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Oral Supplementation with a Nutraceutical Formulation Containing Omega-3 Fatty Acids, Vitamins, Minerals and Antioxidants in a Large Series of Patients with Dry Eye Symptoms: Results of a Prospective Study

Jordi Gatell –Tortajada MD, on behalf of the Large Dry Eye Clinical Study Group (LDECSG)

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Correspondence: Jordi Gatell-Tortajada, MD, PhD; Cornea and Ocular Surface department. Institut Català de Retina. Ganduixer 117; 08022 Barcelona, Spain; Phone: +34932547922; E-mail: jgatell@comb.cat

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Shortened title: Omega-3 fatty acids in a large series of dry eye patients

Abstract (word count 200)

Purpose. To assess the benefits and tolerability of a dietary supplement based on omega-3 fatty acids to relief dry eye symptoms. *Methods.* A total of 1419 patients (74.3% women, mean age 58.9 years) with dry eye syndrome using artificial tears participated in a 12-week prospective study. Patients were instructed to take three capsules/day of the nutraceutical formulation (Brudysec[®] 1.5 g). Study variables were dry eye symptoms (scratchy and stinging sensation, eye redness, grittiness, painful and tired eyes, grating sensation and blurry vision), conjunctival hyperemia, tear breakup time (TBUT), Schirmer I test and Oxford grading scheme. *Results.* At 12 weeks, each dry eye symptom improved significantly ($P < 0.001$) and the use of artificial tears decreased significantly from 3.77 (SD 2.08) at baseline to 3.45 (SD 1.72) ($P < 0.01$). Also, the Schirmer tests scores and the TBUT increased significantly, and there was an increase in patients grading 0-I in the Oxford scale and a decrease of those grading IV-V. Significant differences in improvements of dry eye symptoms were also found in compliant vs. non-compliant patients as well as in those with moderate/severe vs. none/mild conjunctival hyperemia. *Conclusions.* Oral ω -3 fatty acids supplementation was an effective treatment for dry eye symptoms.

Keywords: dry eye symptoms, artificial tears, omega-3 polyunsaturated fatty acids, nutraceutical supplement, ocular inflammation, eye discomfort.

Introduction

Dry eye disease is a common condition, particularly affecting women and the elderly [1]. A wide variation in the prevalence of dry eye disease, ranging from < 0.1% as high as 33% has been reported [2]. This wide variation is related to differences in definitions, diagnostic criteria and study populations (e.g. population surveys or physician assessments). It has been estimated that only 20% subjects with mild symptoms seek medical care as compared to 50% of those with moderate disease and virtually all patients with severe disease [3]. In addition, the burden of dry eye disease to the patient is considerable in relation to impact on visual function, daily activities, social and physical functioning, workplace productivity and health-related quality of life [4,5].

Dry eye is a multifactorial disease of the tears and the ocular surface, in which dysfunction of the lacrimal functional unit with increased osmolarity of the tear film and inflammation of the ocular surface play a prominent role [6]. Studies in tissue culture, animal models and in humans strongly support the role of inflammation as part of the core pathogenesis of dry eye disease [7]. The chronicity of the disease suggests that dysregulation of immune mechanisms leads to a cycle of continuous inflammation. Accordingly, due to newer understanding of the inflammatory-mediated pathogenesis of dry eye disease, anti-inflammatory therapy is considered a causative therapeutic approach, since its objective is to interrupt the inflammatory cascade, rather than other treatment modalities aimed to provide symptomatic relief [8].

Essential polyunsaturated fatty acids omega-3 (ω -3) and omega-6 (ω -6) are the precursors of eicosanoids, which are locally acting hormones that mediate the inflammatory processes [9]. In a literature review of the treatment of dry eye syndrome with ω -3 and ω -6 essential fatty acids, ω -3 supplementation demonstrated an anti-inflammatory effect, inhibiting creation of ω -6 prostaglandin precursors, preventing apoptosis of the secretory epithelial cells in the lacrimal gland, and clearing meibomitis allowing a thinner, more elastic lipid layer to protect the tear film and cornea [10]. Also, other studies have provided evidence of the beneficial effect

of supplementation with ω -3 essential fatty acids in the treatment of dry eye disease [11-16]. Two recent meta-analysis of randomized controlled studies support the use of ω -3 fatty acid supplementation as effective therapy for dry eye syndrome [17,18]. However, further real-world studies are needed to substantiate existing evidence for the use of polyunsaturated fatty acids (PUFAs)-based supplements in the improvement of dry eye disease.

Therefore, a prospective, open-label intervention study was conducted to assess the effect of an oral nutraceutical formulation based on ω -3 PUFAs on the relief of dry eye symptoms in a large series of patients attended in the routine ophthalmological practice.

Materials and Methods

Study Design and Participants

This was an open-label, prospective, non-comparative, intervention and multicenter study carried out in ophthalmological clinics throughout Spain in conditions of daily practice. Patients were recruited by the participating ophthalmologists during a routine ophthalmological appointment. The primary objective of the study was to assess the effectiveness of an oral nutraceutical formulation based on ω -3 PUFAs, vitamins, minerals and antioxidants in the relief of dry eye-related symptoms. Secondary objectives included whether this oral formulation could improve conjunctival hyperemia, tear film stability, ocular surface damage, tear production, and to reduce the use of artificial tears. The tolerability of the product was also evaluated.

Patients of both sexes, aged 16 year or older, contact lenses users and non-users on current treatment with artificial tears due to dry eye disease, who were not completely satisfied with ocular topical treatments were eligible for inclusion in the study. Patients with fish allergy, history of bariatric surgery for morbid obesity, ocular disorders requiring the use of eye drops other than artificial tears, pregnant and breastfeeding women, and those deemed unable to participate according to the ophthalmologist's criteria were excluded. The study was conducted in accordance with the principles of the Declaration of Helsinki for the protection of human subjects, and written informed consent was obtained from all participants.

Study Procedures

Ophthalmologists all over the country were invited by the sales division of the pharmaceutical company who manufacture the supplement (Brudysec[®] 1.5 g, Brudy Laboratories, Barcelona, Spain) to participate voluntarily in the study. Between February 1, 2014 and May 1, 2014, patients who fulfilled the inclusion criteria and signed the informed consent were recruited, with a total of 20 patients per ophthalmologist.

Patients were visited at baseline and at the end of the study (12 weeks). At the baseline visit (visit 0), the patient's eligibility was assessed, the informed consent form was signed, baseline parameters were assessed, and the nutraceutical formulation was prescribed. The following data were recorded: demographics (age, sex), mean daily eye drops of artificial tears, use of contact lenses (categorized as yes/no) and mean daily wear (hours), dry eye symptoms (categorized as 0, none; 1, mild; 2, moderate; and 3, severe) including scratchy and stinging sensation in the eyes, eye redness, grittiness, painful eyes, tired eyes (eye fatigue), grating sensation and blurry vision. Conjunctival hyperemia was rated as none, mild, moderate, and severe. Tear breakup time (TBUT) was measured by instillation of one drop of 2% fluorescein. The time until disappearance of the dye was recorded and the average of three trials was calculated. Tear instability was defined as TBUT < 10 seconds. Tear quantification was assessed with the Schirmer I test, which was applied during a 5-min interval, without anesthesia. The Oxford grading scheme [19] was used to estimate surface damage and according to the intensity of fluorescein staining, ranging from I to V for each panel (0 to I, normal; II to III, mild to moderate; and IV to V, severe).

At the baseline visit, patients were given the nutraceutical formulation (Brudysec[®] 1.5 g) and were instructed to take three capsules one time daily with a main meal (excluding breakfast). The composition of the supplement formulation is detailed in Table 1. This is a concentrated DHA triglyceride having a high antioxidant activity, patented to prevent cellular oxidative damage [20,21]. Ophthalmologists paid special care to insist on the importance of

compliance with the dietary supplement and the benefit that the patient may receive from the supplement.

At the final visit (week 12), data recorded included compliance with treatment with the following question “*Did you take the three capsules every day?*” (Categorized as always, some forgetfulness, much forgetfulness); “*Have you noticed any change in symptoms?*” (categorized as yes or no); assessment of dry eye symptoms and conjunctival hyperemia as at baseline visit; mean daily eye drops of artificial tears; results of TBUT test, Schirmer test, and Oxford grading test; if contact lens wearer, mean daily wear (hours); better tolerance to contact lenses (categorized as yes or no); mean daily eye drops of artificial tears; tolerability to nutraceutical formulation (categorized as fish-tasting regurgitation, nausea, vomiting, diarrhea, none of the above); level of the patient’s satisfaction (categorized as not at all satisfied, satisfied, very satisfied); and clinical assessment of the ophthalmologist (categorized as no improvement, mild improvement, large improvement). Patients could be withdrawn from the study of their own free or according to the ophthalmologist’s criteria due to adverse events, concomitant diseases or any other medical reasons.

Statistical Analysis

Quantitative variables are expressed and mean and standard deviation (\pm SD) or as median and interquartile range (25th-75th percentile) and categorical variables as frequencies and percentages. Differences of continuous variables between the visit 0 (baseline) and the visit at the end of treatment (week 12) were analyzed with the Wilcoxon signed-rank test for paired samples. Changes in each individual dry eye symptoms between the groups of none/mild vs. moderate/severe conjunctival hyperemia, and between compliant (those who always took the three capsules a day) and noncompliant patients (those who reported some or much forgetfulness) were compared with the Mann-Whitney U test. The degree of satisfaction with treatment for patients and clinicians between visits 0 and at 12 weeks were compared with the chi-square (χ^2) test. Statistical analyses were performed with the R Project for Statistical

computing (R 3.0) program (<http://www.r-project.org>). Statistical significance was set at $P < 0.05$.

Results

A total of 1509 patients with dry eye disease were recruited for the study. However, data from 90 patients (6%) were not included in the analysis due to missing data in one and/or the two study visits regarding dry eye symptoms (primary variable of the study) or compliance with the nutraceutical supplement. Therefore, the study population included 1419 patients. Seventy-four percent were women, with a mean (SD) age of 58.9 (15.0) years (range 16-100 years). All patients used artificial tears to relief dry eye symptoms, with a daily mean (SD) of 3.8 (1.6) instillations of eye drops. Contact lens users accounted for 15.9% of the study population ($n = 205$). As shown in Table 2, the mean intensity of dry eye symptoms varied from 1.74 (0.88) for painful eyes to 0.98 (0.92) for blurry vision, with a mean value of 9.67 (6.38) for all symptoms together. Conjunctival hyperemia was mild in 49.9% of patients and moderate in 31.5%. Results of the Oxford grading scale, TBUT and Schirmer test are shown in Table 2.

Data recorded at the final visit (week 12) showed statistically significant improvements in all study variables ($P < 0.001$). The mean (SD) total symptom score decreased from 9.67 (6.38) to 4.22 (4.71) ($P < 0.001$). The mean number of daily instillation of artificial tears also decreased significantly from 3.77 (2.08) to 3.45 (1.72) ($P < 0.01$). As shown in Figures 1 and 2, the Schirmer tests scores and the TBUT increased significantly, reflecting improvement in tear secretion and tear film stability, respectively. Moreover, there was an increase in the percentage of patients grading 0-I in the Oxford scale and a decrease of those grading IV-V (Table 2).

In relation to compliance with the nutraceutical supplement, 66% of patients ($n = 937$) reported having taken always the three capsules daily and 34% reported some or much forgetfulness. Changes in dry eye symptoms according to compliance with ω -3 fatty acids supplementation is shown in Table 3. At the end of treatment (visit at 12 weeks), there were statistically significant mean differences as compared to baseline in all dry eye symptoms

except for blurry vision. Also, when the subgroup of compliant patients ($n = 937$) were stratified according to the intensity of conjunctival hyperemia in the groups of moderate/severe vs. none/mild, the degree of improvement in all dry eye symptoms was significantly higher ($P < 0.001$) among those with moderate/severe conjunctival hyperemia than among those with none/mild conjunctival hyperemia (Table 4).

A total of 1067 patients (79.2%) did not report any adverse event. In the remaining patients in whom adverse events occurred, the most frequent was fish-tasting regurgitation in 14.6%, followed by nausea in 4.6%, diarrhea in 2.7% and vomiting in 0.4%. None of the patients were withdrawn from the study because of adverse events.

In relation to the level of patient satisfaction regarding clinical improvement of dry eye symptoms, 28.2% were very satisfied, 57.5% satisfied, and 14.3% not at all satisfied. Also, 41.2% of ophthalmologists rated clinical improvement as large, 50.4% as mild, and 8.4% as no improvement.

Discussion

This prospective study carried out in a large clinical series of patients with dry eye symptoms and using artificial tears to relieve ocular surface dysfunction, attended in routine daily practice, shows that a dietary supplementation with ω -3 essential fatty acids, antioxidants, vitamins and minerals was useful to improve dry eye symptoms. Other positive effects included a decrease in the use of artificial tears, reduced conjunctival hyperemia and improvement in tear secretion and tear film stability. All individual dry eye symptoms (scratchy and stinging sensation in the eyes, eye redness, grittiness, painful eyes, tired eyes, grating sensation and blurry vision) showed a marked improvement with statistically significant differences between end of treatment and baseline.

Omega-3 and ω -6 fatty acids are essential for ocular surface homeostasis, and they have to be absorbed from the food. It has been shown that ω -3 fatty acids exhibit anti-inflammatory activity by blocking proinflammatory eicosanoids and reducing cytokines [21]. Antioxidant and

ω -3 supplementation improve tear film parameters and decrease ocular surface inflammation [12,16,24]. Dietary supplementation with PUFAs yields positive results in the improvement of dry eye signs and symptoms and it seems that DHA and EPA may constitute the most effective treatment [25]. In a study carried out using data of the Womens' Health Study, in which 4.7% of the sample of 32,470 women aged 45-84 years reported dry eye syndrome, a higher dietary intake of ω -3 fatty acids, particularly DHA, was associated with a lower prevalence of dry eye disease, including a 68% reduction in women who consumed ≥ 5 -6 servings per week compared to ≤ 1 servings per week of tuna fish, which is one of the largest contributors of ω -3 fatty acids in the typical American diet [26]. The use of ω -3 fatty acid supplementation as effective therapy for dry eye syndrome is also supported by data of two meta-analyses [17,18]. In addition, a survey of Australian optometrists' dry eye practices revealed that most practitioners systemic recommend ω -3 fatty acid supplementation and increased dietary intake of ω -3 fatty acids for moderate and severe dry eye disease, respectively [27].

In the recent clinical guidelines for the management of dry eye disease associated with Sjögren syndrome, dietary supplement with ω -3 fatty acids are recommended as anti-inflammatory therapy [28]. Moreover, new research is under way using a large, double-masked, randomized, multicenter clinical trial (DREAM trial) to test the hypothesis that ω -3 supplementation is an effective treatment for dry eye disease [29]. The primary outcome measure is the mean change from baseline in ocular surface disease index score at 6 and 12 months, and patients assigned to the experimental arm will receive 2000 mg EPA and 1000 mg DHA per day (taken in 5 gelcaps), which is a similar amount of DHA than that contained in our nutraceutical formulation.

The tolerability of the nutraceutical formulation was very good, and almost 80% of patients did not report any adverse event. None of the participants discontinued the nutraceutical supplement because of adverse events. Digestive discomfort, particularly fish-tasting regurgitation was the most frequently side effect. On the other hand, in relation to the patient's satisfaction with treatment, only 14.3% were not at all satisfied. Ophthalmologists only rated no improvement of dry eye symptoms in 8.4% of the cases.

Despite the limitation of the open-label design, the lack of a control group, and the treatment period limited to 12 weeks, the large number of participants and the fact that data were obtained in daily clinical practice add strength to the findings.

Conclusion

This study provides evidence of the role of oral supplementation with a nutraceutical formulation composed of ω -3 fatty acids, antioxidants, vitamins and minerals to relief dry eye symptoms. The study was conducted in daily ophthalmological practice and the effects of ω -3 supplementation were assessed in a large sample of patients with dry eye disease using artificial tears. A decrease in the use of artificial tears, a reduction in conjunctival hyperemia and an improvement in tear secretion and tear film stability were also observed. The present results add evidence of the anti-inflammatory effects of ω -3 fatty acids and their clinically beneficial role in the therapeutic strategies of dry eye disease.

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Gamboa Saavedra, José Luís Almeda Jurado, Francesca Mayoral Masana, Laura Martínez Pérez, Antonio Rojano Pastor, Fernando Urbano, Sara Ortíz Ortigosa, Eduardo Conesa, Yolanda Poza, Antonio Pérez Esteban, Cesar Hita Antón, Cristina Miguez García, Carlos Izquierdo Rodríguez, Alejandro Portero Benito, Luciano Doncis, Mahmoud Zabad Wehbi, Sara Núñez Márquez, Almudena Acero Peña, José Zamora Barrios, María Miranda Rollón, M^a Remedios Ortega García, Daniel Cornejo Martín, Rocío Sanjuán Ruíz, Francisco Ortíz Ramirez, M^a Dolores Romero Caballero, M^a Dolores López Bernal, Fernando Aguirre Balsalobre, Begoña Garrido Desdentado, Mónica Perez de Arcelus, M Soledad Leonato Dominguez, Javier Sornichero Martínez, M^a Paz Orts Vila, Concepción Molero Izquierdo, Gema Olea Zorita, Albino Rial Cortizo, Ramón Calvo Andrés , Emilia Tarragó Simó, María Francesca Perena, Manuel Timoteo Barranco, Ester López Navarrete, Eduardo Esteban González, Belén Fernández Pérez, Cristián Jesús Cortés Laborda, Dolores Sosa Domínguez, José Manuel Sandoval, Miguel Quevedo Rondón, Noemí Rosselló Silvestre, Abel Salas Carrascón, Jonatan Amián Cordero, Cinta Murcia Bello, Esther Escrivá Pastor, Salvador García Delpech, Francisco García-Franco Zuñiga, Mar Salvador Herrero, Pilar Dapena Urcola, M^a Victoria Montoya Alfaro, Santiago Montolio Doñate, Alba García López, Juan Sancristobal Epalza, Verónica Rodríguez Méndez, Josu Zarrabeitia Carrandi, David Pérez Silguero, José Ramón Pérez Fernández, Sixto Carrillo Pacheco, Antonio José Gómez Escobar, José Antonio Quevedo Alonso, José Francisco Moreno Galdo, José Azogue Camacho.

Disclosure

This study was supported by Brudy Laboratories, Barcelona, Spain. Neither the author nor the participants cited in the Large Dry Eye Clinical Study Group (LDECSG) list have any conflict of interest to disclose. Brudy Laboratories was not involved in the analysis of data and interpretation of the result. The autor reports no other conflicts of interest in this work.

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TABLE 1. Composition of Brudysec® 1.5 g

Composition	Per capsule	% Reference Intake	Per three capsules	% Reference Intake
Concentrated oil in ω -3 fatty acids	500 mg		1500 mg	
TG-DHA 70%	350 mg	–	1050 mg	–
EPA 8.5%	42.5 mg	–	127,5 mg	–
DPA 6%	30 mg	–	90 mg	–
Vitamins				
Vitamin A (retinol)	133.3 μ g RE	16.66	400 μ g RE	50
Vitamin C (ascorbic acid)	26.7 mg	33	80 mg	100
Vitamin E (d- α -tocopherol)	4 mg α -TE	33	12 mg α -TE	100
Essential trace elements				
Zinc	1.6 mg	16.6	5 mg	50
Cooper	0.16 mg	16.6	0.5 mg	50
Magnesium	0.33 mg	16.6	1 mg	50
Selenium	9.17 μ g	16.6	27.5 μ g	50
Other components				
Tyrosine	10.8 mg	-	32.5 mg	
Cysteine	5.83 mg	-	17.5 mg	
Glutathione	2 mg	-	6 mg	

Abbreviations: TG-DHA: triglyceride-bound docosahexaenoic acid; EPA: eicosapentaenoic acid; DPA: docosapentaenoic acid; RE: retinol equivalents; TE: tocopherol equivalents.

Note: The recommended daily intake is 250 mg of DHA (Regulation [EU] No. 432/2012 of the European Parliament and of the Council, of 16 May 2012) [20]. Brudysec®, Brudylab, SL, Barcelona, Spain.

TABLE 2. Description of variables at baseline (visit 0) and at 12 weeks in 1419 patients with dry eye disease

	Data		
Sex			
Men, %	25.7		
Women, %	74.3		
Age, years, mean (SD)	58.9 (15.0)		
Daily eye drops of artificial tears, mean (SD) [range]	3.77 (2.08) [1-25]		
	Baseline (visit 0)	Visit at 12 weeks	<i>P</i> value
Dry eye symptoms, mean (SD)			
Scratchy	1.31 (0.94)	0.62 (0.69)	< 0.001
Stinging sensation	1.56 (0.90)	0.72 (0.70)	< 0.001
Eye redness	1.42 (0.84)	0.70 (0.72)	< 0.001
Grittiness	1.43 (0.86)	0.68 (0.71)	< 0.001
Painful eyes	1.74 (0.88)	0.79 (0.71)	< 0.001
Tired eyes	1.20 (0.99)	0.50 (0.66)	< 0.001
Grating sensation	1.45 (0.92)	0.58 (0.66)	< 0.001
Blurry vision	0.98 (0.92)	0.33 (0.58)	< 0.001
Conjunctival hyperemia, n (%)			
None	125 (11.9)	398 (40.2)	< 0.001
Mild	523 (49.9)	521 (52.7)	
Moderate	330 (31.5)	68 (6.9)	
Severe	71 (6.8)	2 (0.2)	
Oxford grade, n (%)			
Right eye			
0	180 (13.0)	581 (43.2)	< 0.001
I	460 (33.4)	537 (39.6)	
II	437 (31.6)	173 (12.7)	
III	233 (16.9)	53 (3.9)	
IV	55 (4.0)	8 (0.6)	
V	15 (1.1)	0	
Left eye			
0	169 (12.2)	568 (42.0)	< 0.001
I	471 (34.1)	539 (39.8)	
II	421 (30.4)	182 (13.4)	
III	243 (17.6)	57 (4.2)	
IV	66 (4.8)	6 (0.5)	
V	12 (0.9)	1 (0.1)	
Tear breakup time (TBUT), seconds, median (IQR)			
Right eye	7 (5-10)	10 (7-11)	< 0.001
Left eye	7 (5-10)	10 (7-11)	< 0.001
Schirmer test, mm, mean (SD)			
Right eye	9.06 (4.40)	11.0 (4.43)	< 0.001
Left eye	9.24 (4.62)	11.2 (4.64)	< 0.001
Daily eye drops artificial tears, mean (SD)	3.77 (2.08)	3.40 (1.56)	< 0.01

TABLE 3. Improvement of dry eye symptoms according to compliance with treatment

Dry eye symptoms	Baseline (visit 0)		Visit at 12 weeks		
	Compliant*	Non-compliant†	Compliant	Non-compliant	
Scratchy	1.31 (0.95)	1.31 (0.93)	0.56 (0.66)	0.72 (0.72)	
Stinging sensation	1.58 (0.90)	1.54 (0.88)	0.67 (0.67)	0.83 (0.74)	
Eye redness	1.45 (0.88)	1.40 (0.81)	0.64 (0.64)	0.76 (0.81)	
Grittiness	1.77 (0.89)	1.69 (0.84)	0.75 (0.68)	0.85 (0.75)	
Painful eyes	0.89 (0.96)	0.84 (0.91)	0.28 (0.57)	0.34 (0.60)	
Tired eyes	1.21 (0.98)	1.18 (0.91)	0.47 (0.63)	0.56 (0.70)	
Grating sensation	1.46 (0.95)	1.42 (0.86)	0.54 (0.64)	0.66 (0.69)	
Blurry vision	0.92 (0.93)	0.92 (0.90)	0.33 (0.59)	0.32 (0.56)	
Difference 12 weeks vs. baseline					
Dry eye symptoms			Compliant	Non-compliant	<i>P</i> Value
Scratchy			-0.74 (0.77)	-0.58 (0.66)	< 0.001
Stinging sensation			-0.91 (0.78)	-0.71 (0.70)	< 0.001
Eye redness			-0.80 (0.77)	-0.63 (0.82)	< 0.001
Grittiness			-1.0 (1.07)	-0.84 (0.76)	< 0.001
Painful eyes			-0.65 (1.30)	-0.48 (0.86)	0.049
Tired eyes			-0.74 (0.86)	-0.62 (0.74)	0.029
Grating sensation			-0.91 (0.85)	-0.76 (0.77)	0.003
Blurry vision			-0.70 (1.04)	-0.60 (0.74)	0.116

*Compliant: always took the three capsules every day; †Non-compliant: some/much forgetfulness.

Data as mean (standard deviation, SD).

TABLE 4. Improvement of dry eye symptoms according to the degree of conjunctival hyperemia in the subgroup of 937 compliant patients*

Dry eye symptoms	Baseline (visit 0)		Visit at 12 weeks	
	None/mild	Moderate/severe	None/mild	Moderate/severe
Scratchy	1.09 (0.90)	1.69 (0.93)	0.45 (0.63)	0.877 (0.68)
Stinging sensation	1.41 (0.88)	1.92 (0.84)	0.58 (0.65)	0.89 (0.66)
Eye redness	0.99 (0.70)	2.07 (0.69)	0.45 (0.57)	0.92 (0.63)
Grittiness	1.62 (0.87)	2.08 (0.83)	0.71 (0.69)	0.88 (0.69)
Painful eyes	0.56 (0.78)	1.35 (0.99)	0.19 (0.46)	0.36 (0.61)
Tired eyes	0.99 (0.93)	1.63 (0.98)	0.40 (0.62)	0.64 (0.67)
Grating sensation	1.23 (0.87)	1.85 (0.95)	0.50 (0.64)	0.69 (0.68)
Blurry vision	0.77 (0.84)	1.42 (0.96)	0.23 (0.51)	0.51 (0.69)
Difference 12 weeks vs. baseline				
Dry eye symptoms	None/mild	Moderate/severe	<i>P</i> value	
Scratchy	-0.63 (0.73)	-0.93 (0.82)	< 0.001	
Stinging sensation	-0.83 (0.77)	-1.04 (0.80)	< 0.001	
Eye redness	-0.55 (0.67)	-1.15 (0.74)	< 0.001	
Grittiness	-0.91 (0.83)	-1.15 (1.4)	< 0.001	
Painful eyes	-0.38 (0.63)	-1.11 (0.81)	< 0.001	
Tired eyes	-0.59 (0.79)	-0.99 (2.04)	< 0.001	
Grating sensation	-0.56 (0.68)	-1.02 (0.91)	< 0.001	
Blurry vision	-0.74 (0.75)	-1.15 (0.89)	< 0.001	

*Compliant: always took the three capsules every day.

Data as mean (standard deviation, SD).

LEGENDS

Figure 1. Box plots for the comparison of Schirmer test scores (mm) before and after 12 weeks treatment with oral ω -3 fatty acids supplementation. Data as median, interquartile range (IQR, 25th-75th percentile), maximum and minimum (\circ = above the value of 1.5 IQR; * = above the value of 3 IQR).

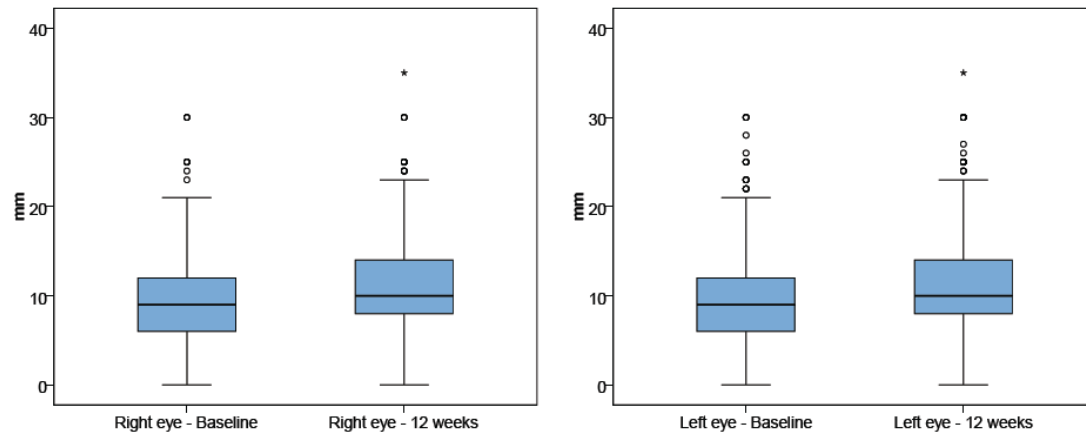


Figure 2. Box plots for the comparison of the tear break up time (TBUT) scores (seconds) before and after 12 weeks treatment with oral ω -3 fatty acids supplementation. Data as median, interquartile range (IQR, 25th-75th percentile), maximum and minimum (\circ = above the value of 1.5 IQR; * = above the value of 3 IQR).

