Tear Film Osmolarity in Subjects with Acute Allergic Rhinoconjunctivitis

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Abstract. Background/Aim: Acute allergic rhinoconjunctivitis is the most common form of ocular allergies. The pathogenetic mechanisms are based on an immunoglobulin E (IgE)-mediated hypersensitivity reaction. On the other hand, tear osmolarity has been suggested to be an index of ocular surface damage and inflammation. These data were the motive to investigate the levels of tear osmolarity in subjects with acute allergic conjunctivitis, before and after administration of artificial tears. Patients and Methods: Forty-five subjects with acute allergic conjunctivitis were randomly divided into three groups, based on the type of artificial tears that they received: Group A (Thera tears), Group B (Wet therapy) and Group C (Tears Naturale free). The eye drops were administered six times a day for 60 days and all subjects underwent grading of subjective symptoms and clinical examination at baseline and at the end of the treatment. Results: The diagnosis of severe eye disease, which was based on ocular surface disease index (OSDI; Allergan, Inc, Irvine, CA, USA) and tear osmolarity values, concerned all patients at baseline. Although the administration of artificial tears significantly ameliorated the symptoms and the ocular variables in all groups, the results were better in the first group. Tear osmolarity was strongly and negatively correlated with tear film breakup time (BUT) and Schirmer I test at 2 months. Contrariwise, symptoms were eliminated, when tear osmolarity was decreased. Conclusion: Acute allergic rhinoconjunctivitis is characterized by tear hyperosmolarity, which can be rehabilitated with the administration of hypotonic artificial tears.

Acute allergic rhinoconjunctivitis is the most common form of ocular allergies, affecting at least 15-20% of the population. It is divided into seasonal (hay fever), which is released by pollen in the spring and summer, and perennial, which appears throughout the year and is induced by dust mites, animal dander and mold allergens (1, 2). The pathogenetic mechanisms of acute allergic conjunctivitis are based on an immunoglobulin E (IgE)-mediated hypersensitivity reaction, where IgE binds initially to high-affinity receptors on mast cells and basophils and then to the aforementioned allergens. The subsequent activation of mast cells results in the release of inflammatory mediators, including histamine, tryptase, prostaglandins, chemokines and leukotrienes (1). Monocytes, eosinophils and platelets also afford low-affinity IgE receptors (2). Subjects experience acute episodes of redness, tearing, ocular and nasal itching, sneezing, congestion and rhinorrhea. Slit lamp examination usually reveals bilateral eyelid edema along with conjunctival swelling, chemosis and papillary reaction (1, 2).
Tear osmolarity has been suggested to be an index of ocular surface damage and inflammation since 1995 (3, 4). Tear hyperosmolarity has been associated not only with dry eye disease (keratoconjunctivitis sicca), exhibiting positive correlation with the severity of the disease, but as well with herpetic keratitis, pterygia, and pseudoexfoliation syndrome (4, 5). Ocular medications have been found to modify tear osmolarity, including anti-glaucomatous drugs, which seem to raise the values, and artificial tears, which reduce tear osmolarity (5). Furthermore, the topical administration of 1% methylprednisolone, in subjects with moderate to severe dry eye syndrome, seems to lower tear osmolarity and cytokine levels (6). The association of tear osmolarity with inflammation has been also highlighted by Türkyilmaz et al., who related tear osmolarity values with the degree of early rheumatoid arthritis (7).

The inflammatory background of acute allergic rhinoconjunctivitis along with the records of tears hyperosmolarity in inflammatory diseases was the motive to investigate tear osmolarity in patients with acute allergic rhinoconjunctivitis. The aim of this study was to estimate the levels of tear osmolarity in subjects with acute allergic rhinoconjunctivitis, assessing in parallel the effect of three levels of tear osmolarity. Moreover, the history of known collagen vascular diseases, or receiving treatment, including antidepressants, or suffering from systemic diseases, such as diabetes mellitus and of autoantibodies, was regarded as exclusion criteria. Subjects included in this study were those with allergy-related conjunctivitis and reported that they were free of other ocular or medical conditions that alter tear production and quality, including incomplete lid closure, entropion, ectropion, nasolacrimal drainage obstruction, history of ocular surgery within the past year, use of contact lenses during the previous month and use of other topical ocular medicaments or artificial tears within 2 hours of checking tear osmolarity. Moreover, the history of known collagen vascular disease, such as secondary Sjögren syndrome or positive serology of autoantibodies, was regarded as exclusion criteria. Subjects suffering from systemic diseases, such as diabetes mellitus and thyroid diseases, or receiving treatment, including antidepressants, diuretics, corticosteroids or immunomodulators, which could impact tear secretion or the ocular surface, were ruled out by the medical history.

**Patients and Methods**

**Patient recruitment.** Forty-five subjects with acute allergic rhinoconjunctivitis were recruited in this study. An experienced allergist referred to us patients with ocular symptoms, who had never been treated by an ophthalmologist. Although acute allergic rhinoconjunctivitis has already been defined (8), we mention that we diagnosed the disease in people suffering from the following symptoms: nasal obstruction, watery nasal discharge, sneezing and itching, and conjunctival symptoms, including itching, injection and tearing. The inclusion criteria also involved the follow indexes: tear film breakup time (BUT) less than 5 seconds, Schirmer test less than 5 mm, and positive corneal and conjunctival staining. Past medical history, including medications, medical conditions, ocular history, within the last 3 months was obtained.

The exclusion criteria comprised any evidence of acute or chronic infection, any inflammatory or allergic condition of the cornea and conjunctiva other than acute allergic rhinoconjunctivitis, incomplete lid closure, entropion, ectropion, nasolacrimal drainage obstruction, placement of punctal plugs or punctal cautery, history of ocular surgery within the past year, use of contact lenses during the previous month and use of other topical ocular medicaments or artificial tears within 2 hours of checking tear osmolarity. Moreover, the history of known collagen vascular disease, such as secondary Sjögren syndrome or positive serology of autoantibodies, was regarded as exclusion criteria. Subjects suffering from systemic diseases, such as diabetes mellitus and thyroid diseases, or receiving treatment, including antidepressants, diuretics, corticosteroids or immunomodulators, which could impact tear secretion or the ocular surface, were ruled out by the medical history.

**Study design.** This study was designed as a prospective study. All subjects included were treated for a run-in period of 7 days with one eye drop of saline six times a day. At the end of this period (time 0 of the study) the subjects were randomly divided into three groups and assigned to a treatment by personnel not involved with the subjects’ examination. The number of the groups was determined according to the type of artificial tears that each patient received: Group A (Thera tears), Group B (Wet therapy) and Group C (Tears Naturale free). The eye drops were administered six times a day for 60 days and the subjects enrolled in the study underwent grading of subjective symptoms and clinical examination at baseline (time 0) and at the end of the treatment (after 60 days).

The parameters evaluated at baseline and at each follow up visit included the ocular surface disease index (OSDI; Allergan, Inc, Irvine, CA, USA), BUT, tear osmolarity test, Schirmer test I, fluorescein corneal and conjunctival staining. Tear osmolarity was measured first and Schirmer test was performed last, in order to minimize the effect of other examinations. The subjects were allowed to know the brand name of the eye drops they were using. They were asked to bring, at all visits, the used boxes of eye drops in order to control the compliance with the study protocol.

The study was conducted in the General Hospital of Athens G. Gennimatas in accordance to the tenets of the Declaration of Helsinki. The protocol used was approved by the ethics committee of the University Hospital. All patients agreed to participate in the study and gave written informed consent.

**Study material.** We used the following types of artificial tears: Thera tears (Akorn, Inc., Lake Forest, Illinois, USA), Wet therapy (Vita Research, Rome, Italy) and Tears Naturale free (Alcon, Inc., Fort Worth, Texas, USA). The characteristics of all drops are depicted in Table I. All artificial tears were preservative-free.

**Symptoms.** Symptoms of dry eye syndrome, such as burning, foreign body sensation, dryness, mucous discharge, itching and photophobia, were assessed with the ocular surface disease index (OSDI; Allergan, Inc, Irvine, CA, USA). The OSDI consists of 12 questions on symptoms within the past week and yields scores ranging from 0 (least severe) to 100 (most severe). A score of 12 is typically used as a cutoff for normal, 13-22 for mild dry eye, 23-32 for moderate dry eye, and ≥33 for severe dry eye (1, 2, 9).

**Tear osmolarity.** Tear osmolarity was measured in each eye with the TearLab® Osmolarity System (TearLab Corporation, San Diego, CA, USA). This new osmometer is a disposable ‘lab-on-a-chip’ system that requires <50 nl of tear fluid for analysis (3). A desktop instrument converts the electrical signals generated from the laboratory card into a quantitative measurement and displays the value on a screen. The system was stored in a temperature and humidity controlled environment, and these values were logged prior to each measurement of tear osmolarity. The system was calibrated at the beginning of each study day according to the manufacturer’s instructions; the test cards used for each tear osmolarity measurement were from the same lot numbers as the test cards used to calibrate the machine each day.

Subjects were instructed not to rub their eyes for at least 10 minutes. Tear samples (50 nl each sample) were collected atraumatically from the lateral tear meniscus (near the lateral canthus) of the right eye and then the left eye. The tip of the TearLab device (Pen 1) was placed gently with care being taken not to induce reflex tearing. Normal tear osmolarity is equivalent to...
normal blood osmolarity, which ranges from 280-295 mOsm/L. A tear osmolarity value of 305 mOsm/l was used as the cutoff for mild dry eye and 316 mOsm/l was used as the cut-off for more severe dry eye disease (3, 4). All measurements were performed by the same investigator. Since inter-eye variability has been found to be associated with an increased severity of DED, the measurement from the eye with the higher osmolarity was used for data analysis.

**BUT and Schirmer test.** Fluorescein strip was wet with a drop-volume of non-preserved saline solution and the strip was touched to the inferior palpebral conjunctiva. Subjects were asked to blink several times. The investigator monitored the integrity of the tear film with a slit lamp and measured up to the time until one or more dry spots appeared in the precorneal tear film from the last blink. A 5-minute Schirmer I test without topical anesthesia was performed to evaluate both basal tear secretion and reflex tearing. A Schirmer test I value of less than 10 mm in 5 minutes was considered abnormal (5).

**Corneal staining.** The degree of staining was measured for each of the five regions of the cornea: central, superior, temporal, nasal, and inferior. The degree of staining was evaluated using the National Eye Institute (NEI) method, for each of the five regions of the cornea (central, inferior, nasal, superior, and temporal) as follow: 1) grade 0 (normal); no staining, 2) grade 1 (mild); superficial stippling and micropunctate staining, 3) grade 2 (moderate); macropunctate staining with some coalescent areas; and 4) grade 3 (severe); numerous coalescent macropunctate areas and/or patches. Each of the five regions was graded on a scale from 0 to 3. The scores of the five areas were added to obtain a total score for each eye.

**Conjunctival staining.** The degree of staining was separately assessed for the three portions of the temporal conjunctiva and the three portions of the nasal conjunctiva on a scale from 0 to 3. The scores for each of the six areas were added to obtain a total score for each eye.

**Statistical analysis.** The statistical program IBM SPSS Statistics 22.0 was used for the data analysis. Descriptive analysis was carried out for age, OSDI scores, tear osmolarity, BUT and Schirmer I test values, as well as corneal and conjunctival staining scores. Non-parametric analysis Kolmogorov-Smirnov was used to check the normal distribution of the variables. The paired two-tailed *t*-test was utilized to calculate the differences in means of the measured variables between baseline and after the administration of artificial tears within each group. If the data failed the normality test, the non-parametric Wilcoxon matched-pairs signed-rank test was used. Independent samples Kruskal-Wallis tests were applied to identify the possible differences in means of the measured variables between the three groups (Mann-Whitney test was used when there was no indication of normal distribution either after Kolmogorov-Smirnov analysis or after Levene’s test for equality of variances). Correlation technique, based on Spearman’s coefficient, was performed to determine the relation among ocular indexes. A *p*-value less than 0.05 was considered to indicate statistical significance.

**Results**

**Demographics.** Forty-five subjects with acute allergic rhinoconjunctivitis were classified into three groups according to the type of artificial tears, which we prescribed to them. The number of males were 8 (0.53%), 9 (0.6%) and 10 (0.67%) in groups A, B and C, respectively. The relative numbers for females were 7 (0.47%), 6 (0.4%) and 5 (0.33%), respectively. The mean distribution of age within each group is presented in Table II. No statistically significant differences in the distributions of gender (Pearson chi-square test, *p*=0.757) and age (one-way Anova, *p*=0.853) were observed among three groups.

| Substances | Excipients | Osmolarity |
|------------|------------|------------|
| Thera tears (preservative free) | Sodium carboxymethyl cellulose 0.25% | Borate buffers Calcium chloride Magnesium chloride Potassium chloride Purified water Sodium bicarbonate Sodium chloride Sodium phosphate Purified water | Hypotonic |
| Wet therapy (no preservatives) | Sodium hyaluronate (MW=14X 105) 0.15% Polyethylene glycol (PEG 400) 0.20% | Purified water Boric acid NaCl, KCl, CaCl₂, MgCl₂ Hydrochloric acid Sodium borate decahydrate Sodium chloride Sodium hydroxide Polidronium chloride Potassium chloride Purified water | Isotonic |
| Tears Naturale free | Hypromellose 2910 (3 mg/ml) Dextran 70 (1 mg/ml) | | Isotonic |
Ocular surface indexes. The mean values of OSDI, tear osmolarity, BUT, Schirmer I test, as well as corneal and conjunctival staining scores are presented in Table II. The mean values of OSDI, tear osmolarity, BUT, Schirmer I test, corneal and conjunctival staining scores exhibited no statistical significant differences at baseline among the three groups. Contrariwise, significant differences in the means of all variables were detected 2 months after the administration of the artificial tears. Actually, tear osmolarity was significantly reduced in all groups, but only in Group A the levels restored to normal (Table II). Furthermore, BUT, Schirmer I test, as well as corneal and conjunctival staining scores were all decreased in three groups, but the values were better in Group A (Table II). The alterations of tear osmolarity, BUT, Schirmer I test, corneal and conjunctival staining scores were all significant between baseline and 2 months after treatment (Table II). The statistical significance of the differences observed in ocular indexes and symptoms of dry eye disease after the administration of artificial tears in all 3 groups are demonstrated in Table III.

Correlations were performed to determine the relation among ocular indexes recorded in three groups. Tear osmolarity recorded in all groups at 2 months treatment, was positively and significantly correlated with tear osmolarity at baseline (Spearman’s coefficient=0.38, p=0.010), with OSDI2 (Spearman’s coefficient=0.64, p<0.001), with OSDI1 (Spearman’s coefficient=0.37, p=0.013), and conjunctival staining at 2 months (Spearman’s coefficient=0.45, p=0.002). On the other hand, it was negatively and significantly correlated with BUT2 (Spearman’s coefficient=-0.78, p<0.001) and Schirmer I test at 2 months (Spearman’s coefficient=-0.60, p<0.001).

BUT2 was positively and significantly correlated with BUT1 (Spearman’s coefficient=0.45, p=0.002) and Schirmer I test at 2 months (Spearman’s coefficient=0.58, p<0.001) among participants. BUT2 recorded in all groups was negatively and significantly correlated with OSDI2 (Spearman’s coefficient= –0.66, p<0.001), corneal (Spearman’s coefficient=0.34, p=0.023), and conjunctival staining at 2 months (Spearman’s coefficient=0.52, p<0.001). A significant negative correlation was also detected in three groups between OSDI2 and Schirmer I test at 2 months (Spearman’s coefficient=-0.57, p<0.001), while the same score was positively correlated with corneal (Spearman’s coefficient=0.49, p=0.001), and conjunctival staining at 2 months (Spearman’s coefficient=0.42, p=0.004).

Moreover, a significant and positive correlation was detected between corneal staining at 2 months and both with corneal staining at baseline (Spearman’s coefficient=0.45, p=0.002), as well as with conjunctival staining at 2 months (Spearman’s coefficient=0.43, p=0.003) among participants. Similarly, the scores of conjunctival staining recorded in three groups at baseline and at 2 months were positively and significantly correlated (Spearman’s coefficient=0.31, p=0.037). Schirmer I tests at baseline and after 2 months were significantly and positively correlated (Spearman’s coefficient=0.30, p=0.044) among participants.

Discussion

In our study we noted that all subjects suffered from severe eye disease at baseline, based on OSDI scores and tear osmolarity values. Moreover, the mean values of OSDI, tear osmolarity, BUT, Schirmer I test, corneal and conjunctival staining scores exhibited no statistical significant differences at baseline among the three groups. Although the administration of artificial tears ameliorated significantly the symptoms (OSDI scores), the tear film osmolarity and the rest ocular variables in all groups, the results were better in the first group. Specifically, the use of hypotonic eye drops altered

| Mean (SD)                          | Group A | Group B | Group C | p-Value |
|------------------------------------|---------|---------|---------|---------|
| Age (years)                        | 41 (5.8)| 41 (5.3)| 40 (5.4)| -       |
| OSDI1 (at baseline)                | 64.0 (7.8)| 66.0 (5.1)| 66.3 (5.6)| 0.891  |
| OSDI2 (at 2 months)                | 19.9 (4.2)| 36.1 (2.0)| 32.8 (4.1)| <0.001 |
| Tear osmolarity (mOsm/L) (at baseline) | 318.1 (8.2)| 324.3 (5.4)| 323.5 (4.4)| 0.059  |
| Tear osmolarity (mOsm/L) (at 2 months) | 292.1 (5.4)| 313.1 (5.9)| 313.3 (4.3)| <0.001 |
| BUT1 (sec) (at baseline)           | 2.7 (0.9)| 2.7 (1.2)| 2.5 (1.1)| 0.751  |
| BUT2 (sec) (at 2 months)           | 7.7 (1.0)| 4.7 (1.2)| 5.3 (0.7)| <0.001 |
| Schirmer test I (mm) (at baseline) | 2.9 (0.9)| 2.9 (0.8)| 2.8 (0.7)| 0.810  |
| Schirmer test I (mm) (at 2 months) | 8.1 (2.4)| 6.1 (1.1)| 5.3 (1.0)| <0.001 |
| Corneal staining score (at baseline) | 1.5 (0.5)| 1.4 (0.5)| 1.4 (0.5)| 0.770  |
| Corneal staining score (at 2 months) | 0.5 (0.5)| 1.0 (0.4)| 0.9 (0.4)| 0.005  |
| Conjunctival staining score (at baseline) | 1.4 (0.5)| 1.5 (0.5)| 1.5 (0.5)| 0.770  |
| Conjunctival staining score (at 2 months) | 0.5 (0.5)| 1.1 (0.3)| 0.9 (0.4)| 0.001  |

*p-Value was extracted using Independent samples Kruskal-Wallis tests.
with the improvement of BUT, corneal and conjunctival staining scores, at 4th and 8th weeks (6). Suzuki seemed to decrease tear osmolarity and cytokine levels, along with significant difference in means of tear osmolarity, measured upon administration of 1% methylprednisolone four times per day (13). On the other hand, topical alteration of tear osmolarity was detected after treatment with autologous serum eye drops (13). The hyperosmolarity of tears observed in subjects with keratoconjunctivitis sicca ranges between 311-425 mOsm/L. It is estimated to be a sensitive (sensitivity 90-95%) and specific (specificity 94-95%) index for the diagnosis of dry eye syndrome (10, 11). Lemp et al. noted that tear osmolarity exhibited 73% sensitivity and 92% specificity for the diagnosis of dry eye syndrome (12). Recent study revealed no significant difference in means of tear osmolarity, measured by TearLab Osmolarity System, between healthy individuals and subjects with dry eye syndrome. Furthermore, no alteration of tear osmolarity was detected after treatment with autologous serum eye drops (13). On the other hand, topical administration of 1% methylprednisolone four times per day seemed to decrease tear osmolarity and cytokine levels, along with the improvement of BUT, corneal and conjunctival staining scores, at 4th and 8th weeks (6). Suzuki et al. assessed tear osmolarity, BUT, Schirmer I test, as well as corneal and conjunctival staining scores in subjects with Dry Eye Syndrome and the measured values were as follow: 309.7±22.3 mOsm/L, 6.1±3.3sec, 10.6±6.6 mm, 4.9±3.6 and 3.5±3.0, respectively. Moreover, they correlated tear osmolarity (measured with a tear osmometer) negatively with Schirmer I test and positively with dry eye severity grade (14).

Bunya et al. measured tear osmolarity with TearLab Osmolarity System in 49 subjects with Sjogren’s syndrome, who had a mean value of 314.5 mOsm/L. Tear osmolarity was significantly and negatively correlated both with Schirmer I test and OSDI. The later finding was attributed to decreased corneal sensitivity (15). Aragona et al. assessed dry eye disease in subjects with Sjogren’s syndrome with corneal fluorescein and conjunctival rose Bengal vital staining, BUT measurements, Schirmer’s I test and conjunctival impression cytology. They revealed that hypotonic sodium hyaluronate eye drops can be more beneficial than isotonic ones in treating the disease (16). Ocular mucus membrane pemphigoid, an autoimmune disease, has been also associated with tear hyperosmolarity (mean value 322.9±33.39 mOsm/L) by Miserocchi et al., who positively correlated it with BUT (mean value 6.60±3.13 sec) in a sample of 40 subjects. They observed no significant correlation of tear osmolarity with Schirmer test or with the OSDI score (17).

Tear osmolarity (measured by TearLab Osmolarity System) has been found to be also increased in parallel with the severity of ocular graft-vs.-host disease, exhibiting high sensitivity (98.4% sensitivity), but less specificity (60.7% specificity). The same study group supported that corneal staining score and OSDI score gradually raised along with the severity of the disease in 63 subjects with different hematologic diseases (18). Türkyilmaz et al. observed that tear osmolarity was positively and significantly correlated with the activity of early rheumatoid arthritis. The observed mean values of tear osmolarity, BUT and Schirmer I test were 314.2±11.4 mOsm/L, 6.9±3.9 sec and 9.4±4.2 mm, respectively (7). Higher tear osmolarity (mean value 320.40±21.80 mOsm/l) has been also noted in diabetic subjects, where it was related to the duration of Diabetes Mellitus (19). The raised proptosis and lid fissure width appeared to be the reasons for tear hyperosmolarity (mean value 290.80±13.58 mOsm), as assessed by an auto-osmometer (OM-6030 AUTO STAT; Daiichi, Kyoto, Japan), in 21 subjects with thyroid ophthalmopathy (20).

Aslan et al. investigated the impact of osmoprotective artificial tears on ocular surface disturbances observed in contact lens wearers. They found that tear osmolarity (measured by TearLab osmolarity system) was elevated within the first hours after the application of contact lenses in subjects who had never wore contact lenses previously. The subsequent installation of osmoprotective eye drops (Optive and Refresh, Allergan) appeared to prevent tear hyperosmolarity (21). Ozsutcu et al. estimated that eyes with pterygium had higher tear osmolarity levels (mean 307mOsm/l), corneal staining (mean 1.2±1.1), and conjunctival redness (mean 0.9±0.9 scores), but lower BUT (mean 10.3±3.4sec) and Schirmer I test (mean 14.8±9.2 mm) values than control eyes (22). A recent study investigated tear osmolarity, using TearLab system, in subjects with glaucoma who received at least one anti-glaucomatous medication (50 subjects) over six months or underwent trabeculectomy (31 subjects) over six months without using any medication. Tear osmolarity was higher in both groups (means 307.0±9.3 and 307.4±11.6mOsm/l, respectively) compared to healthy individuals (mean 301.4 ±7.7mOsm/l).

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|                          | Group A | Group B | Group C |
|--------------------------|---------|---------|---------|
| Tear osmolarity (mOsm/L) | 0.001   | 0.001   | 0.001   |
| BUT (sec)                | <0.001  | 0.001   | 0.001   |
| Schirmer test I (mm)     | 0.001   | 0.001   | 0.001   |
| Corneal staining score   | <0.001  | 0.008   | 0.005   |
| Conjunctival staining score | 0.001 | 0.008   | 0.003   |
| OSDI                     | 0.001   | 0.001   | 0.001   |

BUT: Tear film breakup time; OSDI: ocular surface disease index.

Statistical significance of the differences observed in ocular indexes and symptoms after the administration of artificial tears (p-values extracted by Wilcoxon matched-pairs signed-rank tests).
However, no statistically significant differences neither in tear osmolarity nor in BUT and Schirmer’s test scores were detected among the three groups (23).

Conclusion

This is the first study to investigate tear osmolarity in subjects with acute allergic rhinoconjunctivitis. Even if the sample size was relatively small, but comparable to the sizes used in previous studies assessing tear osmolarity, we concluded that acute allergic rhinoconjunctivitis is an additional cause of tear hyperosmolarity. The inflammatory background of the disease is probably related to these observations. Furthermore, we revealed that the administration of hypotonic artificial tears can prevent from ocular surface damage, rehabilitation tear osmolarity.

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