

# TEAR OSMOLARITY IN PATIENTS WITH SEVERE DRY EYE SYNDROME BEFORE AND AFTER AUTOLOGOUS SERUM TREATMENT: A COMPARISON WITH TEAR OSMOLARITY IN HEALTHY VOLUNTEERS

## SUMMARY

**Introduction:** Dry eye syndrome (DES) is a multifactorial disease of the tears and ocular surface. Recently, treatment with autologous serum eye drops (AS-ed) has been frequently used in these patients. Significant improvement correlates well with clinical, laboratory and subjective findings. It is assumed that one of the key factors in the development of the disease is increased tear osmolality. The aims of our study were to test tear osmolality measurements in clinical practice, to examine if osmolality values differ before and after a 3-month application of 20% AS-ed, and to determine if the values differ between patients with severe DES and healthy individuals.

**Methods:** The study included 35 patients with severe DES (Schirmer test <5 mm/5 min) and 23 healthy volunteers. Tear osmolality values (TearLab Osmolarity System), the Schirmer test (ST1), vital ocular surface staining and subjective feelings (the OSDI questionnaire) were assessed in patients with DES before and after treatment with 20% AS-ed. Further, the tear osmolality values were compared between healthy subjects and patients with DES before and after treatment with AS-ed.

**Results:** The values of OSDI and vital staining significantly decreased in patients with DES after the treatment ( $p < 0.0001$ ). ST1 and tear osmolality did not change significantly after the treatment. ST1 values in healthy individuals were significantly higher ( $p < 0.0001$ ) and the OSDI values significantly lower ( $p < 0.0001$ ) than the results obtained in patients before and after treatment. Tear osmolality was not statistically different between healthy subjects (306 mosmol/l) and patients with DES (302 and 301 mosmol/l before and after treatment respectively).

**Conclusion:** We demonstrated a positive effect of AS treatment on the ocular surface in patients with DES. However, the osmolality values did not differ before and after treatment with AS, and they also did not differ significantly between DES patients and healthy individuals. In accordance with other recent studies, our results raise questions concerning the value of the TearLab Osmolarity System for evaluating therapeutic effect and also as a tool for DES diagnosis.

**Key words:** dry eye syndrome, autologous serum, osmolality

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## INTRODUCTION

Dry eye syndrome (DES) is a multifactorial disease of the tears and ocular surface, which subjectively causes a feeling of dryness, tingling or the presence of sand in the eyes, and which may diminish visual acuity. DES is accompanied by damage to the superficial layers of the eye, inflammation and increased osmolality of tears. Squamous metaplasia of the epithelium appears on the surface of the conjunctiva, there is a reduction in number to extinction of the goblet cells and an increase of apoptotic and inflammatory cells (1, 3, 5, 17).

In addition to treatment of the basic disorder, intensive supplementation of tears is required. However, regular approaches frequently do not bring about either an objective or subjective improvement in patients. As a result, in recent years therapy with the aid of eye drops from auto-

logous serum (AS-ed) has been used with ever increasing frequency on patients with severe form of DES. A significant improvement takes place in clinical and laboratory parameters also according to subjective evaluation by patients (7, 12, 13, 15, 26, 36). The pathogenesis of the origin of DES has not yet been entirely clarified. It is presumed that one of the key factors in the development of the disorder is increased tear osmolality. In the 1970s it was demonstrated that patients with DES have hyperosmolar tears in comparison with healthy individuals, and that the application of isotonic or hypotonic solution brings about a clinical improvement of the disease (9, 10). At present it is assumed that hyperosmolar tears activate signal inflammation molecules in the cells of the ocular surface, thus releasing pro-inflammatory mediators into tears. Chronic inflammation progressively develops, leading to a further impairment of the stability of

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the lachrymal film, a decrease in the number of goblet cells and a reduction in the amount of mucin, increased evaporation of tears and an attendant damage to the tissue of the superficial layers of the eye, including the nerve fibres. The result is an impairment of the trophic and regulatory action of the nerve fibres, a decrease in sensitivity of the cornea and a reduction of the activity of reflexive lachrymation – a vicious cycle develops (3, 25).

On the basis of an evaluation of the results from studies dealing with changes in osmolarity in patients with DES, Farris et al. (8) proposed measurement of osmolarity as the “gold standard” in examining dry eye syndrome. Tear osmolarity is determined according to the temperature of congelment, tension of water vapours or on the basis of changes of electrical impedance (22). In the first studies, osmolarity was measured on the principle of change of the point of congelment (9, 10).

At present, use of the TearLab instrument in particular has been established in clinical practice (TearLab Osmolarity System, TearLab Corp, San Diego, California, USA), enabling measurement of osmolarity in nanolitre volumes of tears taken from the lower lachrymal meniscus, directly in the doctor’s surgery. The instrument uses temperature corrected measurement of electrical impedance in order to provide an indirect evaluation of osmolarity. The first published studies demonstrated that the osmolarity value measured using the TearLab instrument correlated with the incidence and even with the degree of severity of DES (11, 18, 30, 31, 37).

The aim of our study was to test the possibility of using measurement of tear osmolarity using a TearLab instrument in clinical practice, to verify whether a change of osmolarity takes place patients with severe DES following three-month application of AS-ed, and whether osmolarity values differ in patients with severe form of DES from those in healthy individuals.

## METHOD

The study included 35 patients with severe DES (Schirmer test < 5 mm/5 min., time required for disruption of lachrymal film < 5 seconds). The cohort of patients consisted of 28 women and 7 men with an average age of 54 years. Ten patients had DES on a background of a reaction of an implant to the host, 15 patients with primary Sjögren’s syndrome, 3 patients with secondary Sjögren’s syndrome, 3 patients with rheumatoid arthritis, 2 with chronic blepharitis, 1 patient had DES following a laser refractive procedure and 1 patient had DES of unclear etiology. The control group comprised 20 women and 3 men (average age 50 years) without any ocular or systemic pathology. The age of the patients did not differ significantly between the group of healthy volunteers and the patients with DES.

We observed the effect of three-month treatment with locally applied 20% AS-ed prepared according to the above-described procedure (12, 13). The patients applied AS-ed 6-9 x daily; according to the number of applications of artificial tears, always at least 15 minutes after their use. The therapy did not change for 3 months before the commencement of

the study or during the period of administration of AS-ed. A Schirmer test (ST1, without application of anaesthetic, production of tears measured for 5 minutes) was conducted before and after the three-month application of AS-ed, as well as ocular surface staining using fluorescein (evaluated according to the Oxford schema for cornea on a scale of 0-4) and 1% rose bengal (2). Tear osmolarity was measured using the instrument TearLab Osmolarity System (TearLab Corp, San Diego, California, USA). The measurement was conducted on a different day from the clinical examination, in accordance with the manufacturer’s instructions. The evaluation included first of all the right and left eye of the tested individuals, according to the manufacturer’s current recommendation only the higher measured value was evaluated further (19, 28), and the difference in the values between the right and left eye was also observed. Control of measurement and calibration of the instrument was conducted on every testing day before the beginning of measurement. In addition, the patients evaluated their subjective feelings with the help of an Ocular Surface Disease Index questionnaire (OSDI) (27). In the control individuals ST1 and osmolarity were measured, and OSDI was evaluated.

The results are presented as an average  $\pm$  standard deviation. A t-test or pair t-test for parametric data was used for statistical processing, as well as a Mann-Whitney test or Wilcoxon pair test for non-parametric data separation. The statistically significant level was considered to be  $p < 0.05$ .

## RESULTS

There was a significant improvement in the intensity of ocular surface staining (fluorescein, rose bengal) after the application of AS-ed. There was no difference between the ST1 and tear osmolarity values in the patients with DES before and after therapy. Following the application of AS-ed there was a significant improvement in the subjective evaluation by patients (OSDI) (table 1).

The ST1 value was statistically significantly higher in the healthy individuals in comparison with the values of the patients with DES, both before and after treatment. In accordance therewith, the OSDI values of the healthy volunteers were significantly lower than those of the patients. The osmolarity values in the patients did not differ significantly from the values obtained from the healthy individuals either before or after treatment. Neither were any differences in osmolarity between the patients and healthy individuals recorded upon an evaluation of the average of all eyes, even when only the higher values were evaluated (only the value measured in the eye with higher osmolarity). Although the value of the average difference between osmolarity of the right and left eye in the patients with DES was higher than in the healthy individuals, we did not demonstrate statistical significance (table 2).

Pathological osmolarity values (> 316 mosmol/l) were obtained in 8 eyes of 7 patients with DES before treatment, in 6 eyes of 6 patients after treatment and in 4 eyes of 3 healthy volunteers. It was not possible to measure osmolarity in 9 eyes of 7 patients with DES.

## DISCUSSION

In accordance with previously published studies, we demonstrated a positive effect of AS-ed on the condition of eyes of patients with DES (7, 12, 16, 36). After three-month treatment with AS-ed we demonstrated a statistically significant finding in the patients with DES on the basis of a reduction of the degree of ocular surface staining using fluorescein and rose bengal, and on the basis of subjective evaluation by the patients (OSDI questionnaire). There was no difference in the values of the Schirmer test or the osmolarity values.

Although an improvement of ST1 had already been described following the application of AS-ed (7, 12, 16, 36), in accordance with the majority of previously published results we did not record a significant improvement (15, 23, 34). In contrast with the demonstrated positive effects of AS-ok here and in other studies (vital staining, subjective improvement), we did not demonstrate a statistically significant difference between the values before and after application of AS-ed by measuring osmolarity (4). Furthermore, the average osmolarity value measured in patients with DES did not differ from the values obtained from healthy individuals. The average osmolarity values in both groups were within the range of values considered to be normal (275-316 mosmol/l) (35, 37).

The obtained results indicate that measurement of osmolarity using the TearLab Osmolarity System is inconclusive, not only for assessing the effect of therapy, but also for di-

stinguishing patients with DES from healthy individuals. In addition to the studies which appeared at the same time as the introduction of the instrument onto the market, which demonstrated that osmolarity differs significantly between healthy individuals and patients with DES, and also that it is possible to distinguish the intensity of the pathology by means of osmolarity (11, 18, 31, 37), studies have appeared recently whose results demonstrate that the significance of measuring osmolarity using the TearLab system for the diagnosis and monitoring of DES requires more precise determination (4, 6, 14, 20), or that it is not possible to use this system independently for the diagnosis of DES (29, 33). Similarly to our study, Szalai et al. (33) did not demonstrate any difference between the osmolarity values measured by the TearLab instrument between healthy individuals (304 mosmol/l) and patients with DES on a background of Sjögren's syndrome (303 mosmol/l) or patients with DES without Sjögren's syndrome (non-Sjögren; 297 mosmol/l).

Amparo et al. (4) point to the fact that changes in tear osmolarity measured by the TearLab Osmolarity System instrument do not correlate with the OSDI values or staining with fluorescein. Problems with measurement of osmolarity using the TearLab system are documented also by further studies. Li et al. (20) described the fluctuation of values during the course of the day in healthy volunteers and in patients with DES (by up to 22 mosmol/l). Although Yoon et al. (38) demonstrated the reliability of the TearLab Osmolarity System instrument in the measurement of osmolarity of saline solutions, Khanal et al. (14) cast doubt upon this

**Table 1 Average values of observed parameters in patients with DES before and after treatment with 20% AS-ed**

	Rose bengal (Oxford schema)	Fluorescein (Oxford schema)	ST1 (mm/5 min.)	Tear osmolarity (mosmol/l; both eyes)	Tear osmolarity (mosmol/l; only higher value)	OSDI
Before AS-ed	5,0 ± 2,5	1,9 ± 1,1	1,8 ± 2,3	301,8 ± 18,1	307,3 ± 19,4	63,4 ± 12,3
After AS-ed	3,6 ± 2,1 p < 0,0001	1,4 ± 1,0 p < 0,0001	2,4 ± 3,3 p = 0,18	300,8 ± 19,4 p = 0,74	308,8 ± 20,6 p = 0,69	49,6 ± 14,9 p < 0,0001

**Table 2 Average values of observed parameters in healthy individuals and in patients with DES before and after treatment with 20% AS-ed (p value of statistical significance in relation to healthy individuals).**

	OSDI	ST1 (mm/5min)	osmolarity (mosmol/l; both eyes)	Tear osmolarity (mosmol/l; only higher value)	Tear osmolarity – difference between eyes (mosmol/l)
Healthy individuals	10,6 ± 9,7	16,7 ± 7,6	305,6 ± 12,3	311 ± 12,1	10,9 ± 9,7
Patients before treatment	63,4 ± 12,3 (p < 0,0001)	1,8 ± 2,3 (p < 0,0001)	301,8 ± 18,1 (p = 0,22)	307,3 ± 19,8 (p = 0,37)	15,1 ± 15,5 (p = 0,63)
Patients after treatment	49,6 ± 14,9 (p < 0,0001)	2,4 ± 3,3 (p < 0,0001)	300,8 ± 19,4 (p = 0,14)	308,8 ± 20,6 (p = 0,64)	20,4 ± 18,6 (p = 0,10)

conclusion and document that the problem may be directly in the variability of measurements of the instrument itself. For increased reliability they therefore recommend the performance of three measurements during one examination. However, this adds to the financial costs of use of the instrument. Furthermore, a question remains as to whether the instrument is capable of reliably measuring values in patients with DES whose tears are altered both qualitatively (change in composition of ions and proteins, effect of chronic therapy) and quantitatively (problem also with sampling of minimal amount for measuring osmolarity).

The fact that the osmolarity value in patients with DES may genuinely fluctuate pronouncedly is highlighted by Gilbard et al. (10). In accordance with this, advocates of measurement of osmolarity emphasise that it is precisely the more pronounced fluctuation of osmolarity values in patients with DES that is pathognomonic for the disorder, as is the larger difference between the osmolarity of the right and left eye. As a result they recommend the use of always the higher of the measured values for assessment of osmolarity (19, 24, 28). In our study we genuinely recorded a tendency of a larger difference in osmolarity values between the right and left eye, with the difference increasing along the line of healthy individuals – patients before treatment – patients after treatment; however, the values did not reach statistical significance. We did not demonstrate a difference between tear osmolarity in patients with DES and healthy individuals even when we used the higher measured values for statistical evaluation.

In addition to the TearLab instrument, an instrument working on the principle of the change in the point of congealment is also available for clinical use. On a cohort of patients with mild to medium severe DES (median 2 according to Dry Eye WorkShop) (1), Suzuki et al. demonstrated that the re-

sults obtained using this type of instrument corresponded with the intensity of the disorder (according to the DEWS scale) (32). A question remains as to whether the measured value would be reliable also in patients with severe DES, and whether they shall be confirmed also in further studies. For DES the fundamental osmolarity value need not be measured in the lower lachrymal meniscus, but rather local tear osmolarity value on the ocular surface, which may fluctuate pronouncedly due to the impaired stability of the lachrymal film (21). The presented results therefore do not cast doubt upon the role of the changes in osmolarity upon the development of DES, but point to potential problems with the evaluation of the available osmolarity values obtained in regular clinical examination.

## CONCLUSION

Administration of AS-ed to patients with DES brings about an objective (vital staining) and subjective (OSDI) improvement of the patients' condition. We did not demonstrate any difference between the osmolarity value before treatment and after treatment with 20% AS-ed. We also did not demonstrate any difference in the tear osmolarity value between patients with dry eye syndrome and healthy control individuals. These results cast doubt upon the clinical significance of measurement of osmolarity using the TearLab Osmolarity System instrument for monitoring the effect of therapy also from the perspective of DES diagnosis.

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