Effect of Oral Omega-3 Fatty Acid Supplementation on Contrast Sensitivity in Patients With Moderate Meibomian Gland Dysfunction: A Prospective Placebo-Controlled Study

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Purpose: To evaluate the effect of oral supplementation with omega-3 (ω-3) fatty acids (FAs) in improving contrast sensitivity (CS) of patients with moderate meibomian gland dysfunction (MGD).

Methods: In this prospective study, 60 patients with moderate MGD were allocated alternately to treatment and control groups. Both groups received warm compresses, lid massage, and artificial tear substitutes. The treatment group also received oral supplements of 1.2 g ω-3 FAs per day. All parameters were recorded at baseline and at 12 weeks and included Ocular Surface Disease Index scores, CS testing at 3, 6, 12, and 18 cycles per degree (cpd), tear break-up time, Schirmer test I without anesthesia, corneal and conjunctival staining scores, and meibum quality and expressibility.

Results: At the end of 12 weeks, significant improvement in CS was seen in the treatment group in 7 of the 8 testing conditions (3, 6, 12, and 18 cpd photopic and 6, 12, and 18 cpd mesopic), whereas in the placebo group, significant improvement was seen only in 3 of the 8 testing conditions (3 cpd photopic, 6 and 18 cpd mesopic). Ocular Surface Disease Index, tear break-up time, ocular surface staining, and meibum quality and expressibility improved significantly in both groups, but more so in the treatment group. Schirmer scores showed no significant improvement in either group.

Conclusions: Oral supplementation with ω-3 FAs significantly improved CS under both photopic and mesopic testing conditions in patients with moderate MGD. Tear film stability also improved significantly, whereas no effect was seen on aqueous tear production.

Key Words: omega-3 fatty acids, meibomian gland dysfunction, dry eye, contrast sensitivity

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Dry eye disease (DED) has been defined by the International Dry Eye Workshop 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."[1] Dry eye is a frequent cause of ocular discomfort and morbidity with reported prevalence rates ranging from 5% to 30% in populations over 50 years of age.[2,3] Individuals with meibomian gland dysfunction (MGD) form an important subset of dry eye patients with an age-related increase in prevalence from nearly 0% in the first decade of life to up to 68% in patients over 60 years of age.[4–6] MGD may be due to varying mechanisms, including increased meibum viscosity, hyperkeratinization of ductal epithelium, acinar atrophy, and inflammation.[7] It has been proposed that MGD leads to production of substances that destabilize the tear film, for example, fatty acids (FAs), and this change in the tear film composition subsequently results in inflammation of the ocular surface.[4,8–11]

Omega-3 (ω-3) and omega-6 (ω-6) are essential FAs, which need to be obtained from dietary sources because they cannot be synthesized by the body. Although both these essential FAs are required in adequate amounts for normal functioning, they compete for the same enzymes that are part of the inflammatory pathway involving arachidonic acid. Because they have somewhat opposing actions, with ω-3 FAs being predominantly antiinflammatory and ω-6 FAs being proinflammatory, it is the ratio in which these 2 are present that determines shifting of the milieu of the human body to a pro- or an anti-inflammatory state. The ideal ratio of ω-3 to ω-6 FAs in the diet has been variably described as ranging from 1:2.3 to 1:4.[12]

The clinical evidence for antiinflammatory effects of ω-3 FAs is provided by epidemiologic studies with populations that have high amounts of seafood in their diet (a rich source of ω-3 polyunsaturated FAs) having a lower incidence of autoimmune and inflammatory disorders such as psoriasis, asthma, and multiple sclerosis.[13–15] This antiinflammatory effect has been documented at a cellular level too, with ω-3 FA supplementation leading to a decreased capacity of the monocytes to synthesize the proinflammatory interleukin 1 (IL-1) through suppression of IL-1 mRNA and tumor necrosis factor.[16–18] A review of dietary diaries of women enrolled in

the Women's Health Study revealed that a higher dietary intake of dietary ω-3 FAs was associated with a decreased incidence of dry eye syndrome in women.[19] Supplementation with ω-3 FAs has also been shown to have a beneficial effect on dry eyes of varied etiologies including MGD, both by increasing tear secretion and by stabilization of the tear film.[20–24]

Dry eye due to any cause is increasingly being recognized as adversely affecting the physical, social, and psychological quality of life and having a deleterious effect on various aspects of visual function despite a normal visual acuity being documented using standard testing techniques.[25] Reading speed has been found to be significantly lower in patients with DED as compared with controls.[26] DED has also been recognized as being associated with altered contrast sensitivity (CS).[27–29] It is increasingly being appreciated that standard high-contrast tests such as Snellen visual acuity, which are routinely used to assess visual function in the clinical setting, do not effectively simulate real-life situations where much more subtle differences in contrast need to be appreciated, especially in dim light or situations associated with glare. Thus, CS is nowadays being considered as a more specific and accurate indicator of functional visual performance of an individual than Snellen visual acuity or similar high-contrast tests. The tear film forms the first refracting surface of the eye, and the use of artificial tears in dry eye has been found to improve CS.[30] In view of previous literature supporting the positive effect of ω-3 FAs in qualitatively and quantitatively improving the tear film, this study was designed primarily to assess the effect of oral supplementation with ω-3 FAs in improving CS in patients with moderate symptoms and signs of MGD, in addition to seeing their effect on other clinical measures of the tear film, ocular surface, and meibomian glands.

MATERIALS AND METHODS

Patients attending the Cornea Services of the Advanced Eye Centre, at the Post Graduate Institute of Medical Education and Research, Chandigarh, India, and diagnosed to have moderate MGD were prospectively recruited for this study between July 2012 and November 2013. The study was approved by the ethics committee of the institute. Patients were explained in detail about the study, and written consent adhering to the tenets of the Declaration of Helsinki was obtained from each of them. Sixty consecutive patients with moderate MGD who agreed to be a part of the study were allocated alternately to the study and control groups. MGD was classified as mild, moderate, or severe based on criteria published earlier.[31] Briefly, this classification includes the severity of the patients' symptoms and the severity of clinical signs including meibum quality, meibum expressibility, and lid margin signs. Meibum quality is assessed and scored in each of the 8 glands of the central third of the lower lid on a scale of 0 to 3: 0 = clear; 1 = cloudy; 2 = cloudy with debris (granular); and 3 = thick, like toothpaste (total score range, 0–24, scores ≥4 to <8 mild MGD, ≥8 to <13 moderate MGD, and >13 severe MGD). Meibum expressibility is graded on a scale of 0 to 3 in 5 glands in the lower or upper lid, according to the number of glands expressible: 0 = all glands expressible (mild MGD), 1 = 3 to 4 glands expressible (mild MGD), 2 = 1 to 2 glands expressible (moderate MGD), and 3 = no glands expressible (severe MGD).

The inclusion criteria for this study were (1) patients with moderate[31] clinical symptoms and signs of MGD, for example, moderate ocular discomfort, itching, or photophobia; lid margin features of plugging and/or vascularity; meibum quality score ≥8 to <13, meibum expressibility: grade 2; (2) age > 40 years; (3) patients not on any other form of treatment for MGD; and (4) corrected distance visual acuity (CDVA) equal to or better than 20/30 in each eye. The exclusion criteria were (1) a history of contact lens wear; (2) symptoms and signs of mild MGD,[31] that is, minimal to mild symptoms of ocular discomfort, itching, or photophobia; meibum quality score ≥4 to <8; meibum expressibility: grade 1; (3) symptoms and signs of severe[31] MGD, that is, marked symptoms of ocular discomfort, itching, or photophobia with definite limitation of activities; increased lid margin signs including meibomian gland dropout and displacement; meibum quality score ≥13, meibum expressibility: grade 3; (4) infectious or allergic keratoconjunctivitis; (5) lacrimal drainage abnormalities; (6) Schirmer score <10 mm/5 minutes; (7) a history of topical steroid, nonsteroidal antiinflammatory agents, or antiglaucoma medication in the last 6 weeks before enrollment in the study; (8) a history of ocular surgery in the last 6 months; (9) pregnant, nursing, or lactating women; (10) patients taking anticoagulants, antihistamine, retinoids, or antidepressants; (11) patients having malabsorption syndromes; (12) a history of allergy to fish oils; (13) the presence of significant cataracts; and (14) a history of diabetes mellitus or other systemic conditions that may adversely affect CS. All measurements were performed by a single observer throughout the course of the study.

Clinical Assessment

Patients were observed in detail at baseline and at 12 weeks. At every visit, all patients were asked to fill out the Ocular Surface Disease Index questionnaire (OSDI) (Allergan, Inc, Irvine, CA), which is a validated tool to assess dry eye symptoms.[32] It assesses the symptoms of dry eye on a scale of 0 to 100, with higher scores representing a greater degree of disability. For each question asked, 5 responses are possible, each being given a score according to the severity of the symptom experienced by the patient: 0 = none of the time, 1 = some of the time, 2 = half of the time, 3 = most of the time, and 4 = all of the time.

Visual acuity was assessed using Snellen charts and converted to equivalent logMAR units. CS was tested using the FACT (Functional Acuity Contrast Test) function of the Optec Functional Vision Analyzer (Stereo Optical Co, Inc, Chicago, IL). CS testing with FACT uses sine wave gratings, that is, alternate light and dark bars and tests 5 functionally significant spatial frequencies and 9 levels of contrast. It consists of 5 rows of 9 grating patches. The rows increase in spatial frequency from A through E, A [1.5 cycles per degree (cpd)] being the low, B (3 cpd) and C (6 cpd) middle, and D (12 cpd) and E (18 cpd) the high spatial frequencies. The

grating patches in each row uniformly decrease in contrast from 1 through 9 in steps of 0.2 log units. CS is the reciprocal of the physical contrast of the grating. The grating contrast is determined by contrast C = (maximum luminance − minimum luminance) divided by (maximum luminance + minimum luminance), where maximum luminance is the lightest part of the grating and the minimum luminance is the darkest part of the grating. Thus, CS = 1/contrast. The CS testing can be performed either monocularly or binocularly under varying preselected conditions, that is, day (photopic–luminance levels 85 cd/m^2) and night (mesopic–luminance levels 3 cd/m^2), far and near, and with or without glare. For this study, CS was tested uniocularly, for far, without glare under both photopic and mesopic testing conditions. The mesopic testing was performed before the photopic testing.

Tear break-up time (TBUT) was assessed next. A sterile fluorescein strip was dampened with a drop of nonpreserved saline solution, and the strip was touched to the superior bulbar conjunctiva. Patients were asked to blink several times to ensure spreading of the dye evenly. They were then instructed to open their eyes without blinking. The time between the opening of the eyes and the appearance of the first dry spot was measured in seconds 3 times. The average of the 3 measurements was recorded as the final TBUT. The interblink interval was noted and the Ocular Protection Index was calculated as the ratio of TBUT and the interblink interval. After the calculation of TBUT, the corneal and conjunctival staining was assessed using fluorescein and Rose Bengal dyes, respectively. The ocular surface staining was scored using the standardized methods recommended by the 1995 report from the National Eye Institute workshop on clinical trials involving participants with dry eyes.[33]

Total tear secretion (basal and reflex) was assessed using the Schirmer I test without anesthesia using Schirmer strips (Whatman filter No. 41) measuring 5 × 35 mm. This was performed 1 hour after the ocular staining with fluorescein and Rose Bengal. The folded 5-mm end was placed in the lower fornix at the junction of the lateral and middle third of the lower lid. After 5 minutes, strips were removed and a measurement (in millimeters) of the wet area of the strip was made with a scale. Meibum quality was then assessed and scored on a scale of 0 to 3 in each of the 8 glands of the central third of the lower lid. The scores of each gland were totalled to obtain the final score (score range, 0–24). Meibum expressibility was graded from 0 to 3 after assessing 5 glands in the upper or lower lid according to the number of glands expressible.

Intervention

Both groups were given an artificial tear substitute and eyelid hygiene (warm compresses, lid massage once daily) for a period of 12 weeks. In addition, the study group received oral supplementation of a triglyceride formulation of ω-3 FAs with a dosing schedule of 2 capsules in the morning and 2 capsules in the evening [each capsule providing 180 mg eicosapentaenoic acid (EPA) and 120 mg docosahexaenoic acid (DHA), Capsule Osmega manufactured by Geltec Private Limited, Bangalore, India] making a total of 720 mg EPA and 480 mg DHA per day. This supplementation was given for 12 weeks. The duration of treatment was decided based on previous publications.[22,23] Although there is no universally accepted dosing regimen for the use of ω-3 FAs for DED, the dosage chosen in this study (1.2 g/d) was within the "moderate" dose range (2–5 g/d) because patients taking ω-3 FAs within this range have demonstrated no clinical evidence of an increased bleeding tendency.[34–36] The control group received a placebo in the form of capsule vitamin E 400 mg/d (Capsule Evion, Merck Serono Limited, Mumbai, India) for the same duration.

Outcome Measures

The primary outcome measures in both the groups were the improvement in photopic and scotopic CS from baseline to 12 weeks. Secondary outcome measures were improvement in tear film stability as represented by prolongation of TBUT from baseline, increase in tear secretion represented by an increase in the value of Schirmer I test without anesthesia, improvement in ocular surface staining, changes in meibum quality and expressibility, and improvement in patients' symptoms as represented by a decrease in the OSDI score from baseline.

Statistical Analysis

Data from both eyes were collected, but only data from the right eye of each patient were used for analysis in each group. Both within-group and intergroup-comparisons were made. Statistics for continuous data are reported as mean values and SD. The normality of quantitative data was checked by measures of Kolmogorov–Smirnov tests of normality. The Mann–Whitney test was applied for comparison of 2 groups. For time-related variables, the Wilcoxon signed-rank test was applied. Gender was compared using the χ^2 test. $P < 0.05$ was considered to indicate statistical significance. All tests were 2 sided. All calculations were performed using SPSS version 17 (Statistical Packages for the Social Sciences, Chicago, IL).

RESULTS

A total of 60 participants were enrolled with all of them completing the required follow-up of 12 weeks from baseline.

TABLE 1. Baseline Comparison of Photopic and Mesopic CS Between the Placebo Group and Treatment Group

Parameters	Placebo Group, Mean ± SD	Treatment Group, Mean ± SD	*P*
Photopic CS at 3 cpd	78.8 ± 27.3	76.6 ± 26.9	0.67
Photopic CS at 6 cpd	64.5 ± 35.7	59.6 ± 39.0	0.3
Photopic CS at 12 cpd	24.4 ± 13.0	21.2 ± 10.3	0.34
Photopic CS at 18 cpd	5.1 ± 6.5	2.5 ± 3.8	0.13
Mesopic CS at 3 cpd	74.2 ± 21.8	76.6 ± 29.8	0.85
Mesopic CS at 6 cpd	53.0 ± 18.0	42.8 ± 27.3	0.02*
Mesopic CS at 12 cpd	17.7 ± 11.7	13.4 ± 17.9	0.05
Mesopic CS at 18 cpd	1.8 ± 4.1	1.2 ± 3.9	0.5

*$P < 0.05$.

TABLE 2. Within Group Comparison of Photopic and Mesopic CS at Baseline and at 12 Weeks

	Placebo Group, Mean ± SD			Treatment Group, Mean ± SD		
Parameter	**Baseline**	**12 Weeks**	***P***	**Baseline**	**12 Weeks**	***P***
Photopic CS						
3 cpd	78.8 ± 27.3	84.7 ± 22.6	0.008*	76.6 ± 26.9	93.1 ± 22.2	<0.001*
6 cpd	64.5 ± 35.7	67.1 ± 30.2	0.677	59.6 ± 39.0	80.2 ± 34.7	<0.001*
12 cpd	24.4 ± 13.0	25.6 ± 10.8	0.649	21.2 ± 10.3	27.6 ± 9.4	0.001*
18 cpd	5.1 ± 6.4	6.8 ± 7.3	0.136	2.5 ± 3.8	5.8 ± 5.4	<0.001*
Mesopic CS						
3 cpd	74.2 ± 21.8	81.1 ± 17.8	0.292	76.6 ± 29.8	79.0 ± 24.2	0.867
6 cpd	53.0 ± 18.0	61.4 ± 21.8	0.025*	42.8 ± 27.3	68.2 ± 31.8	<0.001*
12 cpd	17.7 ± 11.7	17.8 ± 5.8	0.673	13.4 ± 17.9	24.2 ± 16.9	<0.001*
18 cpd	1.8 ± 4.1	3.9 ± 3.9	0.027*	1.2 ± 3.9	4.3 ± 4.5	0.018*

*$P < 0.05$.

Both the groups were age matched ($P = 0.89$), with the mean age being 53.3 ± 6.9 years (range, 40–65 years) in the treatment group and 53.6 ± 8.7 years (range, 40–74 years) in the placebo group. Of 60 patients, 28 (46.7%) were females and 32 (53.3%) were males. The treatment group consisted of 56.7% females (n = 17) and 43.3% males (n = 13), whereas the placebo group consisted of 36.7% females (n = 11) and 63.3% males (n = 19). The difference in sex distribution between the 2 groups was not significant ($P = 0.12$). Visual acuity in both groups was similar at baseline (0.09 ± 0.17 logMAR in the placebo group and 0.12 ± 0.22 logMAR in the treatment group).

Baseline photopic and mesopic CS at 3, 6, 12, and 18 cpd was similar for the placebo and treatment groups at all frequencies except the mesopic CS at 6 cpd, which was worse for the treatment group ($P = 0.02$) (Table 1). Table 2 shows the within-group comparison of CS from baseline to 12 weeks. Under photopic testing conditions, significant improvement in CS was seen in the placebo group only at 3 cpd ($P = 0.008$), whereas the treatment group showed highly significant ($P < 0.001$) improvement at all tested frequencies (Table 2; Fig. 1). Under mesopic testing conditions, the placebo group showed improvement in CS for 2 of the tested frequencies, that is, at 6 cpd ($P = 0.025$) and 18 cpd ($P = 0.027$), whereas the treatment group showed significant improvement at 3 of the tested frequencies, that is, at 6 cpd ($P < 0.001$), 12 cpd ($P < 0.001$), and 18 cpd ($P = 0.018$) (Table 2; Fig. 2). Intergroup comparison revealed that the change from baseline, that is, improvement in CS was more for the treatment group than for the placebo group for 7 of the 8 testing conditions although the difference reached statistical significance for only 4 (ie, 3 cpd and 6 cpd under photopic and 6 cpd and 12 cpd under mesopic conditions) (Table 3). Compared with the treatment group, the placebo group showed a larger change from baseline to 12 weeks only at 1 testing frequency, which was however not significant, that is, at 3 cpd under mesopic conditions, 9.3% improvement was seen in the placebo group versus 3.2% improvement in the treatment group ($P = 0.552$).

Table 4 shows the comparison of the baseline parameters relating to OSDI, TBUT, Ocular Protection Index, ocular surface staining, Schirmer, and meibum quality and

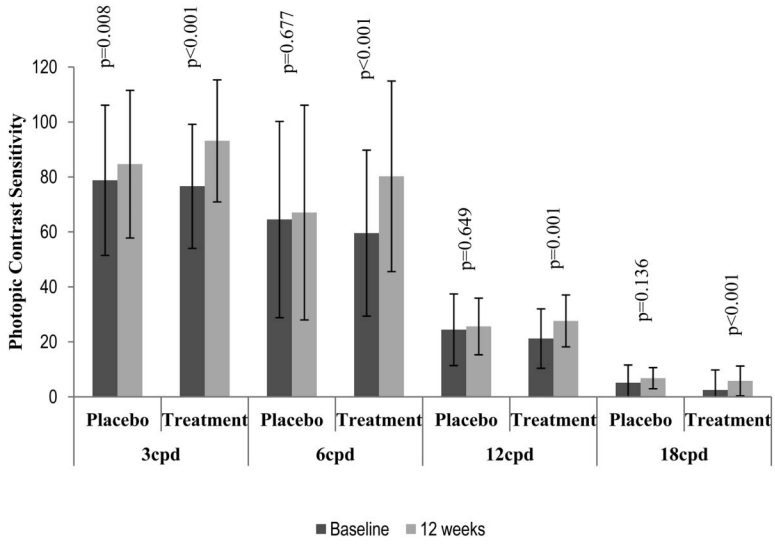

FIGURE 1. Change in photopic CS from baseline to 12 weeks in the placebo and treatment groups at 3, 6, 12, and 18 cycles/degree.

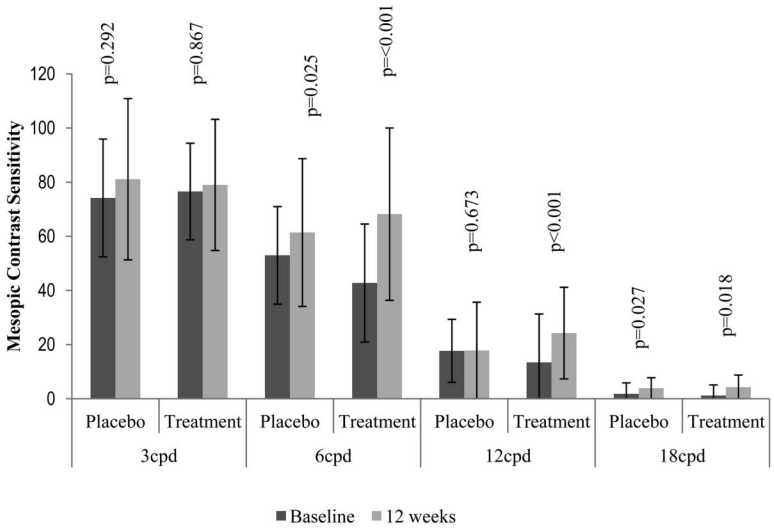

FIGURE 2. Change in mesopic CS from baseline to 12 weeks in the placebo and treatment groups at 3, 6, 12, and 18 cycles/degree.

expressibility. There was no statistically significant difference noted in any of the variables between the treatment and placebo groups. Table 5 shows the within-group comparison of the change in tear film and ocular surface parameters from baseline to 12 weeks in both the groups. All parameters improved significantly in both the placebo and treatment groups at the end of 12 weeks, except for the Schirmer test score, which did not improve in either the placebo ($P = 0.896$) or treatment group ($P = 0.309$). The change from baseline for most of the parameters was however significantly more in the treatment group than in the placebo group (Table 6). Although the Rose Bengal staining score improved significantly for both groups from baseline (81% in placebo and 98% in the treatment group), the difference of the change from baseline was not significant ($P = 0.54$) between the groups.

DISCUSSION

This study demonstrated a beneficial effect of oral supplementation of ω-3 FAs (720 mg EPA and 480 mg DHA daily) in improving the CS and symptoms and signs of DED in patients with moderate MGD. Only patients having moderate changes of MGD were chosen, as those with mild MGD could be expected to significantly improve with the conventional treatments of warm compress, lid massage, and tear substitutes making supplementation with a systemic agent unnecessary. Patients with severe MGD having anatomical changes, such as meibomian gland dropout or retroplacement of meibomian gland orifices, were also excluded because the anatomical changes would not be expected to improve with the intervention offered in this study and could lead to confounding of the results.

Both subjective (OSDI scores) and objective improvements (improvement of TBUT representing a more stable tear film, decrease in ocular surface staining scores, and improvement of meibum quality and expressibility) were demonstrated in the placebo group and the treatment group. Although the improvement in both groups may be attributed partly to unclogging and hence easier expression of meibomian gland secretion as a result of warm compresses and lid massage, the fact that the change from baseline for most of these parameters was significantly more in the group

TABLE 3. Intergroup Comparison of Improvement in Photopic and Mesopic CS From Baseline to 12 Weeks

Parameter	Placebo Group, %	Treatment Group, %	*P*
Photopic CS			
3 cpd	7.5	21.6	0.026*
6 cpd	4	34.7	0.005*
12 cpd	5	30.3	0.057
18 cpd	32	135	0.094
Mesopic CS			
3 cpd	9.3	3.2	0.552
6 cpd	16	59.5	0.015*
12 cpd	0.01	80.6	0*
18 cpd	115.6	261	0.715

*$P < 0.05$.

TABLE 4. Baseline Comparison of Clinical Measures Between the Placebo Group and Treatment Group

Parameters	Placebo Group, Mean ± SD	Treatment Group, Mean ± SD	*P*
OSDI	33.0 ± 11.6	39.2 ± 17.2	0.19
TBUT	4.9 ± 1.6	5.0 ± 1.8	0.975
Ocular Protection Index	0.9 ± 0.4	1.0 ± 0.5	0.338
Fluorescein staining score	3.9 ± 1.1	3.3 ± 1.2	0.184
Rose Bengal staining score	1.7 ± 1.4	1.6 ± 1.1	0.69
Schirmer test score	15.5 ± 6.6	16.0 ± 5.1	0.429
Meibum expressibility	1.7 ± 0.6	1.6 ± 0.5	0.677
Meibum quality	13.8 ± 3.7	14.3 ± 3.7	0.994

TABLE 5. Within Group Comparison of Clinical Measures at Baseline and at 12 Weeks

	Placebo Group, Mean ± SD			Treatment Group, Mean ± SD		
Parameter	**Baseline**	**12 Weeks**	***P***	**Baseline**	**12 Weeks**	***P***
OSDI	33.0 ± 11.6	24.0 ± 10.8	<0.001*	39.2 ± 17.2	13.8 ± 7.5	<0.001*
TBUT	4.9 ± 1.6	7.4 ± 1.9	<0.001*	5.0 ± 1.8	10.2 ± 1.4	<0.001*
Ocular Protection Index	0.9 ± 0.4	1.4 ± 0.6	<0.001*	1.0 ± 0.5	2.0 ± 0.6	<0.001*
Fluorescein staining score	3.9 ± 1.1	1.8 ± 1.3	<0.001*	3.3 ± 1.2	0.2 ± 0.6	<0.001*
Rose Bengal staining score	1.7 ± 1.4	0.3 ± 0.6	<0.001*	1.6 ± 1.1	0.03 ± 0.2	<0.001*
Schirmer test score	15.5 ± 6.6	15.5 ± 5.4	0.896	16.0 ± 5.1	15.2 ± 4.4	0.309
Meibum expressibility	1.7 ± 0.6	1.4 ± 0.5	0.008*	1.6 ± 0.5	0.8 ± 0.5	<0.001*
Meibum quality	13.8 ± 3.7	12.1 ± 3.0	0.001*	14.3 ± 3.7	7.2 ± 3.4	<0.001*

*$P < 0.05$.

receiving ω-3 FA supplementation, points to an additional beneficial effect of these agents in MGD. Omega-3 FAs have been proposed to be beneficial in MGD by competitive inhibition of ω-6 FA metabolism leading to less production of proinflammatory mediators, thus helping to decrease eyelid margin inflammation. A significant change from "unhealthy" to "healthy" meibum was also documented by Macsai in patients with MGD taking oral supplementation of ω-3 FAs.[21]

There are conflicting reports in the literature regarding the effect of oral ω-3 FA supplementation on improvement in aqueous tear production or an increase in the Schirmer score in patients with dry eye. Several investigators have shown an increase in Schirmer scores,[20,22] and this has been attributed to the antiinflammatory properties of ω-3 FAs leading to less inflammation and apoptosis of the lacrimal gland with a consequent increase in tear production. In the present series, however, we did not observe any change in Schirmer scores in either the placebo or the treatment groups, although tear film stability (prolongation of TBUT) improved significantly in both groups, more so in the treatment group. Our findings were similar to those of Olenik et al,[24] who also used ω-3 FA supplementation in MGD and noted improvement in TBUT and meibum expressibility but not in Schirmer scores. Macsai[21] found an approximately 2-mm increase in the Schirmer score in patients with MGD after supplementation with flaxseed oil (a source of ω-3 FAs) but noted that the results did not reach statistical significance. These contradictory reports may be due to the inherent differences in the study populations. In the series of Kangari et al[20] and Wojtowicz et al,[22] although the etiology of dry eye is not specified, Schirmer scores were depressed (<10 mm) in addition to a shortened TBUT, pointing toward predominantly aqueous deficient dry eye, which may have benefited more from the antiinflammatory effects of the ω-3 FAs on the presumably inflamed lacrimal gland. In Macsai's[21] series, although the population studied was of patients with MGD, the mean baseline Schirmer score was also quite low (5.1 ± 3.8 mm) in addition to a low TBUT, and thus a limited benefit of ω-3 FAs in improving tear production was seen although it did not achieve statistical significance. In contrast, in our series and that of Olenik et al[24] the TBUT (<7 seconds) was affected more than the Schirmer test scores (>15 mm) implying a greater contribution of tear film instability and evaporative dry eye as compared with the aqueous deficiency. This may help explain the selective effect of ω-3 FAs in improving TBUT but not Schirmer test scores.

TABLE 6. Intergroup Comparison of Improvement in Clinical Measures From Baseline to 12 Weeks

Parameter	**Placebo Group, %**	**Treatment Group, %**	***P***
OSDI	27	67	<0.001*
TBUT	51	105	<0.001*
Ocular Protection Index	57	95	<0.001*
Fluorescein staining score	55	93	0.001*
Rose Bengal staining score	81	98	0.54
Schirmer test score	−0.2	−4.8	0.595
Meibum expressibility	14.4	51.8	<0.001*
Meibum quality	12.1	49.8	<0.001*

*$P < 0.05$.

Because the tear film forms the first refracting surface of the eye, its disruption can affect multiple components of visual function including an increase in optical aberrations with a resultant decrease in visual acuity and CS. Improvement in CS by instillation of artificial tear substitutes, presumably because of stabilization of the tear film, has been demonstrated previously.[27,28,36] Cuevas et al,[37] in their prospective series of 21 patients with evaporative dry eye caused by MGD, noted no improvement in mesopic CS from baseline, after a 6-week treatment regimen of lid hygiene, unpreserved artificial tears, and 3 weeks of unpreserved steroids. In our series also, the placebo group showed significant improvement from baseline in only 3 of the 8 testing conditions used (ie, at 3 cpd photopic and 6 and 18 cpd mesopic). In contrast, the treatment group had significant improvement in CS from baseline to 12 weeks in 7 of the 8 testing conditions used (the only exception being mesopic CS testing at 3 cpd in which no improvement was seen). Also, the change from baseline was more in the treatment group than in the placebo group in the majority of the testing conditions. These outcomes may be related to the improvement in tear film stability, meibum expressibility, meibum quality, and

decreased ocular surface staining, which although seen in both the treatment and placebo groups, were significantly more in the treatment group of our study cohort. It may be that the improvement in CS is related to the achievement of a particular threshold of tear film stability, rather than having a linear relationship. Supplementation with ω-3 FAs in addition to the conventional treatment modalities of lid hygiene, hot compresses, lid massage, and artificial tear substitutes in the treatment of MGD may help achieve this threshold and consequently improve the CS levels in these patients.

The authors acknowledge a few limitations of this study. Monitoring of the dietary intake of ω-3 FAs was not performed for the study participants in either group. Baseline serum ω-3 FA levels in both the groups and the change in these levels at the completion of the study were also not evaluated. Because all the measurements were recorded by a single observer, the possibility of a bias exists. However, the main outcome measure of this study, that is, the improvement in photopic and scotopic CS is not an observer-dependent parameter and is instead determined by the responses given by the patient to the various stimuli presented. The results relating to this parameter are thus unlikely to be influenced.

In conclusion, to the best of the authors' knowledge, this is the first study to demonstrate improvement in photopic and mesopic CS after oral supplementation with omega-3 FAs in patients with moderate MGD, which forms a large subset of DED. Further large-scale multicentric trials would be helpful to fully elucidate the role of these agents in improving CS in patients with DED of varying etiologies.

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