Short-Term Omega 3 Fatty Acids Treatment for Dry Eye in Young and Middle-Aged Visual Display Terminal Users

Rahul Bhargava, M.S., Prachi Kumar, M.D., and Yogesh Arora, M.S.

Objective: To evaluate the effect of an omega 3 fatty acid (O3FA) oral supplement (2,400 mg/day) for 45 days on dry eye symptoms, tear production, stability, and conjunctival cytology in young and middle-aged visual display terminal (VDT) users.

Methods: Institutional review board approval was obtained, and a randomized, double-blind, interventional study was done; eyes of 256 VDT users were randomized to receive 4 capsules twice daily for 45 days (O3FA group), each containing 180 mg of eicosapentaenoic acid and 120 mg docosahexaenoic acid. The O3FA group was compared with another group (n=266) who received 8 capsules of a placebo (olive oil). Patients were evaluated at baseline, 30 days, and 45 days. The primary outcome measure was an improvement in dry eye symptoms. Secondary outcome measures were improvement in the Nelson grade on conjunctival impression cytology, Schirmer test values, and tear film breakup time (TBUT). Means of groups (pretreatment, day 30, and day 45) were compared with repeated-measure analysis of variance. The relation between the outcome variables and VDT time was evaluated using linear regression.

Results: In the O3FA group, the mean symptom score differed significantly ($P<0.005$) (pretreatment, 30 days, and 45 days); the TBUT and Nelson grade also improved significantly but only after 45 days of intervention. Schirmer test values did not differ significantly after adjustment for multiple comparisons ($P=0.010$). The change was not significant in the placebo group.

Conclusion: Consumption of 2,400 mg/day of O3FA supplement improves symptoms, tear stability, and conjunctival cytology but not tear production in symptomatic VDT users.

Key Words: Visual display terminal users—Omega 3 fatty acids—Conjunctival impression cytology—Correlation analysis—Dry eye syndrome—Tear film breakup time—Schirmer test.

(*Eye & Contact Lens* 2015;0: 1–6)

The role of visual display terminals (VDT) has increased tangentially in all spheres of our day-to-day life; prolonged VDT tasks reduce blink rate, blink amplitude, and blink quality leading to tear film instability.[1] This has led to an upsurge in the incidence of dry eye in youngsters and the office-going population, thereby affecting work performance and productivity. The prevalence of dry eye in VDT users ranges from 30% to 68.5%.[2–4]

From the Laser Eye Clinic (R.B.), Noida, India; Department of Ophthalmology (R.B., Y.A.), School of Medical Sciences and Research, Sharda University, Greater Noida, India; and Department of Pathology (P.K.), School of Medical Sciences and Research, Sharda University, Greater Noida, India.

The authors have no funding or conflicts of interest to disclose.

Address correspondence to Rahul Bhargava M.S., Laser Eye Clinic, Noida 201301, India; e-mail: brahul_2371@yahoo.co.in

Accepted June 23, 2015.

DOI: 10.1097/ICL.0000000000000179

Now, there is uniform consensus that dry eye disease is associated with ocular surface inflammation; this is evidenced by the expression of proinflammatory mediators such as prostaglandins (PGE_2), interleukins (IL-1), and leukotrienes (LTB_4) by ocular surface cells.[5,6] Moreover, long-standing ocular surface inflammation may also alter the epithelial cell morphology and conjunctival goblet cell density.

Essential fatty acids (EFAs) are necessary for health but cannot be synthesized in the body and have to be obtained from dietary sources. The 2 main EFAs are the 18 carbon omega 6 and omega 3 fatty acids (O3FAs). Omega 6 fatty acids not only produce proinflammatory mediators (PGE_2 and LTB_4) but also act as substrates for production of resolvins. In contrast, O3FAs such as eicosapentaenoic acid (EPA) block the synthesis of these lipids, IL-1, and tumor necrosis factor-alpha; a higher O3FA to O6FA ratio exerts an anti-inflammatory effect and vice versa.[7–9]

Although the health benefits of dietary consumption of O3FAs have been documented for dry eye disease in general, safety and efficacy of O3FAs for dry eye in VDT users has not been documented.[10–12] A search of major databases (including MEDLINE) revealed that no randomized trial has been performed to determine this. Second, artificial tear supplements, the most commonly prescribed dry eye therapy, however, do not treat the cause but provide temporary and symptomatic relief and do not reverse metaplastic changes.[13]

Moreover, the staple diet in India, being predominantly vegetarian, is devoid of n-3 long-chain polyunsaturated fatty acids. In this study, we hypothesized that consumption of 2,400 mg/day of oral O3FA supplements for 45 days does improve dry eye symptoms, Nelson grade on conjunctival impression cytology (CIC), and clinical markers such as the Schirmer score and tear film breakup time (TBUT) in symptomatic VDT users when compared with administration of the placebo (olive oil).

METHODS

A randomized, double masked, interventional study was done at three referral eye centers in the northern part of India. The trial was approved by the institutional review boards and the local ethics committee. Written informed consent was obtained from all the participating patients, and the study followed the tenets of the Declaration of Helsinki.

Inclusion Criteria

Selection of Study Participants

A letter was sent to the supervisors in the health management section of regional call-centers, universities, and information

technology (IT) companies to explain the study purpose and to request participation in the study. Two universities, three call-centers, and two IT companies responded and agreed to participate in the study; after reviewing the protocol and potential risks and benefits, permission was granted to conduct the study among employees who were willing. Employees were invited by e-mail to answer a questionnaire; this included information such as demographic characteristics, dietary habits (vegetarian or nonvegetarian), symptoms experienced, total working hrs, and average hrs spent in VDT work each day during the past year. A maximum of three e-mail reminders were sent. Employees who completed the questionnaire were requested to attend a dry eye clinic for ophthalmic checkup. Symptomatic VDT users (those experiencing dry eye symptoms) were identified, and the subjects were enrolled and grading of dry eye disease was done based on their response to the Dry Eye Scoring System (DESS©), a questionnaire of common symptoms of dry eye (Table 1).[14–17]

Exclusion Criteria

Patients with allergic conjunctivitis, history of laser in situ keratomileusis, and contact lens wear, or other causes of dry eye in the office-going population, software professionals, or university students were excluded from the study. Patients with inability to swallow soft-gel capsules, those on regular course of aspirin or anticoagulants (cyclooxygenase-2 inhibitors), and those allergic to fluorescein were also excluded. Systemic (tetracyclines and corticosteroids) or topical medications (other than artificial tear supplements) that could affect the tear film or meibomian gland functions (beta-blockers, benzodiazepines, and antihistamines) were discontinued 3 weeks before intervention. Moreover, patients were instructed not to use artificial tear preparations, 2 hr before testing.

Randomization, Masking, and Sample Size Calculation

To calculate the sample size and to compare the mean difference in dry eye symptoms between both groups, a pilot study was first done on 50 subjects. The mean decrease in the symptom score in the omega-3 group was 0.7 and in the placebo group was 0.52. The common SD was 0.64. Assuming 1:1 randomization, 90% power (alpha=0.05), and a precision error of 5% to detect a difference of 20% or more in the symptom score between both groups, the estimated sample size in each group was calculated to be 266 (www.stat.ubc.ca/~rollin/stats/ssize/n2.html).

TABLE 1. *Dry Eye Questionnaire and Scoring System (DESS©)*

	Score (Maximum 18)			
Symptom	Absent (0)	Sometimes (1)	Frequent (2)	Always Present (3)
Itching or burning				
Sandy or gritty sensation				
Redness				
Blurring of vision				
Ocular fatigue				
Excessive blinking				

Scores of 0 to 6 were mild, 6.1 to 12 were moderate, and 12.1 to 18 indicated severely symptomatic dry eye.[13]

DESS © Bhargava R. Laser Eye Clinic, Noida, India.

The allocation codes were generated by disk operating system–based software in the department of community ophthalmology at our institute. Patients were randomly allocated to one of the two groups by parallel assignment. The codes were sealed in green envelopes and were opened by a health care personnel not involved in patient care. The O3FA group received 4 capsules, each containing 180 mg of EPA and 120 mg docosahexaenoic acid (DHA), twice daily for 45 days (1,440 mg of EPA +960 mg DHA/day). The placebo group received 4 capsules containing olive oil, twice daily for 45 days. The subjects were masked to the contents. The two types of capsules and packs were similar to each other. The subjects were instructed to return the bottles of study capsules at the 1-month visit, and any unused capsules were counted to determine patient compliance with the study protocol, wherein another pack with 120 capsules were provided to them. The subjects were instructed to eat a normal diet and not to take any other additional dietary supplements. Figure 1 shows the flowchart for enrollment, randomization, intervention, follow-up, and analysis.

OUTCOME MEASURES

Patients were seen at baseline, 30 days, and 45 days after the start of dietary supplementation. The primary outcome measure was the change from baseline in subjective dry eye symptoms (a reduction from baseline representing an improvement). A score of 0 to 3 was assigned to dry eye–related symptoms such as ocular fatigue, blurring of vision, itching or burning, sandy or gritty sensation, and redness, respectively (DESS); when symptom-free, 0; sometimes present, 1; frequently present, 2; and always present, 3. A score of 0 to 6 was mild, 6.1 to 12 moderate, and 12.1 to 18 severely symptomatic dry eye (Table 1).

The secondary outcome measures were a change in the Schirmer test value (increase in the amount of wetting representing an improvement), TBUT (increased time [in sec] representing an improvement), and Nelson grade at day 45 (reduction in the grade representing an improvement). The relation between the time spent

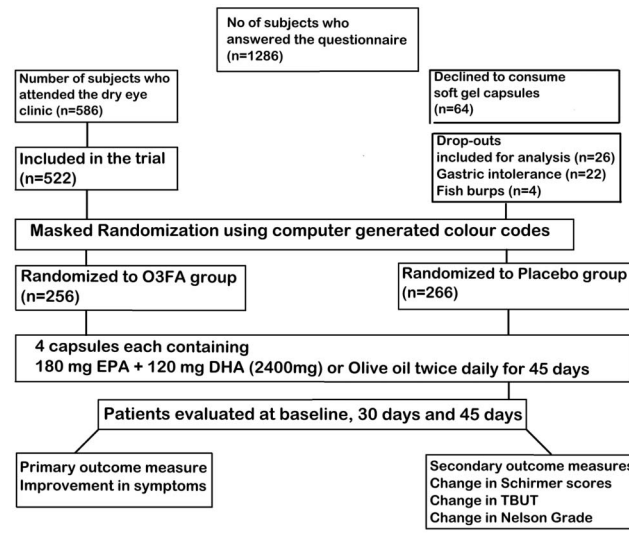

FIG. 1. Flowchart showing enrollment, randomization, intervention, follow-up, and analysis.

in front of the VDT (predictor variable) and the outcome variables was also evaluated.

OCULAR EXAMINATION AND TEAR FUNCTION TESTS

The participants were instructed to visit the dry eye clinic in the morning, and all the tests were performed at the same time of the day (between 10 AM and 12 PM) in a dimly lit room. A detailed ocular examination was performed by an independent investigator (who was not a study surgeon, K.S.); this included recording of corrected distance visual acuity and slit-lamp examination, including assessment of lid margins, eye lashes, and meibomian gland orifice for any blockage or occlusion.

Tear film tests were performed at baseline, 30 days, and 45 days after the start of dietary supplementation, followed by completion of the dry eye questionnaire. The independent investigator (K.S.) was masked to the information obtained from the questionnaire.

One eye of each patient was selected at random for examination. TBUT was performed first as excessive eyelid manipulation at this stage may adversely influence the results. A sterile fluorescein strip containing 1 mg fluorescein sodium (Madhu Instruments, Delhi, India) was applied over the inferior bulbar conjunctiva. The strip was moistened with normal saline solution before application. Excessive solution was shaken off the strip. The patient was instructed to blink naturally, without squeezing, several times to distribute the fluorescein. The tear film was observed on the slit-lamp using the cobalt blue filter. The interval between the last complete blink and the first appearance of a dry spot on the cornea was recorded with a timer. Three readings were taken in succession and averaged. A TBUT of less than 10 s was considered consistent with dry eye. The subject then waited for another 30 min, and a Schirmer test with anesthesia (0.4% oxybuprocaine hydrochloride) was performed with eyes closed. The length of wetting less than 6 mm was considered consistent with dry eye.

To ensure uniformity and eliminate bias, CIC was performed by a single examiner who was masked to information obtained from the questionnaire. CIC was performed as per the technique described previously.[15,16] The mounted slide was first examined under the light microscope with ×100 low-power field (×10 objective lens). After localization, cells were then analyzed with ×400 final magnification (×40 objective). At least 10 high power field were examined for goblet cells and epithelial cells. Grading and scoring was done according to the criteria suggested by Nelson et al.[18] Nelson grades 0 and 1 were regarded as normal, whereas grades 2 and 3 were considered to represent abnormal cytology.

STATISTICS

Statistical analysis was performed on an intent-to-treat basis using IBM, SPSS Statistics version 22 (IBM Inc.). One eye of each patient was selected at random for examination and subsequent evaluation. Independent *t* tests were performed to ensure group similarities at baseline; the assumptions of performing *t* tests were met. Chi-square tests were used for proportions. A one-way repeated-measures analysis of variance (ANOVA) was conducted to determine whether there were significant differences in mean test values over the course of 45 days of intervention (O3FA or placebo). There were no outliers, and data were normally distributed, as assessed by a box plot and Shapiro–Wilk test ($P>0.05$), respectively. The assumption of sphericity was violated, as assessed by the Mauchly test of sphericity. Therefore, a Greenhouse–Geisser correction was applied. A post hoc (Tukey) test was performed using the Bonferroni correction, to determine where differences occurred; the F-statistic was reported as F (*df* time, *df* error)=F value, P value. A P value less than 0.005 was considered statistically significant. A regression analysis was performed to study the effect of the daily hr spent at VDT and the outcome variables (Schirmer, TBUT, and Nelson grade).

RESULTS

Participants

A total of 1,286 subjects answered the e-mail questionnaire. Of these, 586 (45.5%) subjects attended the dry eye clinic. However, 64 (10.9%) subjects were purely vegetarian and declined to consume any soft-gel capsules. A total of 522 (40.6%) patients were recruited in the trial. Two hundred fifty-six patients were assigned to the O3FA group and 266 to the placebo group.

Compliance

At the first follow-up visit (day 30), 22 (8.5%) patients in the O3FA group were irregularly taking the supplements because of bad taste (fish burps) and gastric intolerance, which was severe enough to warrant cessation of the trial; another four (1.5%) subjects in the O3FA group (although compliant) expressed their inability to continue the trial for the same reasons. In the placebo group, 7 (2.6%) patients developed transient rashes after the start of dietary supplementation. However, these were not severe enough to warrant discontinuation of treatment. All dropouts (n=26) were included for analysis based on the last-observation-carried-forward method.

The difference in sex distribution in the two groups was not significant (chi-square test, $P=0.921$). The mean VDT use time was 7.9±1.3 (range, 5–10 hr) and 8.2±1.4 (range, 5–12 hr) in O3FA and placebo groups, respectively ($P=0.016$).

Table 2 shows the mean age, mean baseline symptom score, TBUT, Nelson grade, and Schirmer score before random allocation in both groups; the intergroup differences regarding these variables were not statistically significant at baseline. Table 3 shows the intergroup differences between outcome variables (symptoms, TBUT, Nelson grade, and Schirmer score) in 30 days, and Table 4 shows intergroup differences in 45 days, after intervention.

At baseline, in the placebo group, 22% patients had abnormal Schirmer scores, 43% had abnormal TBUT, and 28% had abnormal cytology. In the O3FA group, 24% patients had abnormal Schirmer scores, 41% had abnormal TBUT, and 32% had abnormal cytology; examination of CIC specimens under a light microscope revealed an

TABLE 2. *Baseline Characteristics of Both Groups*

Parameter	O3FA Group	Placebo Group	*P* (*t* Test)
Age (yr)	28.9±4.2	29.6±5.5	0.123
Symptom score	8.1±2.7	7.8±1.9	0.418
Schirmer score (mm)	16±6	15.6±6.6	0.624
TBUT (sec)	8.7±2.8	8.9±0.3	0.484
Nelson grade	1.2±0.8	1±0.9	0.306

TBUT, tear film breakup time.

TABLE 3. *Mean Test Values in O3FA and Placebo Group at Day 30*

Parameter	O3FA Group	Placebo Group	*P* (*t* Test)
Symptom score	6.4±2	7.7±1.9	<0.001
Schirmer score (mm)	15.7±6.2	15.5±6.6	0.881
TBUT (sec)	8.9±2.9	9.1±0.2	0.848
Nelson grade	1.2±0.8	1±0.9	0.533

TBUT, tear film breakup time.

increase in the nuclear–cytoplasmic ratio of nonsecretory epithelial cells along with reduction in goblet cell density (Fig. 2).

Dry Eye Symptoms

In the O3FA group, repeated-measures ANOVA revealed that mean symptom scores differed significantly (F [1.279, 120.210]= 180.040, $P<0.005$). The post hoc test revealed that O3FA dietary intervention elicited a significant reduction ($P<0.005$) in symptoms from baseline to 30 days of intervention (mean score of 8.1±2.7 vs. 6.4±2, respectively). After intervention (45 days), the symptom score was reduced to 3.9±2, which was significantly different ($P<0.005$) from the score before treatment and after 30 days. In the placebo group, mean symptom scores did not differ significantly (F [1.439, 149.667]=6.338, $P=0.010$).

Tear Film Breakup Time

In the O3FA group, the mean TBUT scores were significantly different (F [1.228, 115.439]=160.584, $P<0.005$). The post hoc test revealed that O3FA intervention did not elicit a significant improvement in TBUT from baseline to 30 days (mean score of 8.7±2.8 sec vs 8.9±2.9 sec). However, after intervention, TBUT increased to 10.9±2.3 sec, which was significantly different ($P<0.005$) from that of at baseline and after 30 days. Short-term O3FAs (45 days) elicits a significant reduction in TBUT but not after 30 days of intervention. In the placebo group, mean TBUT scores did not differ significantly (F [1.354, 140.783]=22.575, $P=0.135$).

Conjunctival Impression Cytology

Repeated-measures ANOVA in the O3FA group revealed that there was a significant difference in the mean Nelson grade (F [1.324, 124.410]=85.048, $P<0.005$). The post hoc test revealed that the O3FA intervention did not elicit a significant change ($P=0.041$) in the Nelson grade from pretreatment to 30 days of intervention (mean score of 1.2±0.8 vs. 1.2±0.8). After intervention (45 days), the Nelson grade was reduced to 0.7±0.65, which was significantly different ($P<0.005$) from the score before treatment and after 30 days. In the placebo group, mean scores for the Nelson grade were not significantly different (F [1.278, 132.871] =5.382, $P=0.015$).

TABLE 4. *Mean Test Values in O3FA and Placebo Group at Day 45*

Parameter	O3FA Group	Placebo Group	*P* (*t* Test)
Symptom score	3.9±2	7.6±2	<0.001
Schirmer score (mm)	16±6	15.6±6.6	0.106
TBUT (sec)	10.9±2.3	9.2±0.2	<0.001
Nelson grade	0.7±0.6	0.9±0.9	0.005

TBUT, tear film breakup time.

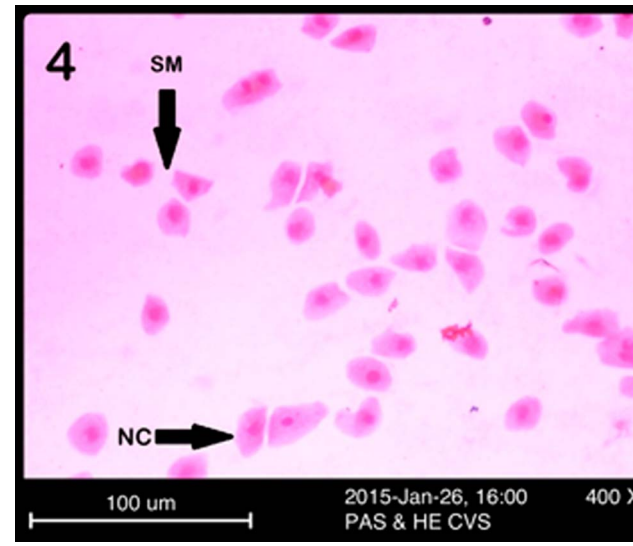

FIG. 2. Photomicrographs of impression cytology specimens, stained with periodic acid-Schiff and hematoxylin-eosin at ×400 with squamous metaplasia. Arrows showing a normal cell (NC) and increased nuclear–cytoplasmic ratio (SM). full color online

Schirmer Test

Repeated-measures ANOVA in the O3FA group revealed that the difference in the mean Schirmer scores was not significant (F [1.224, 115.019]=36.519, $P=0.010$). In the placebo group, the mean Schirmer scores were not significantly different (F [1.60, 166.517]=2.134, $P=0.132$).

In both groups, linear regression established that daily time spent on VDTs could significantly predict the test outcomes. In the O3FA group, regression results were as follows: dry eye symptom severity (F [1, 93]=148.693, $P<0.0005$), Schirmer scores (F [1, 93]=18.055, $P<0.005$), TBUT scores (F [1, 93]= 104.728, $P<0.005$), and Nelson grade (F [1, 93=164.820], $P<0.005$), respectively. In the O3FA group, time spent working on VDTs accounted for 61%, 16%, 55%, and 64% variability in symptoms, Schirmer score, TBUT, and Nelson grade, respectively. In the placebo group, these values were 59%, 21%, 53%, and 55%, respectively (Figs. 3–6).

DISCUSSION

The results of this study demonstrated that O3FAs (2,400 mg/day) for 45 days elicit a significant improvement in dry eye symptoms at all time points (baseline–30 days, 30 days–45 days, and baseline–45 days); there was a significant improvement in the TBUT and Nelson grade, but only after 45 days of therapy; it is probable that supplementing the diet with high amounts of O3FAs may prevent the inflammation from blocking meibomian gland ducts or change the fatty acid composition of meibum and increase goblet cell density, only when prescribed for a reasonable time duration. In a randomized clinical trial in symptomatic VDT users (n=478), dietary O3FAs (1,200 mg/day) were associated with a significant improvement in dry eye symptoms and TBUT, when prescribed for a duration of 3 months, further substantiating the observations of this study.[17]

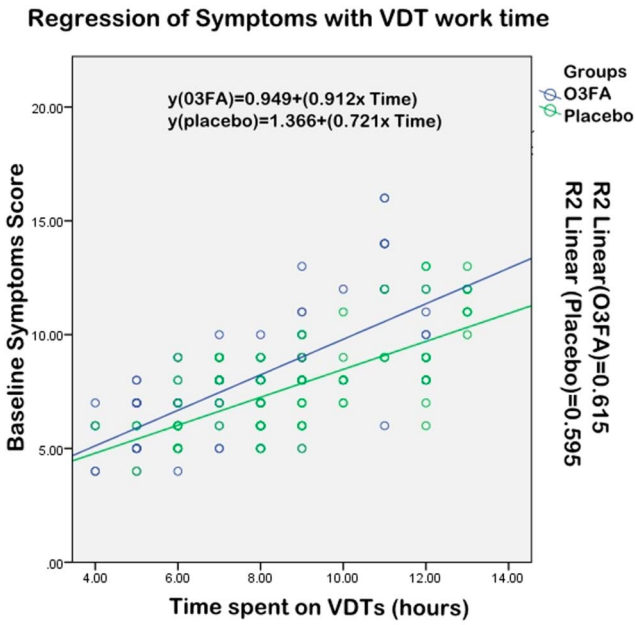

FIG. 3. Scatter plot showing linear regression of symptoms with visual display terminal (VDT) work time. full color online

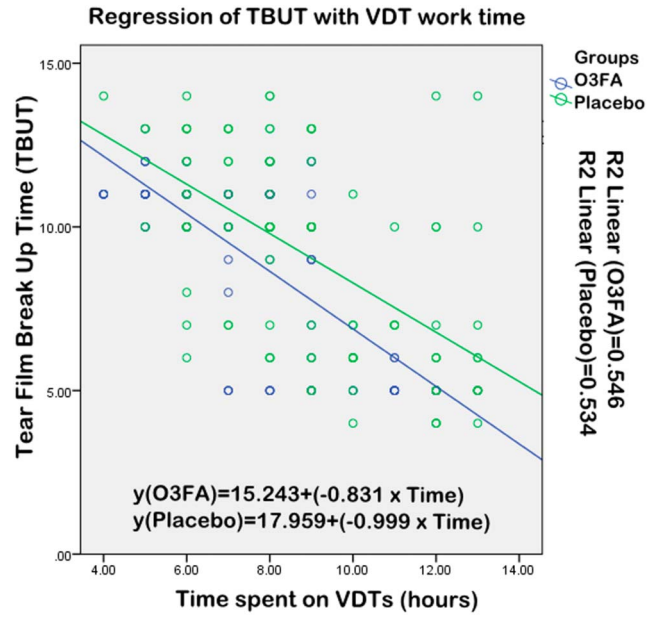

FIG. 5. Scatter plot showing regression of tear film breakup time (TBUT) with visual display terminal (VDT) work time. full color online

On the contrary, in a meta-analysis of randomized controlled trials involving 790 participants in 7 independent studies, Liu et al. found that although O3FAs were consistently associated with improvement in TBUT, improvement in symptoms was not significant. This could be explained by the fact that 6 of the 7 randomized controlled trials were underpowered (n=272, overall) as compared with the adequately powered trial (n=518), showing significant improvement in the symptom score in 3 months.[14,19,20]

Ocular surface inflammation is known to decrease aqueous tear production, and decreasing inflammation with T-cell inhibitors (e.g., cyclosporine A) increases Schirmer scores, so it was surprising that dietary intervention did not elicit a significant change in Schirmer test scores, at 30 days or 45 days after intervention in either study group. A study by Wojtowicz et al. observed a significant improvement in mean Schirmer scores in 3 months. This contradiction could be due to the shorter duration of treatment in our study, with less sustained reduction in inflammation and lacrimal gland apoptosis.[21]

These observations suggest that not only an optimal dose but also the duration of O3FA intervention, may be the crucial determinant

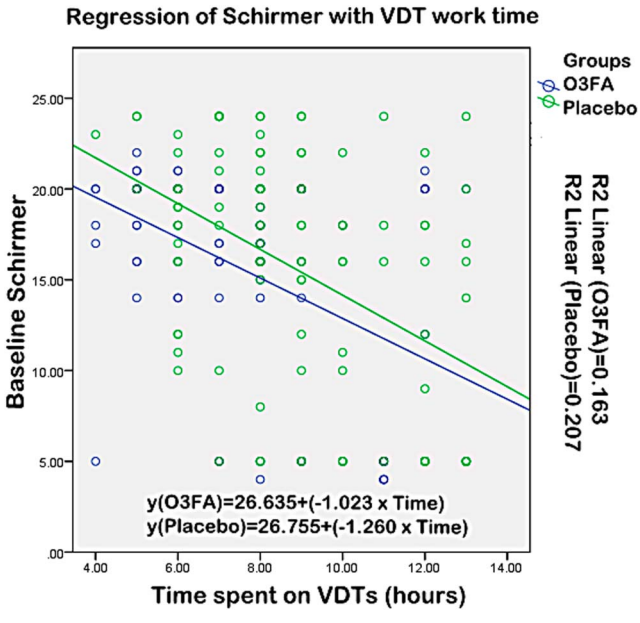

FIG. 4. Scatter plot showing regression of the Schirmer score with visual display terminal (VDT) work time. full color online

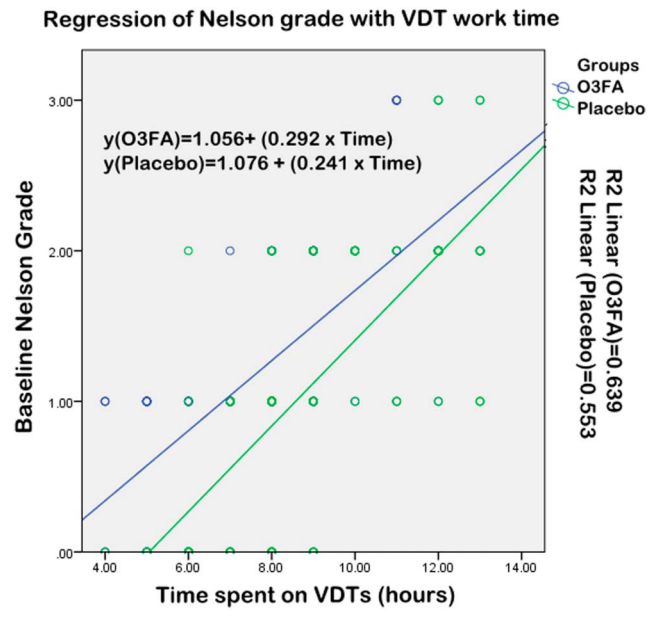

FIG. 6. Scatter plot showing regression of the Nelson grade with visual display terminal (VDT) work time. full color online

for achieving therapeutic benefit, irrespective of the cause of dry eye. Shorter duration of therapy could probably explain the insignificant improvement in tear production in this study.

With the rapid advances in IT, VDT use among office workers has increased considerably in recent years; on average, an office worker spends approximately 5 to 12 hr/day on VDT. It seems that apart from conditions such as ambient humidity, type of VDT, and workstation ergonomics, time spent on the VDT also influences patient's symptoms. This study found that time spent on VDT could significantly predict dry eye symptom severity, TBUT, and cytologic changes (Nelson grade). Uchino et al. found that VDT use of more than 4 hr was associated with a significantly higher risk of dry eye; another cross-sectional study estimating the prevalence of dry eye in VDT users found an increased risk of dry eye in workers using a VDT for more than 8 hr/day (odds ratio=1.94; 95% confidence interval, 1.22–3.09).[22,23]

CONCLUSIONS

In conclusion, O3FAs in a dose of 2,400 mg/day for 45 days does improve dry eye symptoms, tear film stability, and Nelson grade in symptomatic VDT users when compared with administration of a placebo (olive oil). However, a longer duration of treatment may be required for improvement in parameters such as tear secretion. Time spent on VDT significantly predicts dry eye symptom severity.

REFERENCES

1. Cardona G, García C, Serés C, et al. Blink rate, blink amplitude, and tear film integrity during dynamic visual display terminal tasks. *Curr Eye Res* 2011;36:190–197.
2. Uchino M, Schaumberg DA, Dogru M, et al. Prevalence of dry eye disease among Japanese visual display terminal users. *Ophthalmology* 2008;115: 1982–1988.
3. Bhargava R, Kumar P, Kaur A, et al. The diagnostic value and accuracy of conjunctival impression cytology, dry eye symptomatology, and routine tear function tests in computer users. *J Lab Physicians* 2014;6:102–108.
4. Schlote T, Kadner G, Freudenthaler N. Marked reduction and distinct patterns of eye blinking in patients with moderately dry eyes during video display terminal use. *Graefes Arch Clin Exp Ophthalmol* 2004;242:306–312.
5. The definition and classification of dry eye disease: Report of the definition and classification subcommittee of the international dry eye workshop. *Ocul Surf* 2007;5:75–92.
6. Apostol S, Filip M, Dragne C, et al. Dry eye syndrome. Etiological and therapeutic aspects. *Oftalmologia* 2003;59:28–31.
7. Rosenberg ES, Asbell PA. Essential fatty acids in the treatment of dry eye. *Ocul Surf* 2010;8:18–28.
8. Calder PC. N-3 polyunsaturated fatty acids and inflammation: from molecular biology to the clinic. *Lipids* 2003;38:343–352.
9. Spite M, Clària J, Serhan CN. Resolvins, specialized pro-resolving lipid mediators, and their potential roles in metabolic diseases. *Cell Metab* 2014;19:21–36.
10. Roncone M, Bartlett H, Eperjesi F. Essential fatty acids for dry eye: A review. *Cont Lens Anterior Eye* 2010;33:49–54.
11. Oleñik A, Mahillo-Fernández I, Alejandre-Alba N, et al. Benefits of omega-3 fatty acid dietary supplementation on health-related quality of life in patients with meibomian gland dysfunction. *Clin Ophthalmol* 2014;8:831–836.
12. Oleñik A, Jiménez-Alfaro I, Alejandre-Alba N, et al. A randomized, double-masked study to evaluate the effect of omega-3 fatty acids supplementation in meibomian gland dysfunction. *Clin Interv Aging* 2013;8:1133–1138.
13. Kumar P, Bhargava R, Kumar M, et al. The correlation of routine tear function tests and conjunctival impression cytology in dry eye syndrome. *Korean J Ophthalmol* 2014;28:122–129.
14. Bhargava R, Kumar P, Kumar M, et al. A randomized controlled trial of omega-3 fatty acids in dry eye syndrome. *Int J Ophthalmol* 2013;6:811–816.
15. Bhargava R, Kumar P. Oral Omega-3 fatty acids treatment for dry eye in contact lens wearers. *Cornea* 2015;34:413–420.
16. Bhargava R, Kumar P. Conjunctival impression cytology in computer users. *J Ophthalmic Pathol* 2014;3:4.
17. Bhargava R, Kumar P, Phogat H, et al. Oral omega-3 fatty acids treatment in computer vision syndrome related dry eye. *Cont Lens Anterior Eye* 2015;38: 206–210.
18. Nelson JD, Havener VR, Cameron JD. Cellulose acetate impressions of the ocular surface. Dry eye states. *Arch Ophthalmol* 1983;101:1869–1872.
19. Turner RM, Bird SM, Higgins JP. The impact of study size on meta-analyses: Examination of underpowered studies in Cochrane reviews. *PLoS One* 2013;8:e59202.
20. Liu A, Ji J. Omega-3 essential fatty acids therapy for dry eye syndrome: A meta-analysis of randomized controlled studies. *Med Sci Monit* 2014;20:1583–1589.
21. Wojtowicz JC, Butovich I, Uchiyama E, et al. Pilot, prospective, randomized, double-masked, placebo-controlled clinical trial of an omega-3 supplement for dry eye. *Cornea* 2011;30:308–314.
22. Dehghani A, Tavakoli M, Akhlaghi M, et al. Prevalence of ocular symptoms and signs among professional computer users in Isfahan, Iran. *J Res Med Sci* 2008;13:303–307.
23. Uchino M, Yokoi N, Uchino Y, et al. Prevalence of dry eye disease and its risk factors in visual display terminal users: The Osaka study. *Am J Ophthalmol* 2013;156:759–766.