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# Surface activity of tear fluid in patients with primary Sjögren's syndrome

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## Summary

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Rupture of the precorneal tear film leads to formation of a dry spot on the cornea with ocular irritation and symptoms of dry eye. One of the factors determining the stability of the tear film is its surface activity. The purpose of this study was to examine the surface activity of tear fluid from patients with Sjögren's syndrome. Tear fluid was sampled from the eyes of 16 patients with primary Sjögren's syndrome. The surface activity of the sample was measured on a Wilhelmy balance. Maximum and minimum surface tension was  $72.2 \pm 1.7$  and  $52.9 \pm 7.4$  mN m<sup>-1</sup>, respectively. Corresponding values in a previously studied group of normal subjects were  $71.5 \pm 1.3$  and  $46.6 \pm 3.8$  mN m<sup>-1</sup>, respectively. The difference in minimal surface tension was statistically significant ( $P < 0.001$ ). Reduced surface activity may be caused by dysfunction of the Meibomian glands and suggests a mechanism for causing the symptoms of dry eyes.

## Introduction

The precorneal tear film provides a continuous liquid surface for the eye. This is important both for the refractive properties of the eye and for the welfare of the corneal and conjunctival epithelia. The tear film is not stable, and if the eye is kept open, it will eventually rupture. A dry spot is formed on the epithelial surface. This gives rise to irritation of the eye and provokes blinking.

The precorneal tear film is often considered to consist of three layers (Holly, 1980). In direct contact with the epithelial surface is a layer of mucus originating from goblet cells and other epithelial cells (Inatomi *et al.*, 1995). Overlying the mucus layer is the aqueous layer, produced mainly by the lachrymal glands. It has recently been suggested that there is no clear distinction between these two layers (Chen *et al.*, 1997; McCulley & Shine, 1997). The most superficial layer of the tear film is formed by lipids originating mainly from the Meibomian glands.

The symptom of dryness of the eyes in patients with Sjögren's syndrome is generally attributed to dysfunction of the lachrymal gland, which is subject to lymphocytic infiltration in the disease process originally described as keratoconjunctivitis sicca in the thesis by Henrik Sjögren (Frost-Larsen *et al.*, 1980; Roberts, 1991). Although it is well established that there are major differences in the water layer between normal tear fluid and tear fluid in keratoconjunctivitis sicca (Friedlaender, 1992), it has

recently been suggested that there are also abnormalities of the lipid layer of the tear film (Danjo & Hamano, 1995; Shimazaki *et al.*, 1998) as well as in mucin production (Pflugfelder *et al.*, 1997; Jones *et al.*, 1998) in Sjögren's syndrome.

One of the important functions of the lipid layer of the tear film is to reduce the surface tension at the air/liquid interface (Tiffany, 1994; Bron & Tiffany, 1998). Abnormal surface properties of the tear film may cause instability of the film with premature rupture leading to sensation of gravel and irritation of the eyes with frequent blinking. The purpose of this study was to examine the surface properties of tear fluid in patients with primary Sjögren's syndrome, using a recently described technique (Zhao & Wollmer, 1998, 2001).

## Materials and methods

### Patients

All 16 female patients in this study were seen at regular intervals at the Sjögren's Syndrome Research Centre at Malmö. They accepted to participate by their own free will after receiving written and oral information. The patients fulfilled the Copenhagen classification criteria for primary Sjögren's syndrome, i.e. they had at least two abnormal test results for keratoconjunctivitis sicca and at least two abnormal results for xerostomia (stomatitis sicca; Manthorpe *et al.*, 1986). Their mean age was 63 years (range 35–79).

The measurements made in patients were compared with a group of normal subjects previously reported (Zhao & Wollmer, 1998). There were 20 normal subjects (nine women and 11 men) with a mean age of 39 years (range 17–63). The sampling of tear fluid as well as the measurements of surface activity was performed by the same person in both normal subjects and in patients, and the studies were overlapping in time.

### Measurements of the surface activity of tear fluid

Tear fluid was sampled with a thin, flexible intravenous cannula made of nylon. The outer diameter of the cannula was 0.75 mm and the inner diameter 0.50 mm. The subject was lying in the supine posture while tear fluid was gently aspirated as the tip of the cannula was moved along the inferior fornix. Aspiration was always performed first in the right eye and then in the left eye. The volume of aspirated fluid was estimated by measurement of the distance of catheter filled with fluid.

Surface tension was measured with a Wilhelmy balance (Biegler Electronic, Mauerbach, Austria). A Teflon trough (115 × 18 mm, depth 17 mm) was filled with 35 ml 0.9% saline. The measurements were made at room temperature. A platinum plate, partly immersed in the liquid, is suspended in a balance. The trough contains a movable barrier, which changes the area into which the platinum plate is immersed. The duration of a cyclic area change to 20% of the initial area is 3 min. A baseline recording of the surface tension of saline was first established. The surface tension of saline is 73 mN m<sup>-1</sup> and is completely independent of area change. The aspirated tear fluid was then added to the trough. A stable recording of surface tension vs. area was rapidly obtained, and the maximum ( $\gamma_{\max}$ ) and minimum ( $\gamma_{\min}$ ) surface tension of the third cycle were

recorded.  $\gamma_{\max}$  and  $\gamma_{\min}$  are presented in absolute values (mN m<sup>-1</sup>), and corrected for the yield of tear fluid, using regression equations between yield and surface tension found in normal subjects (Zhao & Wollmer, 1998).

A representative tracing from a measurement of surface tension after aspiration of tear fluid is shown in Fig. 1. Surface tension decreases when the surface is compressed to reach a minimum value of approximately 45 mN m<sup>-1</sup>. When the surface is expanded again, surface tension increases. The tracing shows hysteresis in that for a given surface area, surface tension is lower during compression than during expansion.

### Statistical analysis

Data are presented as mean ± SD unless otherwise indicated. The group of patients was compared with the group of normal subjects by Student's t-test. P-values <0.05 were considered significant.

### Results

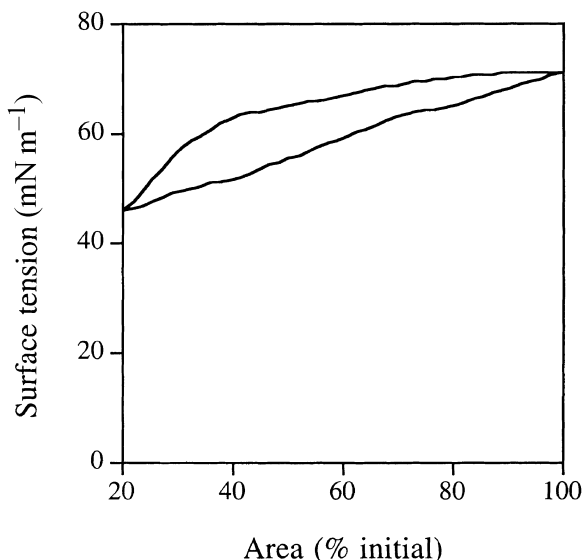
Tear fluid could be sampled from all patients with no or minimal discomfort. The volume obtained was 0.4 ± 0.9 ml. This was very similar to the yield of tear fluid in normal subjects (0.3 ± 0.2 ml, P>0.05).

The mean values for  $\gamma_{\max}$  and  $\gamma_{\min}$  obtained in the patients and in normal subjects are shown in the Table. Mean  $\gamma_{\max}$  and  $\gamma_{\min}$  were higher in patients with primary Sjögren's syndrome than in normal subjects. The largest difference was observed for  $\gamma_{\min}$ , and this difference was highly significant (P<0.001). There was, however, considerable overlap between patients and normal subjects, the range for patients being 41–67 mN m<sup>-1</sup> and that for normal subjects 38–58 mN m<sup>-1</sup>. The difference remained significant if  $\gamma_{\min}$  was corrected for the yield of tear fluid and also if the mean value between the two eyes for each subject was analysed. The difference in  $\gamma_{\max}$  did not quite attain statistical significance (P = 0.07).

### Discussion

This study shows reduced surface activity of tear fluid in patients with primary Sjögren's syndrome compared with normal subjects. This points mainly to a defect of the lipid layer produced by the Meibomian glands. Main functions of the lipid layer are reduction of the surface tension of the tear film and reduction of the rate of evaporation from the eye (Bron & Tiffany, 1998). Reduced surface activity may cause early break-up of the tear film with formation of dry spots on the epithelium. This results in symptoms of dry eye.

Sampling of tear fluid with the technique used in this study is minimally invasive and does not cause any irritation of the eyes (Zhao & Wollmer, 1998). When a sample of tear fluid is added to the trough of the Wilhelmy balance, its surface-active components accumulate at the air/liquid interface, resulting in a reduction in surface tension. When the area of the trough is



**Figure 1** Surface activity of tear fluid obtained from a patient with primary Sjögren's syndrome. Surface tension decreases as the area is compressed. Surface tension is lower during compression than during expansion of the surface.

|                           | $\gamma_{\max}$       |             | $\gamma_{\min}$       |               |
|---------------------------|-----------------------|-------------|-----------------------|---------------|
|                           | (mN m <sup>-1</sup> ) | (% pred)    | (mN m <sup>-1</sup> ) | (% pred)      |
| Patients (32 eyes)        | 72.2 ± 1.7            | 101.5 ± 5.2 | 52.9 ± 7.4**          | 111.3 ± 23.5* |
| Normal subjects (40 eyes) | 71.5 ± 1.3            | 100.0 ± 1.6 | 46.6 ± 3.8            | 100.0 ± 6.9   |

\*P<0.01, \*\*P<0.001.

reduced, the surface-active molecules become more closely packed, and there is further decrease in surface tension.

Surface activity as measured in this study reflects the quantity as well as the quality of surface-active material in the tear fluid. We have previously demonstrated correlations between the yield of tear fluid and  $\gamma_{\max}$  and  $\gamma_{\min}$  in normal subjects (Zhao & Wollmer, 1998). Based on these regression equations, it is possible to account for the yield of tear fluid (Table 1). In this study, it was possible to obtain approximately equal amounts of tear fluid in the patients as in the normal subjects. Significant reduction in surface activity was therefore noted both in the absolute value of  $\gamma_{\min}$  and in the value corrected for yield. The reduction in surface activity of the tear fluid therefore does not seem to be caused by reduced yield of tear fluid, but rather a change in its composition. This could be a reduced content of surface-active components or a change in their composition.

In addition to Meibomian lipids, other dissolved substances, for example, mucin, may contribute to the surface activity of tear fluid (Holly, 1973; Zhao & Wollmer, 1998). There is some recent evidence to suggest abnormalities in the Meibomian glands in patients with Sjögren's syndrome. Danjo & Hamano (1995) described abnormal non-contact specular microscopy of the lipid layer in patients with Sjögren's syndrome and Shimazaki et al. (1998) showed destruction of the Meibomian glands in a large proportion of patients. There are also recent reports of reduced goblet cell density and reduced expression of epithelial membrane mucin in patients with Sjögren's syndrome (Pflugfelder et al., 1997; Jones et al., 1998). Our finding of reduced surface activity of tear fluid is compatible with reduced function of the Meibomian glands and/or reduced mucin production and thus supports the notion of involvement of these glands in the disease process.

Reduced surface activity adds to the instability of the tear film and indicates one possible mechanism causing the symptoms of dry eyes in patients with Sjögren's syndrome. Measurement of surface activity by our technique is simple and may be used in clinical routine. As for other measurements of tear fluid properties in Sjögren's disease (Roncin et al., 1992; Virtanen et al., 1997), however, there was substantial variability between patients and a considerable overlap between patients and normal subjects. There was a substantial difference in age between the patients and normal subjects in this study. Although we did not find any influence of age on  $\gamma_{\max}$  and  $\gamma_{\min}$  in the study of normal subjects, an effect of age cannot be ruled out. Further work is therefore

**Table 1** Maximum and minimum surface tension of tear fluid from patients and normal subjects. In addition to absolute values, results are presented as a predicted value, accounting for the yield of tear fluid.

needed to assess the clinical usefulness of measurement of the surface activity of tear fluid.

In summary, we have found reduced surface activity of tear fluid in patients with Sjögren's syndrome, reflecting abnormal composition of the tear fluid. Reduced surface activity may be caused by dysfunction of the Meibomian glands and suggests a mechanism for causing the symptoms of dry eyes.

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