as some continue to improve rather than regress to the mean as one might expect.

## Conclusion

Dry Eye etiology through diagnostic testing associated with subjective response is difficult to uncover due to the many intrinsic and extrinsic factors. The ONIT study showed that OSDI, TBUT, conjunctival staining, lid inflammation, phenol red, meniscus height and corneal staining significantly improved through ingestion of supplements with Omega-3 by the end of the eight-week investigation. Osmolarity scores did not show improvement although this might be due to the short duration of our study. The tear film is complex and the formula tested utilized not only high quality essential fatty acids, but seven other key anti-inflammatory ingredients to help improve the objective signs and subjective symptoms in study participants. The improvement in OSDI scores by reducing patient symptom could be an indication of decrease ocular surface inflammation and rapid stabilization of the tear film.

## Acknowledgment

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