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Omega-3 Fatty Acids Supplementation Improves Dry Eye Symptoms in Glaucoma Patients: Results of a Prospective Multicenter Study

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Keywords: antioxidants; dry eye symptoms; nutraceutics; omega-3; polyunsaturated fatty acids.

Abstract (word count 250)

Purpose: To assess the effectiveness and tolerability of a dietary supplement with a combination of omega-3 fatty acids and antioxidants on dry eye symptoms caused by chronic instillation of antihypertensive eye drops in glaucoma patients.

Patients and Methods: A total of 1255 glaucoma patients with dry eye symptoms related to antiglaucoma topical medication participated in an open-label uncontrolled prospective and multicenter study, and were instructed to take three capsules/day of the nutraceutical formulation (Brudypio® 1.5 g) for 12 weeks. Dry eye symptoms (graded as 0 to 3 [none to severe]), conjunctival hyperemia, tear breakup time (TBUT) Schirmer I test, Oxford grading scheme, and intraocular pressure (IOP) were assessed.

Results: After 12 weeks of use of the dietary supplement, all dry eye symptoms improved significantly ($P < 0.001$) (mean 1.3 *vs.* 0.6 for scratchy, 1.4 *vs.* 0.7 for stinging sensation, 1.6 *vs.* 0.7 for grittiness; 1.0 *vs.* 0.4 for tired eyes, 1.1 *vs.* 0.5 for grating sensation, and 0.8 *vs.* 0.3 for blurry vision). The Schirmer test scores and the TBUT also increased significantly. There was an increase in the percentage of patients grading 0-I in the Oxford scale and a decrease of those grading IV-V. Compliance was recorded in 62.5% of patients. In compliant patients, mean differences at 12 weeks *vs*. baseline of dry eye symptoms were statistically significant as compared to non-compliant patients.

Conclusions: Dietary supplementation with Brudypio® may be a clinically valuable additional option for the treatment of dry eye syndrome in patients with glaucoma using antiglaucoma eye drops. These results require confirmation with an appropriately designed randomized controlled study.

INTRODUCTION

Patients with glaucoma frequently suffer from some degree of ocular surface dysfunction secondary to long-term instillation of topical antihypertensive eye drops. Dry eye syndrome is a mulfactorial disease associated with inadequate tear film volume, tear film instability and damage to the ocular surface.[1-4] It is accompanied by increased osmolarity of the tear film, and inflammation of the ocular surface. The symptoms of ocular surface disease may include dryness, burning or stinging, itching, irritation, tearing, photophobia, redness, fatigue, fluctuating visual acuity, and blurred vision.[5] Also, there is a poor relationship between dry eye signs and symptoms.[6] These visual disturbances and discomfort often compromise compliance with intraocular pressure-lowering medications and impair the quality of life and the patients' physical, social, and psychological functioning.[7,8]

Ocular surface dysfunction is a common morbidity in glaucoma patients, in part due to the fact that its prevalence, as in glaucoma, increases with age. Symptoms and signs of dry eye syndrome are seen in approximately 15% of the elderly population and are reported in 48% to 59% of patients with medically treated glaucoma.[9-12] Baudouin et al.[13] reported that moderate or severe ocular dysfunction syndrome was found in 63% of patients with severe glaucoma, and in 41% of those with mild glaucoma, with severity directly related to IOP. One in six patients with glaucoma presented symptoms of dry eye syndrome severe enough so that they need some form of treatment.[14] However, the diagnosis of ocular surface dysfunction in glaucoma patients is frequently overlooked since the focus of management is mainly put on the evaluation of intraocular pressure (IOP) and markers of glaucomatous disease progression. On the other hand a significant proportion of dry eye population has a coexisting glaucoma, and in these patients chronic topical therapy with antihypertensive eye drops can facilitate a ocular

discomfort. In a retrospective study of 190 patients aged 45 years or older seen at an Ocular Surface Diseases and Dry Eye clinic in Baltimore, 11% were found to have coexisting glaucoma.[15] Dry-eye type was predominantly characterized by a combined evaporative and aqueous tear deficiency (86% of cases).

Treatment of dry eye syndrome is mainly directed to reduce symptoms, usually by the application of artificial tears.[2,16,17] Also, artificial tear administration in glaucomatous patients with dry eye avoids improper confirmation of visual field progression.[18] On the other hand, inflammation and oxidative stress may play a key role in the development of dry eye syndrome.[13,19,20] Omega-3 polyunsaturated fatty acids supplementation has been shown to potentiate the antioxidant defences, to relief the bothering symptoms and signs of eye dryness by improving the lubrication and tear stability, and reducing the ocular surface inflammation either in glaucoma patients,[21] in pure dry eye patients,[22-24] in patients suffering from meibomian gland dysfunction,[25,26] and after photoreactive keratectomy.[27]

The present open-label intervention study carried out in a large sample of patients with glaucoma was designed to assess the effectiveness and tolerability of oral supplementation with a combination of omega-3 essential fatty acids and antioxidants in dry eye-related symptoms derived from chronic instillation of topical eye hypotensive drugs.

MATERIALS AND METHODS

This was an open-label, intervention, non-comparative, prospective and multicentre study carried out during routine ophthalmological appointments in conditions of daily practice. The objective of the study was to assess the effectiveness of an oral nutraceutical formulation based on omega-3 polyunsaturated fatty acids, vitamins,

minerals, and antioxidants in the relief of dry eye and conjunctival irritation symptoms secondary to the use of antihypertensive eye drops in patients with chronic glaucoma. The tolerability of the oral nutraceutical formulation was also evaluated. The duration of the study was 12 weeks.

Patients of any age and sex who were otherwise healthy, diagnosed with chronic glaucoma and treated with topical antiglaucoma medications were eligible to participate in the study during a routine ophthalmological examination when the reason of consultation was poor tolerance to antihypertensive eye drops due to associated sign and symptoms of dry eye syndrome and conjunctival hyperemia. Dry eye symptoms included painful eyes, tired eyes, blurry vision, stinging sensation, or eye irritation. The intensity of eye complaints was sufficiently important to be the reason of consultation. Eligibility also included users and non-users of artificial tears. Patients with fish allergy, atopy or history of allergic disorders, history of bariatric surgery for morbid obesity, pregnant women, and patients currently treated with vitamins or any other dietary supplements were excluded from the study, as were those deemed unable to participate in the study according to the clinician's criteria. 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.

A total of 65 ophthalmologists all over the country were invited to participate voluntarily in the study by the sales division of the pharmaceutical company who manufacture the supplement (Brudypio® 1.5 g, Brudy Laboratories, Barcelona, Spain). The composition of the supplement formulation is shown in Table 1. The products were provided to the investigators by Brudy Laboratories. Between September 1, 2013 and December 31, 2013, eligible patients who gave consent to take part in the study were recruited by the participating ophthalmologists, with a total of 20 patients per clinician.

Patients were visited at baseline and at the end of the study (12 weeks). At the baseline visit (visit 0), the patient's eligibility and baseline parameters were assessed, and the nutraceutical formulation was prescribed. The assessed baseline parameters were demographics (age, sex), use of artificial tears and mean daily eye drops, current type of hypotensive eye medication and mean daily eye drops, dry eye symptoms (categorized as 0, none; 1, mild; 2, moderate; and 3, severe) including scratchy and stinging sensation in the eyes, grittiness, painful eyes, tired eyes (eye fatigue), grating sensation, blurry vision, and other. 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[28] 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. Goldman applanation tonometry was used for intraocular pressure (IOP) determination.

At baseline, patients were also instructed to take three capsules of the study medication (Brudypio® 1.5 g). Ophthalmologists were instructed to emphasize the importance of taking the nutraceutical formulation as prescribed in order to help patients to improve their compliance and increase the benefit they may receive from the supplement, as well as to ensure the validity of the final data of the study

At the end of the study (week 12), data recorded included compliance with treatment ("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, Oxford grading test, and IOP; 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 (± SD) when distribution was normal or as median and interquartile range (25th-75th percentile) when distribution departed from normality, 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 analysed 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 visit 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

None of the 65 ophthalmologists invited to take part in the study declined participation. The number of patients recruited by each ophthalmologist ranged between 10 and 20. A total of 1290 patients with chronic glaucoma and dry eye symptoms related to topical use of hypotensive eye drops were recruited for the study. However, 35 patients (2.7%) were not included in the analysis due to missing data in the final visit at 12 weeks regarding whether or not they had been taken the three capsules/day of the nutraceutical supplement. Therefore, the study population included 1255 patients, which were visited at baseline and after 12 weeks. Sixty-two percent were women, with a mean age of 63.6 (12.8) years (range 18-97). All patients used hypotensive eye drops, with a large variety of fixed and unfixed combinations and a mean (SD) eye drops instillation of 1.7 (2.0) (range 1-32) per day. Also, 88.3% of patients used artificial tears to relief dry eye symptoms, with a daily mean (SD) of 3.4 (1.6) instillations of eye drops. The mean intensity of dry eye symptoms varied from 0.7 (0.8) for painful eyes to 1.6 (0.8) for grittiness. Conjunctival hyperemia was mild in 48.8% of patients and moderate in 33.5%. Results of the Schirmer test, TBUT, Oxford grading scale, and IOP are shown in Table 2.

Data recorded at the end of the study (visit at 12 weeks) showed statistically significant improvement in all study variables ($P < 0.001$). As shown in Figures 1 and 2, the Schirmer test scores and the TBUT increased significantly, reflecting improvement in tear secretion and tear film stability. 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. A significant difference in IOP values was also observed (Table 2).

In relation to compliance with treatment, 62.5% of patients reported having taken the three capsules always, and the remaining 37.4% reported some or much

forgetfulness. Changes of dry eye symptoms according to compliance with omega-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 in favour of the compliant group except for painful eyes and tired eyes. In addition, among patients who were compliant with the oral nutraceutical formulation, the degree of improvement of each individual dry eye symptom was significantly higher ($P < 0.001$) among those with moderate/severe conjunctival hyperemia than in patients with none/mild conjunctival hyperemia (Table 4).

A total of 960 patients (76.5%) did not report any adverse events. In the remaining 23.5% of patients in whom adverse events occurred, the most frequent was fish-tasting regurgitation in 16.9% of cases, followed by nausea in 4.7%, diarrhea in 1%, and vomiting in 0.3%. 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, 21.9% were very satisfied, 60% satisfied, and 18% not at all satisfied. Also, 31.3% of ophthalmologists rated clinical improvement as large, 56.4% as mild, and 12.4% as no improvement.

DISCUSSION

The present study carried out in a very large clinical series of patients with chronic glaucoma and ocular surface dysfunction due to long-term instillation of antihypertensive eye drops, shows that dietary supplementation with essential fatty acids and antioxidants appears effective to relief symptoms of dry eye syndrome. Other positive effects included a decrease in the use of artificial tears, although this cannot be considered clinically significant, reduced conjunctival hyperemia, and improvement of

tear film parameters A 3-month treatment of the supplement prescribed as three capsules a day was associated with a clinical improvement of all characteristics symptoms of dry eye (scratchy and stinging sensation, redness, grittiness, blurry vision, etc.) with statistically significant differences for comparisons between end of treatment and baseline. Omega-3 and omega-6 fatty acids cannot be synthesized in the body and must be obtained from diet. In this respect, incorporation of omega-3 into the diet is encouraged by many dieticians and health care professionals.

Chronic topical therapeutic management of glaucoma has the potential to deleteriously alter the ocular surface, mostly secondary to the preservative of eye drops (such as benzalkonium chloride [BAK]) rather than the active IOP-lowering drug component.[29] Chronic treatment with preserved topical drugs combined with age-related dry eye make glaucoma patients at risk of developing ocular surface disease with evidence of dry eye syndrome. Dry eye syndrome is a recognized group of disorders that culminate in the production of common signs and symptoms affecting the ocular surface and the tear film. Ocular inflammation is one of the single most common accompanying findings.[30] It has been shown that omega-3 supplementation has an anti-inflammatory effect [21,23], inhibiting creation of omega-6 prostaglandin precursors. Omega-3 essential fatty acids also demonstrate anti-inflammatory action in the lacrimal gland preventing apoptosis of secretory epithelial cells. Supplementation of essential fatty acids clears meibomitis, allowing a thinner, more elastic lipid layer to protect the tear film and cornea.[25,31] On the other hand, the guidelines proposed by the International Dry Eye Workshop[32] suggest that anti-inflammatory therapy needs to be instated in patients with moderate subjective discomfort, annoying visual symptoms, tear breakup times < 10 seconds, and Schirmer scores < 10 mm (wetting in 5 min). Oral omega-3 fatty acid intake is a recommended anti-inflammatory treatment modality at this stage.

The present results suggest significant improvements of dry eye symptoms and other related parameters, resulting from the antioxidant-anti-inflammatory properties of omega-3 fatty acids supplementation, add evidence to findings of previous studies.[21-23,25,26] However, as far as we are aware, this is the first study in which the effectiveness and tolerability of this nutraceutical supplementation was examined in patients with glaucoma and dry eye symptoms. In a study of patients on long-term treatment with antihypertensive eye drops with glaucoma and dry eye disorders, in which the oral supplement was Brudysec 1.5 g (very similar to that used in our patients), the main signs and symptoms of dry eye were significantly improved after 3 months of treatment as compared to unsupplemented patients.[21] Also, in a randomized controlled trial of omega-3 fatty acids in dry eye syndrome, administration of one capsule containing 325 mg eicosapentaenoic acid (EPA) and 175 mg docosahexaenoic acid (DHA) for 3 months (264 eyes) was associated with statistically significant differences as compared to placebo (254 eyes) in symptom scores, Schirmer test, TBUT values, Rose Bengal score (as a measure of ocular surface integrity), and conjunctival impression cytology scores. These excellent results are in agreement with our study findings.[33] Moreover, we found a significant decrease in IOP values but this observation is difficult to be interpreted because of the normal diurnal variation of IOP measurements. Also, changes in antihypertensive eye drops during the study period were not evaluated.

Recently, in a randomized, double-blind, placebo-controlled study, Bae et al.[34] reported that Korean Red Ginseng supplementation given for 8 weeks significantly improved tear film stability and total ocular surface disease index score in patients with glaucoma and established topical hypotensive therapy, confirming previous findings of an earlier study performed by the authors.[35] Ginseng (the root of *Panax ginseng*)

harbour a variety of active components, including ginsenoides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids.

Recent advances in understanding the pathophysiology of dry eye syndrome has led to evolution of newer modalities of treatment. Omega-3 fatty acids modulate the inflammatory process and nutritional supplementation has a promising role in dry eye. Dietary intervention with omega-3 fatty acids and antioxidants not only causes symptomatic relief but improves clinical markers of dry eye, probably in inherent stability of the tear film as seen by changes in TBUT and Schirmer test scores. Other lines of research include the role of the dopaminergic system and the usefulness of dopamine receptor (DA_2 and DA_3) agonists to influence the modulation of IOP.[36] In an experimental study in rats with induced ocular hypertension, dietary supplementation with a combination of alpha-lipoic acid (ALA) and superoxide dismutase (SOD) for 8 weeks versus no product, showed lack of fluorescence in the retinal ganglion cells and on astrocytes of the optic nerve, indicating that an increase of ALA and SOD exerts an anti-apoptotic effect and protects against oxidative stress.[37]

Our study has some important limitations, including the fact that differences according to type of glaucoma or topical antihypertensive medications were not assessed and the open-label design. Despite well-known disadvantages of an open-label design (e.g. introduction of bias through unblinding), open-label trials are less complex and can be conducted at lower costs, which could be used to recruit more patients and to improve the value of results of clinical studies. In the present case, the open-label design was very useful to recruit a large number of patients diagnosed of glaucoma with dry eye symptoms in order to replicate the favorable results obtained in previous studies[21,22] using an oral omega-3 supplementation in the patients with dry eye syndrome attended in routine daily practice. Some variables measured in the study may

vary with time of the day. However, the time of day the measurements were conducted was not controlled nor the time of the last drop instillation. Moreover, it may be argued that 12 weeks of administration of the nutraceutical supplement are few, but given the large dose administered, 1 g of DHA/day, improvement of dry eye symptoms can be obtained even before reaching the 3-month period. In a previous study by our group in patients with meibomian gland dysfunction, significant increases in TBUT as compared with baseline were already observed after 1 month of essential fatty acid supplementation.[25] Finally, patients enrolled in the study can be considered broadly representative of the population of patients with glaucoma in Spain diagnosed and managed by their ophthalmologists in the outpatient setting.

In conclusion, the administration of a nutraceutical supplement based on omega-3 polyunsaturated fatty acids combined with vitamins, antioxidants and minerals during a 3-month period in glaucoma patients using chronic instillation of antihypertensive eye drops may be an effective and well tolerated treatment for dry eye syndrome. Further studies with a longer treatment period and better design, such as randomized controlled trials (RCTs), are necessary to assess the long-term effects and confirm the effectiveness of this supplement. This nutritional supplement, however, may be a clinically valuable additional option for dry eye in patients with glaucoma using antiglaucoma eye drops.

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DISCLOSURE

This study was supported by Brudy Laboratories, Barcelona,Spain. Neither the author

nor the participants cited in the Dry Eye Clinical Study Group (DECSG) list have any conflict of interest to disclose. The participation of the sponsor was limited to distributing and collecting Case Record Forms from the participating ophthalmologists, but without any involvement in the tasks of creation of the database, perform statistical analyses, interpretation of the results or writing the manuscript. The author reports no other conflicts of interest in this work.

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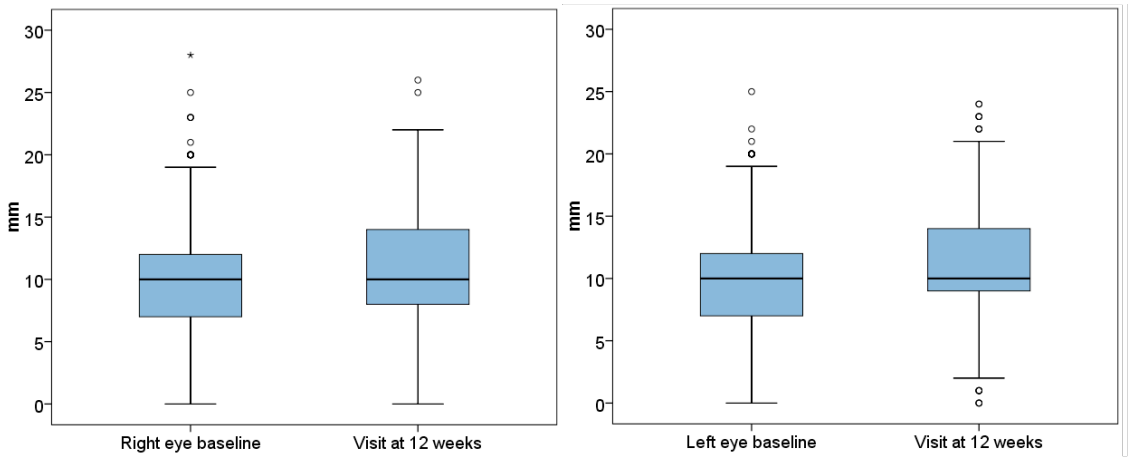

Figure 1. Changes in Schirmer tests scores in the right and left eyes at baseline (visit 0) and at visit at 12 weeks ($P < 0.001$, Wilcoxon test).

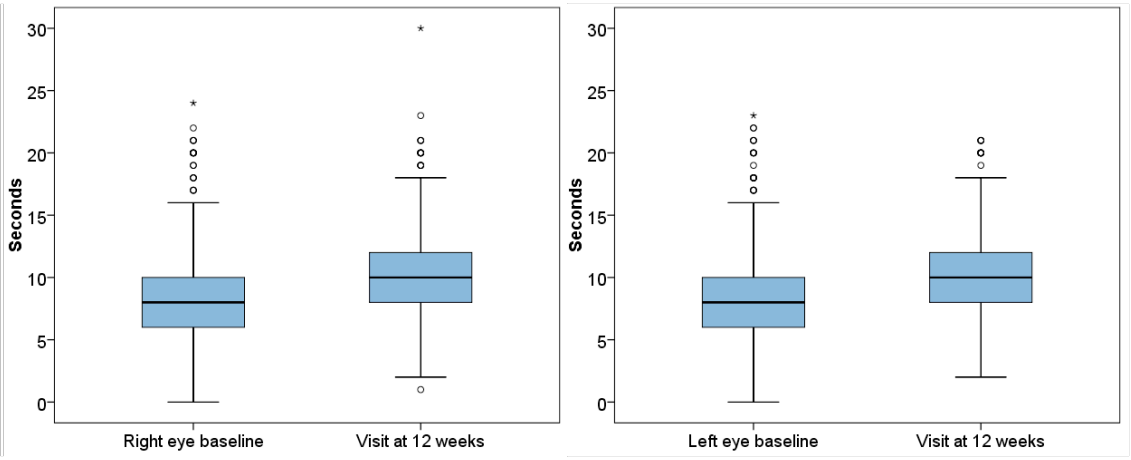

Figure 2. Changes in tear instability, TBUT in the right and left eyes at baseline (visit 0) and at visit at 12 weeks ($P < 0.001$, Wilcoxon test).

TABLE 1. Composition of Brudypio® 1.5 g.

Composition	Per capsule	% recommended amount in 1 capsule	Per three capsules	% recommended amount in 3 capsules
Concentrated oil in ω-3 fatty acids, mg	500		1500	
TG-DHA 70%	350	_	1050	_
EPA 8.5%	42.5	_	127,5	_
DPA 6%	30	_	90	_
Vitamins				
Vitamin A, µg RE (retinol)	133.3	17	400	50
Vitamin C, mg (ascorbic acid)	26.7	33	80	100
Vitamin E, mg (d-α-tocopherol)	4 α-TE	33	12 α-TE	100
Vitamin B1, mg (thamine)	0.36	33	1.1	100
Vitamin B2, mg (riboflavin)	0.46	33	1.4	100
Vitamin B3, mg (niacin equivalent NE)	5.33	33	16	100
Vitamin B6, mg (pyridoxine)	0.46	33	1.4	100
Vitamin B9, µg (folic acid)	66.7	33	200	100
Vitamin B12, µg (cobalamin)	0.83	33	2.5	100
Essential trace elements				
Zinc, mg	3.33	33	10	100
Cooper, mg	0.33	33	1	100
Manganese, mg	0.66	33	2	100
Selenium, µg	18.3	33	55	100
Other components				
Lutein, mg	3.33		10	
Zeaxanthin, mg	0.33		1	
Glutathione, mg	2		6	
Lycopene, mg	2		6	
Coenzyme Q10, mg	2		6	
Anthocyanins, mg	5		15	
Oleuropein, µg	67		200	

TG-DHA: triglyceride-bound docosahexaenoic acid; EPA: eicosapentaenoic acid; DPA: docosapentaenoic acid. Dosage tested is 3 capsules per day, which correspond to 100% of the recommended daily amounts of the included vitamins and minerals.

TABLE 2. Description of variables at baseline (visit 0) and at 12 weeks in 1255 glaucoma patients with dry eye symptoms

	Data		
Sex			
Men, %	477 (38.0%)		
Women, %	778 (62.0%)		
Age, years, mean (SD)	63.6 (12.8)		
Hypotensive medication, daily eye drops, mean (SD)	1.7 (2.0)		
Artificial tears users, n (%)	959 (88.3)		
Daily eye drops, mean (SD)	3.4 (1.6)		
	Baseline (visit 0)	Visit at 12 weeks	*P* value
Dry eye symptoms, mean (SD)			
Scratchy	1.3 (0.8)	0.6 (0.7)	< 0.001
Stinging sensation	1.4 (0.8)	0.7 (0.7)	< 0.001
Grittiness	1.6 (0.8)	0.7 (0.7)	< 0.001
Painful eyes	0.6 (0.8)	0.3 (0.5)	< 0.001
Tired eyes	1.0 (0.9)	0.4 (0.6)	< 0.001
Grating sensation	1.1 (0.9)	0.5 (0.6)	< 0.001
Blurry vision	0.8 (0.8)	0.3 (0.6)	<0.001
Conjunctival hyperemia, n (%)			
None	106 (9.2)	335 (31.6)	< 0.001
Mild	561 (48.8)	615 (58.0)	
Moderate	385 (33.5)	105 (9.9)	
Severe	98 (8.5)	8 (0.6)	
Oxford grade, n (%)			
Right eye			
0	159 (12.9)	458 (38.0)	< 0.001
I	466 (37.7)	543 (45.0)	
II	383 (31.0)	164 (13.6)	
III	173 (14.0)	34 (2.8)	
IV	50 (4.1)	5 (0.4)	
V	6 (0.5)	1 (0.1)	
Left eye			
0	153 (12.4)	462 (38.4)	< 0.001
I	472 (38.3)	530 (44.0)	
II	368 (29.8)	175 (14.6)	
III	186 (15.1)	30 (2.5)	
IV	46 (3.7)	5 (0.4)	
V	10 (0.8)	1 (0.1)	
Tear breakup time (TBUT), seconds, median (IQR)			
Right eye	8 (6-10)	10 (8-12)	< 0.001
Left eye	8 (6-10)	10 (8-12)	< 0.001
Schirmer test, mm, mean (SD)			
Right eye	9.69 (4.02)	11.0 (3.70)	< 0.001
Left eye	9.81 (4.06)	12.1 (18.7)	< 0.001
Daily eye drops artificial tears, mean (SD)	3.45 (1.62)	3.40 (1.56)	0.003
Intraocular pressure (IOP), mm Hg, mean (SD)			
Right eye	16.4 (2.92)	16.1 (2.70)	< 0.001
Left eye	16.5 (2.95)	16.1 (2.60)	< 0.001

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	1.3 (0.8)	1.2 (0.8)	0.6 (0.7)	0.6 (0.7)
Stinging sensation	1.5 (0.8)	1.3 (0.8)	0.7 (0.7)	0.7 (0.7)
Grittiness	1.6 (0.8)	1.4 (0.8)	0.7 (0.2)	0.8 (0.7)
Painful eyes	0.7 (0.9)	0.6 (0.8)	0.3 (0.5)	0.3 (0.5)
Tired eyes	1.0 (0.9)	1.0 (0.9)	0.4 (0.6)	0.5 (0.6)
Grating sensation	1.2 (0.9)	1.0 (0.8)	0.4 (0.6)	0.5 (0.6)
Blurry vision	0.8 (0.9)	0.7 (0.8)	0.3 (0.6)	0.3 (0.5)

Dry eye symptoms	Difference 12 weeks *vs*. baseline		
	Compliant	Non-compliant	*P* value
Scratchy	-0.7 (0.7)	-0.6 (0.7)	< 0.001
Stinging sensation	-0.8 (0.7)	-0.7 (0.7)	< 0.001
Grittiness	-0.9 (0.8)	-0.7 (0.7)	< 0.001
Painful eyes	-0.4 (0.7)	-0.3 (0.6)	0.060
Tired eyes	-0.6 (0.8)	-0.5 (0.7)	0.120
Grating sensation	-0.7 (0.8)	-0.5 (0.7)	< 0.001
Blurry vision	-0.5 (0.7)	-0.4 (0.6)	0.015

*Compliant: always took the three capsules every day: †Non-compliant: some/much forgetfulness. Compliant (781; 62,2%) and Non-compliant (474; 37,8%) are self-reported data.

Data as mean (standard deviation, SD).

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

Dry eye symptoms	Baseline (visit 0)		Visit at 12 weeks	
	None/mild	Moderate/severe	None/mild	Moderate/severe
Scratchy	1.2 (0.7)	1.7 (0.8)	0.5 (0.6)	0.8 (0.8)
Stinging sensation	1.2 (0.7)	1.9 (0.8)	0.5 (0.6)	0.9 (0.7)
Grittiness	1.3 (0.8)	2.1 (0.7)	0.6 (0.7)	0.9 (0.7)
Painful eyes	0.4 (0.7)	1.0 (0.9)	0.1 (0.4)	0.4 (0.6)
Tired eyes	0.7 (0.8)	1.4 (0.9)	0.3 (0.6)	0.6 (0.7)
Grating sensation	0.9 (0.8)	1.6 (0.9)	0.3 (0.5)	0.6 (0.7)
Blurry vision	0.5 (0.7)	1.1 (0.9)	0.9 (0.5)	0.4 (0.6)

Dry eye symptoms	Difference 12 weeks *vs*. baseline		
	None/mild	Moderate/severe	*P* value
Scratchy	-0.6 (0.7)	-0.9 (0.7)	< 0.001
Stinging sensation	-0.7 (0.7)	-1.0 (0.8)	< 0.001
Grittiness	-0.7 (0.7)	-1.2 (0.8)	< 0.001
Painful eyes	-0.2 (0.5)	-0.7 (0.8)	< 0.001
Tired eyes	-0.4 (0.6)	-0.8 (0.9)	< 0.001
Grating sensation	-0.7 (0.7)	-1.0 (0.8)	< 0.001
Blurry vision	-0.3 (0.6)	-0.7 (0.8)	< 0.001

*Compliant: always took the three capsules every day

Data as mean (standard deviation, SD).