

# Examination of tear film and its dynamics using ophthalmological imaging methods

Doctoral thesis

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Budapest  
2011

## INTRODUCTION

The sufficient tear volume and the fine tear film are essential for the maintenance of the healthy ocular surface. Tear nourishes, moistens and protects the cornea and the conjunctiva. The smooth and even precorneal tear film forms the first refractive surface of the human optical system, and it is required for the good visual quality.

The quantitative and qualitative differences of the tear cause dry eye disease, which is a multifactorial disease. One of the known risk factors of dry eye is the ocular allergy. The local allergic inflammation on the ocular surface causes tear film instability, and evaporative dry eye. In allergic patients, several morphological and functional abnormalities of the conjunctiva develop not only during the pollen season but also outside the season. However, it is not known; whether the tear film instability and the thickening of the tear film lipid layer caused by the acute allergic inflammation remain outside the season as well.

The lacrimal functional unit is sensitive to any irritating agent, so several minimally invasive or non-invasive methods have been developed to observe the steady state conditions of the ocular surface, and for a better understanding of the physiology of the tear film and the pathomechanisms of the ocular surface diseases. The Tearscope Plus is suitable for the complex examination of the ocular surface. It is used widespread to measure the non-invasive tear film break up time, and to detect the interference pattern of the tear lipid layer. By this instrument the tear meniscus can be visualised. The tear meniscus height (TMH) is measurable using Tearscope, and the total tear volume is estimated from TMH. However, little information is available in the literature about the reliability and accuracy of this examination technique.

In the last decades, it turned out that the break up of the tear film leads to significant changes in the results of some modern ophthalmological instruments, like corneal topography and wavefront analyser. By the help of these new instruments changes of the tear film can be detected non-invasively. Results of previous studies highlight that not only the break up of the tear film, but even the build up process is able to influence the topographical regularity indices and the higher order aberrations of the cornea as well, however the direct relations between the postblink tear film motions and the changes of corneal topographical parameters have not been proved. Additionally, it is not known, whether the build up of tear film can cause changes on wavefront higher order aberrations of the eye similar to the corneal aberrations.

## **PURPOSES**

1. The aim of our study was to investigate, whether allergic inflammation defines tear film instability or eye symptoms outside the pollen season in patients suffering seasonal allergic conjunctivitis.
2. Our question was, if any inflammation activity is detectable on the ocular surface with measuring C3a complement level in allergic patients outside the pollen season.
3. The aim of this study was to create an examination method of the lower tear meniscus height (LTMH) using Tearscope Plus device with digital capturing process and a subjective analysis method and to evaluate the reliability of the new method and to compare LTMH measured by Tearscope and optical coherence tomography (OCT).
4. The purpose of the study was to compare the postblink changes of topographical regularity indexes and corneal higher order aberrations calculated from the same corneal topography map and to reveal, which parameter is the most specific for detecting the dynamic changes of the tear film.
5. Our purpose was to evaluate the lipid spreading time, measuring with Tearscope Plus in normal population, and to examine, whether there is a relation between the tear lipid motion and the alterations of the topographical parameters.
6. Our question was, whether the early changes and the built up process of the tear film are able to influence the postblink changes of the spherocylindrical refractive errors and the wavefront higher order aberrations of the eye.
7. Finally, our aim was to find a connection between the postblink alteration pattern of the spherocylindrical refractive errors or the wavefront higher order aberrations and the tear film status.

## PATIENTS AND METHODS

The studies followed the tenets of the Declaration of Helsinki. All participants were advised of the properties and the aim of the examination, and their informed consent was taken. The study was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics.

1. In the first study 23 normal subjects and 13 ragweed-allergic patients participated. The investigation was carried out from November to May, outside the ragweed's flowering season. The non-invasive tear break up time (NIBUT), the lower tear meniscus height (LTMH), and the interference pattern of the tear lipid layer was detected using Tearscope Keeler Plus. Additionally, subjects were asked about their eye symptoms, and they scored the frequency and severity of the symptoms. The tear parameters and the symptoms' scores of the two examined groups were compared.

2. Non reflex, open eye tear samples were collected from the participants of the previous study, and the absolute amount of C3a complement activation product was measured. The complement activation level of the non-allergic group was compared to the allergic group, and we examined the relation between the tear parameters and the measured complement activation.

3. In subjects of the first investigation, the lower tear meniscus was captured five times after voluntary complete blinks using Tearscope Plus attached to a digital slitlamp. The pictures were evaluated by three independent observers in two separate occasions. The observers measured the height of the lower meniscus, which was visible as a white band near the edge of the eyelids across the head of the Tearscope. At the first time, they had obeyed general measuring principles, and several months later they re-evaluated the pictures after a meeting, which detailed the analysing rules. The interobserver and interblink coefficients of variation were calculated at both times. Additionally, 14 subjects' LTMH was measured by Tearscope Plus and RTVue optical coherence tomography (OCT), and the results were compared.

4. In the control group of the first investigation, sequential (three corneal map per seconds) corneal topographic measurements were taken with the TMS-1 videokeratoscope in a 10 second-long period just after a voluntary complete blink, and the sequential measurements were repeated four times. The postblink alteration pattern of the surface regularity index (SRI), the surface asymmetry index (SAI) and the corneal higher order aberrations (HOA RMS, Coma RMS, and spherical RMS) at 4 mm diameter were determined. Fourth-order polynomial trend lines were fitted by polynomial regression to sequence of the time series parameters. We distinguished three alteration patterns. The trends, which started with a decrease and showed an initial significant minimum, were called type 1 trend; the trends which started with an increase and showed an initial significant maximum were called type 2 trends; remaining trends were called type 0 trends. According to the repeated topographical series, the typical trend type of every subject was determined, and the incidence of the different trends was determined at each topographical parameter. In case of type 1 trends, time to reach the minimum value (time to minimum) was measured. We compared the time to the minimum of each parameter and the tear parameters determined in previous investigation.

5. On the participants of the topographical study, the postblink motion of the lipid layer was recorded in a 10 second long period just after a voluntary complete blink using Tearscope Plus. The video recording was repeated three times. Three independent observers measured the time between complete blink and termination of visible movement of the lipid layer (lipid spreading time) on the videos. We examined the relation between the lipid spreading time and the time to the minimum of the different topographical parameters determined in the previous investigation.

6. In 38 normal subjects, sequential (about 6 wavefront map per seconds) wavefront measurements were taken by the Wasca Asclepion Zeiss wavefront analyser in a 15 seconds long period after complete, voluntary blinks. The wavefront data were derived at 4 mm diameter pupil. The spherocylindrical refraction and the wavefront higher order aberrations were calculated (higher order aberration (HOA) RMS, Coma RMS, and spherical RMS). The mean value and the range of the measured parameters were calculated in 3 second long periods, which demonstrate the general pattern of alterations in refractive errors and aberrations of the whole examined population. The differences of the mean values and the

ranges between 3 second long periods were analysed. To analyse the individual characteristics, by polynomial regression fifth-order polynomial trend lines were fitted in order to determine the change pattern of the time series parameters. The polynomial trend fitted to the raw data is called value trend. The fluctuation around the value trends was assessed by the absolute differences between the original data and the value trend. The changes in time of the fluctuation were modelled by fifth-order polynomials, and these polynomials are called fluctuation trends. We distinguished three alteration patterns of the value and the fluctuation trends. The trends, which showed initial significant minimum or maximum were called regular type 1 or regular type 2 trends; the remaining trends were called irregular trends. The proportions of the type 1 and 2 trends among the regular value and fluctuation trend lines were determined.

7. On subjects of the wavefront study, the Schirmer test was performed and fluorescein break up time (BUT) was measured in order to characterize the tear film status. We compared the rates of the regular type 1 and type 2 values and the fluctuation trends of spherocylindrical refraction and wavefront aberrations in participants with a normal tear status and those that had abnormal BUT or Schirmer test results. We determined the mean time to the minimum of values and fluctuation trends in both examined groups.

## RESULTS

1. Outside the pollen season, we did not find significantly different values of NIBUT and LTMH in patient suffering seasonal allergic conjunctivitis compared to the non-allergic patients. Additionally, the NIBUT and LTMH of both examined groups agree with the other published results of non-dry eye patients examined by the same measuring methods. In both examined groups, the wave interference lipid pattern was the most common, which characterized normal lipid layer thickness and the distributions of the different lipid patterns were similar. We did not find any significant correlations between tear parameters. The total score of all eye symptoms was considerably greater in SAC patients than in non-allergic participants, but the difference was not significant.

2. In our investigation, we examined the activity of the inflammation on the ocular surface, the collected tear sample of the 4 control subjects was not enough for the analysis. There was a general trend for higher C3a complement activation level in the allergic group compared to the normal controls, but no statistically significant difference was found. There was a significant but weak inverse correlation between the median of the lipid pattern grade and the absolute amount of the C3a complement activation level.

3. In examination using the Tearscope Plus to assess the LTMH, significant differences, strong, and significant correlations were found between the meniscus height measured by the three different observers before and after the meeting, respectively. The post-meeting interobserver coefficient of variation (COV) was significantly lower than the pre-meeting interobserver COV. The post-meeting interobserver COV decreased under the interblink COV. We found significant correlation between the LTMH measured by the Tearscope and the OCT, but the LTMH with the OCT were significantly greater in same subjects. The bias between the two methods and the ratio of the results increases with increasing meniscus height.

4. In one subject of the 23 participants, sequential topographical measurement was not performed because of frequent blinks in examination of postblink changes of topographical parameters. The most frequent postblink alteration pattern was the type 1 trend in topographical regularity indexes and higher order corneal aberrations, except Coma RMS,

which showed type 1 and type 2 trends in equal numbers. The incidence of the type 1 trend was the highest for SRI index (82%). The average times of the type 1 trend's minima were between 3-4 seconds, but the time to minimum of different parameters did not show significant correlation with each other, and the results of the NIBUT, the LTMH and the lipid layer pattern.

5. The mean time of the lipid spreading was  $5.09 \pm 1.90$  s in the study population. Significant, but weak relation was found between the time to minimum of the type 1 SRI trends and the mean time of the lipid spreading. We were not able to confirm a relationship between the lipid spreading time and the time to minimum of other examined topographical parameters or the results of NIBUT, LTMH and lipid layer pattern.

6. In our investigation, we examined the postblink alteration pattern of spherocylindrical refractive errors and wavefront aberrations, the mean values of the 3 second long periods did not exhibit significant differences in the first 15 seconds after a blink, except in cases of spherical refractive error. For the cylindrical dioptr and Coma and HOA RMS, the range of measured data decreased significantly after the first 3 seconds. For all examined parameters, the rates of type 1 trend among the regular value and fluctuation trends were >50%. The occurrence of type 1 trend was significantly larger than 50% only in the case of value trends for the cylindrical refractive error and fluctuation trends for HOA RMS.

7. In the study, we examined the relation between the tear film status and the postblink changes of the wavefront aberrations. Only the percentages of the type 1 fluctuation trend for HOA RMS and Coma RMS were significantly higher of subjects with normal tear status than of those with abnormal results. The mean times to minimum of fluctuation trends were between 3 to 5 seconds in patient with good results of BUT and Schirmer test.

## CONCLUSIONS AND NEW FINDINGS

1. Our study was the first examination of tear film status in seasonal allergic conjunctivitis outside the pollen season. According to our results, seasonal allergic inflammation did not cause permanent tear film instability. Alteration in the tear lipid layer or the eye symptoms, and increased complement activation were not observed outside the pollen season.

2. We evaluated the reliability and accuracy of the non-invasive measuring technique of the lower tear meniscus height (LTMH) using the Tearscope Plus device with digital capturing process and a subjective analysing method. The Tearscope Plus is appropriate with detailed analysing method to determinate the LTMH non-invasively, but its accuracy – compared to the OCT method – decreases in case of greater LTMH, which should be considered in the examination of patients with dry eye.

3. Our study was the first examination, which analysed the relation between the postblink temporal changes of the topographical regularity indices and corneal higher order wavefront aberrations, which were calculated from the same topographical measurements. The previously published typical postblink topographical alteration pattern (early decrease and reaching a minimum) related to tear motions was detected with great prevalence only in case of SRI index. According to our results, SRI index – which indicates smoothness of the central corneal surface – seems to be the most useful topographical parameter to detect the postblink tear film dynamics.

4. The new outcome of our topographical investigation is that we found a relation between the temporal alteration of topographical SRI index and the postblink tear lipid spreading time. This result confirms our previous conclusion that the SRI index seems to be the most useful topographical parameter to represent the tear film dynamics.

5. The new outcome of our wavefront study was the demonstration of the decrease in the fluctuation of the estimated higher order wavefront aberration 3 to 5 seconds after blink, which might be caused by the tear film dynamics. Based on this finding, it is recommended to

capture the single wavefront measurements during this period to diminish the fluctuation of the results.

## OWN PUBLICATIONS

### Publications in the theme of the dissertation

- Kosina-Hagyó K**, Veres A, Fodor E, Mezei Gy, Csákány B, Németh J. (2011) Tear film function in patients with seasonal allergic conjunctivitis outside the pollen season. Int Arch Allergy Immunol, DOI: 10.1159/000324657 **IF<sub>2009</sub>: 2.542**
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- Kosina-Hagyó K**, Veres A, Fodor E, Lang Zs, Csákány B, Németh J. (2010) Kinetic analysis of topographical parameters and interference pattern of tear lipid layer in normal subjects. Ophthalmic Physiol Opt, 30: 790-799. **IF<sub>2009</sub>: 1.148**
- Hagyó K**, Csákány B, Lang Zs, Németh J. (2009) Variability of higher-order wavefront aberrations after blinks. J Refract. Surg, 25: 59-68. **IF<sub>2009</sub>: 2.320**

### Other publications

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- Tapasztó B, Veres A, **Kosina-Hagyó K**, Somfai GM, Németh J. (2011) OCT imaging of lid-parallel conjunctival folds in soft contact lens wearers. Optom Vis Sci, (accepted for publication)
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