2018

Is daily supplementation with omega-3 fatty acids effective in reducing the severity of dry eye syndrome in adult patients?

Julie A. Laureni
Philadelphia College of Osteopathic Medicine

Is daily supplementation with omega-3 fatty acids effective in reducing the severity of dry eye syndrome in adult patients?

Julie A. Laureni, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 15, 2017

ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not daily supplementation with omega-3 fatty acids is effective in reducing the severity of dry eyes in adult patients with dry eyes syndrome (DES).

Methods: Three randomized controlled trials are included in this review that were published in 2013, 2016 and 2017.

Data sources: The author of this paper performed the research as well as selected the articles for review by conducting searches on PubMed, Embase and Cochrane Library.

Outcomes: The outcome measured is the severity of dry eyes symptoms measured subjectively by each patient through a 12-item questionnaire after a minimum of one month and maximum 12 weeks of treatment. The Ocular Surface Disease Index (OSDI), *(Allergan, Inc.),* scale was used to measure subjective outcomes in all studies. An average score for each group was calculated as well as the change in scores between the first and the last day of studies.[1,2,3]

Results: In Deinema et al (2017), for patients taking krill oil supplementation, dry eye symptoms improved 18.6+/-2.4 points (mean change in baseline score) over three months per OSDI scores.[1] In Epitropoulo et al (2016), in the treatment group symptoms improved 17.0+/-2.6 points over three months.[2] In Kangari et al (2013), symptoms improved 9.4+/-0.6 points over one month patients receiving treatment while the placebo group reported a 1.2+/-0.3 point worsening of symptoms.[3] All data described above was statistically significant ($p < 0.005$).

Conclusions: It can be concluded that daily omega-3 essential fatty acid supplementation is effective for reducing the severity of dry eye syndrome in adults, especially those with mild-moderate DES after 90 days.

Key Words: Dry eye syndrome; Omega-3 fatty acids

INTRODUCTION

Dry eyes are a manifestation of a disorder that is best known as dry eye disease (DED)[1], meibomian gland dysfunction (MGD)[2] or dry eye syndrome (DES)[3]. This is a multifactorial disease of the lacrimal gland that involves an inflammatory response at the ocular surface with debilitating irritation as well as profound visual impairment.[4] It occurs when the eye is not properly lubricated with tears as a result of either poor production, excessive evaporation or improperly balanced components.[4]

This systematic review paper evaluates three randomized clinical trials (RCT's) in order to compare the efficacy of daily supplementation with oral omega-3 (ω-3) fatty acids for reducing the severity of dry eyes in adult patients with DES. Earlier studies reported that intake of ω-3 fatty acids, through dietary consumption of fish or by oral supplementation, have anti-inflammatory effects within the body. This was first seen by a reduction of autoimmune disease incidence, and later on for the benefit of other disorders like DES.[5] Current research suggests that omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) block pro-inflammatory mediators at the surface of the eye while providing symptomatic relief.[1,2,3]

Healthy eyes require protection from multiple layers of tears in order to function properly.[6] First, a lipid layer helps spread the tear film evenly over the surface. Next, an aqueous protein layer nourishes the cornea. Lastly, a mucous layer provides continuous lubrication.[6] DES involves either the decreased production of tears (aqueous-deficiency) or increased evaporative loss, however it is usually a mixture of both.[4] In deficiency, tears fail to be made and cannot complete lubrication. In evaporation, tears are lost and abnormal lipids levels exist.[4,6] In either type, increased osmolarity of the tear film results in release of pro-inflammatory cytokines (IL-1, IL-6 and TNF-α),[1] which activates sensory nerves and triggers dry eye symptoms.[6] The poor quality of tears focuses light improperly on the retina and blurs the vision reversibly.[6] Most patients suffer mild to moderate discomfort chronically.

An estimated 14.5% of adults in the United States suffer from dry eyes, including 17.9% of women and 10.5% of men affected.[7] Up to 30% of Americans over the age of 50 are reportedly affected and the prevalence is expected to increase with the aging population.[7] Post menopausal women are especially at risk due to changes in hormone levels.[5] In addition, DES is now affecting younger generations due to constant computer use that reduces the frequency of blinking.[4,6] Other risk factors include contact lens (CL) use, low humidity environments, previous eye surgery, presence of systemic disease and certain medications[4,6] All of these factors have been known to reduce the quality and quantity of tears.[6]

It's estimated that the annual cost of managing dry eye in the U.S is $55 billion.[8] No data is available on the number of healthcare visits for dry eyes annually. However, it is stated to be the most common reason for seeking eye care.[7] Most patients present with non-specific irritative symptoms such as burning, pruritus, foreign body sensations, excessive tearing, blurry vision, photophobia and redness.[6,7] Other complaints relate to vision impairment and include difficulty reading, driving or performing daily activities.[4] Ultimately, quality of life can be significantly reduced in DES to a degree that has been reported to be equivalent to angina pectoris.[7]

Artificial tears (AT's), available over-the-counter, are the mainstay of treatment.[6] They enhance the viscosity of tears and provide only short-term relief from irritation without addressing inflammation.[4,6] Warm compresses are an option for extra support.[4] First line medical therapies includes topical immunosuppressant drugs that reverse the inflammatory mechanism.[4,6] This includes Restasis® (cyclosporine emulsion) 0.05%, cytokine activation inhibitor and Xiidra® (lifitegrast solution) 5%, an integrin antagonist.[4,6] Both products are expensive without insurance but can potentially offer long-term relief.[4,6,7] Ultimately, for most patients, there is no permanent solution and treatment is long-term with a combination of methods.[4,6,7]

Omega-3 is a polyunsaturated fat essential for normal growth and development of the human body.[4,9] Benefits in the eye include increased levels of fatty acids in secretions, which improves tear film quality and prevent evaporation, thus reducing DES symptoms.[4,6] When digested omega-3 favors anti-inflammatory pathways via the blockade of cytokines and competitively inhibits pro-inflammatory pathways.[1,2,7] Consuming cold-water fish (salmon, tuna and sardines) with high amounts of ω-3 helps raise levels in the body.[9] However, fish have high mercury levels as well as other toxins and cannot be consumed in quantities that would benefit the eye without causing other health risks.[1,9]

This method of treatment is being proposed because omega-3 supplements are marketed for and recommended by practitioners for DES but research has been inconsistent. Omega-3 is best absorbed by the human body in its natural triglyceride form, however, during manufacturing it gets converted into an ethyl ester via distillation, which is necessary for toxin elimination. [1,9] Most omega-3 products are available in this poorly absorbed formula. Newer re-esterified formulas have been converted back into a triglyceride for better absorption. [2,9] In addition, it has been suggested that phospholipid form, as in krill oil, has even greater bioavailability. This paper will compare the three different types of omega-3 by measuring patient reported symptoms.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not daily supplementation with oral omega-3 fatty acids is effective in reducing the severity of dry eye symptoms in adult patients with clinically diagnosed DES. It is hypothesized that daily intake is associated with an improvement in symptoms and result in a better quality of life.

METHOD

Three randomized controlled trials (double-blind, placebo-controlled) are reviewed in this paper that focused on a population of adult patients (18 -90 years old) with a history of DES. The

intervention of choice is daily oral supplementation with ω-3 fatty acids containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The experimental groups received ω-3 fatty acids and are compared to the control groups who received a visually matched placebo. Outcome measured is the severity of dry eyes symptoms measured subjectively by each patient through a 12-item questionnaire, after a minimum of one month and maximum 12 weeks of treatment. Physical discomfort, visual impairment or environmental triggers were inquired about in the assessements.[1,2,3]

The author of this paper performed the research as well as selected the articles for review by conducting searches on PubMed and Cochrane Library. Each of the three articles had been published data in peer-reviewed journals in the English language. The search criteria included 'Dry eye syndrome' & 'Omega-3 fatty acids' as keywords. When selecting studies, the inclusion criteria consisted of studies that were RCT's published between 2006 and 2016, studies that used a regimen of EPA and DHA omega-3 fatty acids in the experimental group and studies that used the OSDI questionnaire. Exclusion criteria were studies with participants under the age of 18, studies that allowed use of other therapies, and studies specific to CL use, computers or diseases. In each study, statistics were reported as the mean change in score (OSDI scale) from baseline at day one +/- standard error the mean (SEM), as well as in p-value for statistical significance ($p<0.05$).[1,2,3] Treatment safety was based on the number of reported adverse events.

Table 1: Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Deinema, 2017[1]	RCT	60	≥18	Mild-to-moderate dry eye symptoms (OSDI score: 18-65); Tear osmolarity of ≥316 mOsm/L in at least one eye; IOP <21 OU; BCVA ≥20/40 OU	Co-morbid ocular pathology; Uncontrolled systemic disease; Systemic disease contraindicating omega-3 supplements; Allergy to fish/seafood, nuts, oil or gelatin; Current use of oral ω-3 supplements; Contact lens use within one month or intended use over course of study; History of ocular surgery or trauma; Active ocular infection or allergy; Use of topical ocular medications (steroids, NSAIDs, or cyclosporine) and systemic anti-coagulants in the 3 prior months; Use of	6	5 capsules/day for 3 months of either: a) Krill oil: 945 mg/day EPA & 510 mg/day DHA. OR b) Fish oil: 1000 mg/day EPA & 500 mg/day DHA. *Total 1500mg daily.*

					any prescription or supplement that affect tear production or vision.		
Epitropoulos, 2016[2]	RCT	122	21-86 (>18)	MGD stage 1,2; Tear osmolarity of ≥312 mOsm/L in at least one eye on 2 visits	MGD stage 3; Use of topical cyclosporine 0.05%, corticosteroids, NSAIDs, glaucoma medication, or oral ω-3 fatty acids within 3 weeks of screening; (+) History of refractive surgery within 1 year; Use of systemic medication that affects ocular surface.	17	4 softgels/day for 12 weeks: 1680 mg/day EPA & 560 mg/day DHA (re-esterified). *Total 2240mg.*
Kangari, 2013[3]	RCT	73	45-90	TBUT <10 seconds in both eyes; No use of artificial tears for past 3 months	Active allergies or infection at ocular surface; Presence of pterygium or pinguecula; Use of topical steroidal, NSAID, glaucoma, or anti-allergy eye drop in past month; (+) History of refractive surgery, contact lens use, blood/coagulation disorder, gastric ulcer, or fish oil/gelatin allergy; Use of medication that interferes with tear production; (+) History of any surgery or use of ω-3 supplements in past 3 months; Currently undergoing head/neck radiotherapy.	9	2 capsules/day (AM & PM) for 1 month: 360 mg/day EPA & 240 mg/day DHA. *Total 600mg daily.*
Abbreviations: Ocular Surface Disease Index (OSDI); Meibomian gland dysfunction (MGD); Tear breakup time (TBUT); Eicosapentaenoic acid (EPA); Docosahexaenoic acid (DHA); Non-steroidal anti-inflammatory drug (NSAID)							

OUTCOMES

The Ocular Surface Disease Index (OSDI), *(Allergan, Inc.),* scale was used to measure subjective outcomes in all studies. This is a validated 12-item survey that ranks symptoms using a 5-point scale (0 = none of the time, 1 = some of the time, 2 = half the time, 3 = most of the time, 4 = all of the time). Each patient completed a questionnaire at every follow-up. The total score range is from 0 (none, no disability) to 100 (maximum, full disability) with higher values representing greater disability. It was important to calculate each subject's average score per session as well as the change in scores between the first and the last day of studies.[1,2,3]

RESULTS

This paper investigates three randomized controlled trials (RCT's) that assessed the efficacy of ω-3 fatty acid supplementation in the treatment of DES. Methods of data collection as well as inclusion and exclusion criteria are discussed above *(see Table 1).* All three studies randomized their subjects to either control or experimental treatments group(s), assignments to which the participants, clinicians and investigators were blind during allocation and throughout the studies. All three studies used a placebo that was visually comparable to the treatment

received by experimental group(s). Although the specific placebo varied among each study, ω-3 regimens were also different. Treatment efficacy from all three studies was reported as continuous data that could not be converted to dichotomous data.[1,2,3] Treatment safety is reported as numbers needed to harm (NNH) and was converted into dichotomous format.

All three studies used the OSDI for symptom assessment as well as patients previously diagnosed with DES, which was of mild to moderate severity in Deinema et al (2017) and Epitropoulo et al (2016). In addition all groups in each study had similar OSDI scores at baseline. All three papers concluded that ω-3 does reduce the severity of DES symptoms, specific parameters are described below *(table 2)*.[1,2,3]

Table 2: Outcomes of Included Studies

Study	Duration	# Participants (n)	Significant Intervention	Mean change from baseline score (scale of 100)	p-value	95% CI
Deinema, 2017[1]	90 days	54	Krill oil (1500mg/day)	-18.6+/-2.4	p = 0.02	N/A
Epitropoulos, 2016[2]	90 days	105	Re-esterified (2240mg/day)	-17.0+/-2.6	p = 0.002	-12.0 (-19.4 to -4.5)
Kangari, 2013[3]	30 days	64	DHA & EPA (600mg/day)	-9.4+/-0.6	P = 0.004	N/A
	30 days	64	Placebo	+1.2+/-0.3	P = 0.049	Note: symptoms worsened

Deinema et al (2017), is a double-masked, placebo-controlled study *(table 3)*. It enrolled 60 adult patients that were randomly assigned to one of three groups. Assessments occurred in four visits over 90 days for the 54 that completed the study. EPA/DHA is a phospholipid in krill oil and is a triglyceride in fish oil, the later being studied more frequently. The placebo was a 1500mg dose of oleic acid (olive oil). While CL use was forbidden, AT use was permitted throughout the study. In addition, subjects were asked about dietary changes at each visit. The outcome measured was dry eye symptoms severity on the OSDI scale. Factors affecting the outcome include the small size of participants (n=54), recruitment from only one treatment center, high 1500mg dosing, and type of lipid received by participants.

In patients taking krill oil supplementation, dry eye symptoms improved 18.6 points over

three months as measured by OSDI scores. Meanwhile the placebo group reported a 10.5+/-3.3 point improvement. This represents a reduction from baseline, in other words, an improvement of symptoms for the krill oil group (mean change in baseline score = -18.6+/-2.4, p = 0.02).

Compared to placebo, only the krill oil group score was statistically significant at day 90 relative to day 1. The outcome was not significant and therefore not reported for fish oil. This means that ω-3 in phospholipid form of krill oil may offer superior benefits for DES symptoms compared to triglyceride form of fish oil. Outcomes were not significant for any group at the 2nd or 3rd follow-up and not reported.[1] However, data trends showed improvements for each throughout the study, suggesting greater outcome with longer duration of therapy.

Table 3: Treatment Effect in Deinema et al (2017)[1] *(Scores at day 30,60, 90 not reported)*

	Baseline	**Mean change from baseline +/- SEM (scale of 100)**
Krill Oil (n=18)	30.5 +/- 2.4	-18.6+/-2.4, p=0.02
Fish Oil (n=19	36 +/- 3.4	Not reported
Placebo (n=17)	31.7 +/- 2.6	-10.5 +/-3.3

Epitropoulo et al (2016), is a multi-centered, double-masked, placebo-controlled study *(table 4)* that enrolled 122 adult patients that were randomly assigned to group 1 or 2. For the 105 participants that completed the study, assessments took place in 3 visits over 90 days. The EPA/DHA provided was in re-esterified form. The placebo was a dose of linoleic acid (safflower oil), a ω-6 fatty acid. CL and AT use was allowed except before visits for 12 and 2 hours, respectively. Subjects kept daily food diaries and dietary changes were not allowed. The outcome was dry eye symptoms severity on the OSDI scale. Factors affecting the outcome include the use of re-esterified ω-3, the female majority of participants, high dosing with 2240mg daily. In addition, the choice of ω-6 as a placebo could worsen inflammation as it has been shown to have this effect in the body, which is opposite to that of omega-3.

In the experimental group, dry eye symptoms improved 17 points over three months as measured by OSDI scores. Meanwhile the control group had only 5.0+/-2.7 point improvement.

These values represent a reduction from baseline, in other words, an improvement of symptoms with treatment (mean change in baseline score = -17.0+/-2.6, p = 0.002, CI = -19.4 to -4.5).

Compared to the control, the score of the treatment group was statistically significant at 12 weeks relative to day 1. This means that the re-esterified omega-3 benefits DES symptoms, although it is uncertain whether it is superior to the usual triglyceride form. Outcomes were not significant at 6-weeks, although both groups had less symptoms at this visit.[2]

Table 4: Treatment Effect in Epitropoulo et al (2016)[2] *Mean change from baseline +/- SEM (scale of 100)*

	Baseline	6 weeks	Mean Change	95% CI	12 weeks	Mean Change	95% CI
Omega-3 (n=54)	32.4+/-19.2	21.0+/-14.4	-11.4+/-2.6	-4.0(-11.2 to 3.3); p=0.285	15.5+/-11.0	-17.0+/-2.6	-12.0 (-19.4 to -4.5); p=0.002
Placebo (n=51)	27.1+/-22.9	19.6+/-17.0	-7.4+/-2.6		22.0+/-19.3	-5.0+/-2.7	

Kangari et al (2013), is a double-masked, placebo-controlled study *(table 5)*. It randomly assigned 73 patients, ages 45-90, to group 1 or 2. Only 64 completed the study and attended each of two visits within one month. The specific type of EPA/DHA provided was not reported. The placebo was a medium chain triglyceride. CL and AT use was forbidden throughout the study. The outcome measured was dry eye symptom severity, on the OSDI scale, at day 30. Factors affecting the study outcome include the small number of participants (n=64), recruitment from only one center, small dosing of 600mg/day, the short study duration compared to others, lack of dietary control over the subjects, and older ages of patients who are at higher risk for DES. The paper did not mention criteria for disease severity during enrollment.

In the treatment group, dry eye symptoms improved 9.4 points over three months as measured by OSDI scores. This represents a reduction from baseline, in other words, an improvement of symptoms by 26% (mean change from baseline = -9.4+/-0.6; p = 0.004). The treatment group's score was statistically significant at day 30 relative to day one. Surprisingly, the control had a 1.2+/-0.3 point decline (p=0.049), meaning that symptoms worsened by 4%. This suggests that not having the treatment was powerful enough to overcome any placebo effect that occurs when taking the treatment alone causes positive outcomes.[3]

Table 5: Treatment Effect in Kangari et al (2013)[3]			
	Baseline Score	**Day 30 Score**	**Mean change from baseline +/- SEM (scale of 100)**
Omega-3 (n=31)	38.7+/-16.5	29.3+/-15.9	-9.4+/-0.6 (p = 0.004)
Placebo (n=33)	36.4+/-13.8	37.6+/-13.5	+1.2+/-0.3 (p = 0.049)

This discussion pertains to 3 different RCT studies that each compared experimental treatment by ω-3 (EPA & DHA) with placebos. Epitropoulos et al (2016) and Kangari et al (2013) each evaluated a single type of omega-3, however, two different forms (krill and fish oil) were assessed in Deinema et al (2017). Compliance was only assessed in Deinema et al (2017), Epitropoulos et al (2016) by count of returned medication containers. Epitropoulos et al (2016) sent daily medication remainders to their subjects via text, which most likely increased their compliance and improved their data.

Each study took place at ophthalmology clinics in symptomatic patients having a history of clinically diagnosed DES. Deinema et al (2017) was conducted in Melbourne, Australia using mild-moderate DES patients. Epitropoulos et al (2016) recruited patients with stage 1 or 2 MGD from various U.S. clinics. Kangari et al (2013) used a private clinic in Tehran, Iran. Outcomes specific to race, diet and climate cannot be accounted for in this paper considering each study was conducted on a different continent from the others.

Analysis of the OSDI scores from the treatment groups was compared to controls in each of the three studies. In Deinema et al (2017), each treatment under investigation appeared to show improvement but statistically only the outcome of krill oil was significant at 90 days. In addition, both Epitropoulos et al (2016) and Kangari et al (2013) reported significant treatment effect at 90 and 30 days, respectively. The former also reported worsening of symptoms for the control suggesting a preventative effect by ω-3.

In Deinema et al (2017), the number of reported adverse events was used for assessment of treatment safety. From this data, the risk of harm was calculated and reported in numbers needed to harm (NNH). Formulas and calculations can be found in table 6. A NNH of 4 means

that for every 4 people treated with fish oil (3 people for krill oil), one person has a bad event. While 53 events were reported, 51 of the events were mild (well-tolerated), 2 were moderate (interfered with activity) and none were severe (life-threatening). The most common were colds (24.5%), sore throat (11.3%), headache (13.2%), GI events (nausea, bloating, heartburn; 11.3%) and remaining 39.6% not associated with treatment. Ultimately, while side effects are noticeable, omega-3 has low toxicity and remains a feasible treatment option.

Table 6: Adverse Events (NNH) of Treatment in Deinema et al (2017)

	# of events	CER (control event rate) = events/total # subjects	EER (experimental event rate) = events/total # subjects	RRI (relative risk increase) = (EER-CER)/CER	ARI (absolute risk increase) = EER-CER	NNH (numbers needed to harm) = 1/ARI
Placebo, 17	20	1.2%	N/A	N/A	N/A	N/A
Fish Oil, 18	19	1.2%	1.0%	0.2%	0.2%	4
Krill Oil, 15	18	1.2%	0.8%	0.3%	0.5%	3

DISCUSSION

For many decades, the potential health benefits of ω-3 consumption have been the focus of a multitude of scientific research areas. Despite speculation, omega-3 has not been associated with a rate reduction in cardiovascular events,[9] risk reduction in cancer[5] nor in the prevention of Alzheimer's disease.[5] It is however, approved in prescription for severe (≥500 mg/dL) hypertriglyceridemia, serving as secondary prevention in coronary heart disease (CHD).[9] Furthermore, investigation in depressive disorders continues.[5,6] Ultimately, the exact role of omega-3 on inflammatory processes in the human body must be further explored.

In Deinema et al (2017) and Epitropoulos et al (2016), subjects younger than 18 were excluded, as they are unlikely to be affected so unlikely to seek treatment. However, Kangari et al (2013) excluded patients under the age of 45, which means this study focused on an older population who are more likely to be afflicted. [1,2,3] Meanwhile none of the studies allowed participation by patients with ocular or systemic diseases that, compared to the general adult population, are more prone to DES and more likely to present with it clinically.[1,2,3]

Significant data from each of the studies was collected at a specified point in time during ω-3 intervention. The most dramatic improvement in symptoms occurred at three months as in Deinema et al (2017) with krill oil (18.6 point score reduction). This is compared to 3 months in Epitropoulos et al (2016) with re-esterified ω-3 (17.0 point reduction), and one month in Kangari et al (2013) with unspecified low-dose DHA/EPA (9.4 point reduction). Point reduction means that symptoms improved and represents a positive outcome. The author's decision to restrict article selection to studies using OSDI may have placed data in favor of this hypothesis.

CONCLUSION

It can be concluded that daily ω-3 fatty acid supplementation is effective for reducing the severity of dry eye syndrome in adults, especially those with mild-moderate disease, after 90 days of use. Based on the data presented in this paper, krill oil (>1500mg) offers the greatest treatment effect but also causes the most side effects. Re-esterified formulas (2240mg) are the second most effective. The longer the treatment, the better the symptoms. This is attributed to the anti-inflammatory effect of ω-3 that has been demonstrated in prior studies.[1,5] Ultimately, daily ω-3 fatty acid supplementation has capacity to improve quality of life for DES patients.

While the type, the dose, and the duration of omega-3 treatment all influential the outcome of treatment, however additional trials are needed to clarify which factor is most important. Currently studies are being conducted to assess the treatment effect of ω-3 along with ω-6 supplementation.[1,2] Meanwhile, future studies are necessary to evaluate ω-3 in combination with and in contrast to the first line therapies including Restasis and Xiidra. In addition, is also important to compare the side effect profile of re-esterified oils to krill oils. Overall, a multicenter clinical trial with an increased number of participants and longer treatment duration must take place in order to assess the efficacy and safety of krill oil and re-esterified ω-3 fatty acids long-term.

References

1. Deinema LA, Vingrys AJ, Wong CY, Jackson DC, Chinnery HR, Downie LE. A randomized, double-masked, placebo-controlled clinical trial of two forms of omega-3 supplements for treating dry eye disease. Ophthalmology. 2017;124(1):43-52. doi:10.1016/j.ophtha.2016.09.023.

2. Epitropoulos AT, Donnenfeld ED, Shah ZA, et al. Effect of oral re-esterified omega-3 nutritional supplementation on dry eyes. Cornea. 2016;35(9):1185-1191. doi:10.1097/ICO.0000000000000940.

3. Kangari H, Eftekhari MH, Sardari S, et al. Short-term consumption of oral omega-3 and dry eye syndrome. Ophthalmology. 2013;120(11):2191-2196. doi:10.1016/j.ophtha.2013.04.006.

4. Messmer EM. The pathophysiology, diagnosis, and treatment of dry eye disease. Dtsch Arztebl Int. 2015.112(5):71-81; doi: 10.3238/arztebl.2015.0071.

5. Kiecolt-Glaser JK, Belury MA, Andridge R, Malarkey WB, Hwang BS, Glaser R. Omega-3 supplementation lowers inflammation in healthy middle-aged and older adults: a randomized controlled trial. Brain Behav Immun. 2012 Aug;26(6):988-95. doi: 10.1016/j.bbi.2012.05.011.

6. Shtein, RM. Dry Eyes. Up-to-date. https://www-uptodate.com.ezproxy.pcom.edu/contents/dry- eyes?source=search_result&search=dry%20eyes&selectedTitle=1~150. Updated April 7, 2017. Accessed October 5, 2017.

7. Lemp, MA. Advances in understanding and managing dry eye disease. Am J Ophthalmol. 2008;146:350-356. doi:10.1016/j.ajo.2008.05.016.

8. Paulsen AJ, Cruickshanks KJ, Fischer ME, et al. Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life. Am J Ophthalmol. 2014;157(4):799-806. doi:10.1016/j.ajo.2013.12.023.

9. Omega-3 Fatty Acids. Lexi-Drugs. http://online.lexi.com.ezproxy.pcom.edu:2048/lco/action/doc/retrieve/docid/patch_f/691. Updated 12/4/17. Accessed 12/1/17.