Title:

Influence of conjunctival folds on calculated tear meniscus volume along the lower eyelid

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Tables: 3

Figures: 6

Word count: 2793

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Purpose: When calculating tear meniscus volume (TMV), tear meniscus height (TMH), radius (TMR) and cross-sectional area (TMA) are mostly measured at the centre of the lower lid margin. Lid-parallel conjunctival folds (LIPCOF) are known to influence the tear meniscus regularity. The aim of this study was to analyse the influence of LIPCOF on TMA measured by optical coherence tomography (OCT) and consequently, the calculated tear meniscus volume (TMV).

Methods: Using OCT (Cirrus-HD; Carl Zeiss Meditec, Jena, Germany), TMH, TMR and TMA of 42 subjects (13M, 29F; mean age 27.3 SD±8.4 years) were measured directly below the pupil centre, plus at temporal and nasal locations perpendicularly below the limbus, where LIPCOF was also evaluated and graded. TMV for the different locations was calculated. Correlations between LIPCOF and the tear meniscus parameters were analysed using the Spearman Rank-Order coefficients. Differences between tear meniscus parameters at the different locations were evaluated by the paired t-test.

Results: Central TMV (5.30±1.42x10^{-2}µl/mm) was significantly positively correlated to LIPCOFsum (2.4±1.2) ($r=0.422$; $p<0.05$). The calculated temporal TMV was greater by 0.53x10^{-2}µl/mm compared to the central TMV ($p=0.037$), while there was no significant difference in tear volume between the other locations.

Conclusions: Using OCT it was possible to investigate the influence of LIPCOFs on TMH, TMR, and for the first time on TMA, at central and paracentral positions along the lower lid margin. The presence of LICPOFs results in an irregularity of tear meniscus with a difference in the amount of predicted tear volume while measuring TMH or TMR at the different locations.

Key words: tear meniscus, optical coherence tomography, LIPCOF, conjunctival folds, tear volume.

INTRODUCTION

The tear fluid on the eye is present in three sections: at the exposed area between the lids covering the cornea and sclera, in the tear menisci at the lid margins, and in the conjunctival sacs of the upper and lower lid.[1] The tear menisci along the superior and inferior lid margins represent 75% to 90% of the tear film volume at the ocular surface,[2] although a lower estimate of 27% has been made.[1] The shape of the lower central meniscus is described to be roughly wedge-shaped in sagittal section, with a concave anterior surface, and posterior and peripheral surfaces that bathe and moisten the hydrophilic mucosae of the cornea and bulbar conjunctiva or palpebral conjunctiva.[3] However, the cross-sectional profile of the meniscus is likely to have a more complex shape,[3] with a parabolic anterior profile[4] and a posterior surface that is influenced by the shape of the underlying conjunctiva at the paracentral lid locations.[5]

At the central lid location, the evaluation of tear meniscus parameters is regarded as an indicator of tear film volume.[6, 7] The tear meniscus can be characterized by tear meniscus height (TMH), tear meniscus radius (TMR) or cross-sectional tear meniscus area (TMA), and these have been shown to be significantly correlated to one another at the central tear meniscus.[8-11] For paracentral positions along the lower eyelid, however, the relationship between meniscus height, radius and cross-sectional area has not yet been published.

The volume of the tear meniscus (TMV) has traditionally been calculated from TMH, TMR or TMA of the central lower tear meniscus multiplied by the length of the lid margin.[12, 13] Since the meniscus is spread along the eyelid margins, variations in the measured meniscus parameters along the lid are likely to influence the

calculation of the lower lid tear meniscus volume. Lid parallel conjunctival folds (LIPCOF) are folds in the inferotemporal and inferonasal quadrant of the bulbar conjunctiva, parallel to the lower lid margin. LIPCOF can be observed with the slit-lamp or by optical coherence tomography (OCT), and they have been found to correlate with dry eye symptoms.[5, 14-19] Like conjunctivochalasis, LIPCOFs are assumed to alter the measurement of the tear meniscus area.[16, 18, 20, 21]

Using a portable digital meniscometer (PDM) it was shown that an increase in LIPCOF grade is associated with a higher TMH and a larger TMR at the nasal and temporal locations of the tear meniscus.[22] Furthermore, it was suggested that LIPCOF also impacts the central TMH evaluation, and that the presence of LIPCOF may cause the central TMH measurement to overestimate the actual central tear meniscus volume.[23] However, TMH and TMR measurements are limited to one dimension and describe only the anterior surface of the tear meniscus and do not account for the posterior section of the meniscus, so the volume of the LIPCOF is likely to influence the cross-sectional tear meniscus area (TMA).

Consequently, the aims of this study were: (i) to investigate the influence of LIPCOFs on TMH, TMR and on TMA, measured by optical coherence tomography (OCT) at the central and paracentral position of the lower lid and (ii) to analyse the influence of LIPCOF on the calculated tear meniscus volume at the different locations.

MATERIALS AND METHODS

Subjects

Forty-two subjects (male = 13, female = 29) were randomly selected from the staff and students of the Höhere Fachschule für Augenoptik Köln (Cologne School of Optometry), Cologne, Germany. The mean age of the subjects was 27.3 ± 8.4 (SD) years (range, 20 to 67 years). Subjects were excluded if they were pregnant or breast-feeding; had a current or previous condition known to affect the ocular surface or tear film; had a history of previous ocular surgery, including refractive surgery, eyelid tattooing, eyelid surgery, or corneal surgery; had any previous ocular trauma; were diabetic; were taking medication known to affect the ocular surface and/or tear film; and/or had worn contact lenses during the preceding two weeks prior to the study.

All subjects gave written informed consent before participating in the study. All procedures obtained the approval of the Cardiff School of Optometry and Vision Sciences Human Ethics Committee and were conducted in accordance with the requirements of the Declaration of Helsinki.

Instrumentation and procedures

OCT images of the lower tear meniscus were obtained during a single session using Cirrus HD-OCT (Carl Zeiss Meditec, Jena, Germany). This instrument uses spectral domain OCT (SD-OCT), with a wavelength of 840nm to achieve an axial resolution of 5μm. The cross-sectional images of the tear meniscus in this study were taken using five vertically-oriented raster lines. In this mode, five parallel vertical lines of 3 mm length and a line distance of 0.25 mm were scanned; each line was composed of

4096 A-scans. Tear meniscus scans were performed directly below the pupil centre, plus temporally and nasally tangential to the limbus (Figure 1).

OCT images were taken of the lower tear meniscus of the right eye in primary gaze, in a randomized order of the three locations by a single observer. To minimise diurnal and inter-blink variation, all measurements were taken in the morning between 10 and 12 o'clock and 3 to 4 seconds after a normal blink.

The OCT images were stored as jpeg files and image distortions were corrected as described previously by Bandlitz et al., 2014.[24] Using ImageJ 1.48 software (http://rsbweb.nih.gov/ij) on the OCT images, tear meniscus height (TMH) was measured as the distance of the intersection of the meniscus with the cornea/sclera and with the eyelid (Figure 2 A). Tear meniscus radius (TMR) was calculated by applying a three-point circle fit technique (Figure 2 B). Tear meniscus area (TMA) was analyzed by the segmented-line function in ImageJ, where only the area of tear meniscus, but not the area of LIPCOF tissue, was marked (Figure 2 C).

Lid-parallel conjunctival folds were evaluated clinically without fluorescein using a slit-lamp microscope (BQ900, Haag-Streit, Koeniz, Switzerland) using 25x magnification (Figure 3). The LIPCOF evaluation was performed in the area tangential to the temporal and nasal limbus, on the bulbar conjunctiva above the lower lid, at the same location where TMH, TMR and TMA were measured. LIPCOF grade was classified using an optimized grading scale (Table 1).[15, 25] LIPCOFsum was based on the sum of nasal and temporal LIPCOF scores. Care was taken to differentiate LIPCOF from micro-folds. This was done by evaluation of the fold thickness; the thickness of

a single LIPCOF is approximately 0.08mm, while that of a micro-fold is 0.01mm.[23, 26, 27]

The study was conducted in a room with controlled temperature (20 to 23°C) and humidity (44 to 53%). Analysis of OCT tear meniscus parameters was masked against LIPCOF grading.

Lower tear meniscus volume calculation

As suggested by Palakuru et al.[6], the volume of the lower tear meniscus can be calculated from the cross-sectional TMA measured in the center of the eyelid multiplied by an average lid length of 25mm. Since the lower lid is curved along its length, a multiplication factor of 1.294 was suggested by Tiffany et al.[28]. However, in this calculation it is assumed that TMA is equally distributed along the lid. To account for variation in TMA and the influence of LIPCOFs on the tear volume along the lid, the volume that is present at the three different locations was calculated. According to Bitton et al.[29], it was assumed that TMA is similar across an eyelid length area of 1 mm at the location of the OCT cross-sectional scan and that in this small area the curvature of the lid is negligible. In consequence the following formula was used to calculate the tear volume at the temporal, central and nasal area:

TMV [µl] = *TMA [mm^2] x 1 mm of lower lid length*

Statistical methods

Data were tested for normality using the Shapiro-Wilk test and appropriate statistical tests were applied. Correlations were calculated with Pearson correlation (or Spearman rank in non-parametric data). The differences between the locations along the lower lid were calculated with the paired t–test.

RESULTS

Differences of tear meniscus parameter at the different locations

Mean values and standard deviations for the tear meniscus parameters at the different locations are summarised in Table 2. Compared to TMH measured in the central location, TMH at the temporal location was 0.088±0.102mm higher and at the nasal locations was 0.044±0.081mm higher ($p<0.001$). Temporal TMH was also found to be 0.044±0.130mm higher than nasal TMH ($p<0.05$). Compared to TMR measured in the central location, TMR at the temporal location was 0.063±0.061mm larger ($p=0.009$). However, no significant differences were found between nasal TMR and central TMR ($p=0.073$) or temporal TMR ($p=0.804$). Compared to TMA measured in the central location, TMA at the temporal location was 0.0053±0.0159mm^2 greater ($p=0.037$), while there was no significant difference between nasal TMA and central TMA ($p=0.110$) or temporal TMA ($p=0.628$). Consequently, the calculated temporal TMV was increased by $0.53x10^{-2}$µl/mm compared to the central TMV ($p<0.05$), while there was no statistically difference in tear volume between the other locations.

Correlations between LIPCOFs and tear meniscus parameters

Temporal LIPCOF grade (1.4±0.9) was significantly positively correlated to all temporal tear meniscus parameters (temporal TMH:r=0.547;p<0.001; temporal TMR:r=0.520;p<0.001; temporal TMA:r=0.368;p=0.02). Nasal LIPCOF grade (0.6±0.8) was correlated to nasal TMR (r=0.369;p=0.018), but not to nasal TMH (p=0.095), nor to nasal TMA (p=0.278). LIPCOFsum (2.4±1.2) was significantly correlated to central TMH (r=0.393; p=0.01), central TMR (r=0.350;p=0.02) and central TMA (r=0.422; p<0.05).

Calculated tear meniscus volume at the different locations

Significant correlations were observed between the centrally calculated TMV (5.30±1.42x10^{-2}µl/mm) and the centrally measured TMH (r=0.968;p<0.001) and TMR (r=0.837;p<0.001) (Figure 4-5). Temporal calculated TMV (5.83±2.13x10^{-2}µl/mm) was correlated to temporal TMH (r=0.796;p<0.001) and temporal TMR (r=0.743;p<0.001), while nasal calculated TMV (5.45±1.94x10^{-2}µl/mm) was correlated to nasal TMH (r=0.897;p<0.001) and nasal TMR (r=0.830;p<0.001) (Figure 4-5).

To account for any difference in the amount of predicted tear volume while measuring an equal TMH or TMR at the different locations, a linear regression analysis for each location was calculated and formula given in the graph (Figures 4 and 5). In order to allow the clinician to compare the amount of calculated TMV typical values of 0.1 to 1.0 for TMH and TMR were used as an independent to calculate the dependent TMV for each location (Table 3).

DISCUSSION

The aim of the study was to use optical coherence tomography to investigate the influence of LIPCOFs on TMH, TMR, and for the first time on TMA (and therefore TMV), at the central and para-central positions along the lower lid margin. For the central TMH, an increasing height was correlated to LIPCOFsum. This is in concordance with a recently published study in which a slit-lamp with image analysis software was used to measure the central tear meniscus.[23] On the high-resolution, cross-sectional OCT images used in the present study, it was furthermore possible to analyse TMR and TMA, which for the central lid position were also correlated to LIPCOFsum. Temporal LIPCOF seemed to impact temporal TMH, TMR and TMA, while nasal LIPCOF only appear to impact nasal TMR. This difference between temporal and nasal is likely to be caused by the unequal LIPCOF grades at these locations. However, it has to be mentioned that LIPCOF grades in this study were small due to that the subjects were normals and had no dry eyes. It was suggested that for LIPCOF grades greater than or equal to 2, an irregularity of TMH and TMR along the lower lid could be expected.[22] Nemeth et al.[30] suggested that the sensitivity and specificity of LIPCOF grading for discriminating between normal and dry eyes were best with the cut-off between LIPCOF degrees 1 and 2, which supports other findings of LIPCOF being a good discriminator between normal and dry eye patients.[14, 22] From this it can be hypothesized that an irregularity in TMH and TMR in the central zone of the lower tear meniscus would be caused by LIPCOFs and therefore is an indicator for dry eye patients. Others reported a relationship between tear meniscus irregularity and dry eye symptoms before,[31-33] however in these studies the degree of LIPCOFs was not analysed.

TMH and TMR at the para-central location was higher or flatter, respectively, compared to the central location, which is in agreement with our previously published

study.[22] Interestingly, tear meniscus area, and therefore tear meniscus volume, was not increased for the nasal location while it was for the temporal location. From this it might be hypothesized the nasal degree of LIPCOFs increase TMH and TMR, but the effect is not sufficient to also influence TMA and consequently tear volume at this location. This is likely to be caused by the fact that the tissue of the conjunctival folds protrudes into the cross-sectional area of the meniscus fluid (Figure 2 C). While doing so, TMH and TMR is rising, but since the tear volume is only displaced by the folds it remains constant. On the other hand, for the temporal area with the higher LIPCOF degrees, LICPOFs also cause an increase in TMA and, therefore, tear volume. However, the increase in tear volume at the temporal location is different from the increase in tear volume that would be expected from measuring TMH or TMR at the central location or nasal location (Table 3). Consequently, for a constant TMH or TMR, the associated TMA value was different at each of the three locations (central, nasal, and temporal) (Figure 6).

For the temporal TMA, Gumus et al.[34] reported a significant increase after cauterization of conjunctivochalasis. This means that by reducing the amount of conjunctival tissue in the cross-sectional tear meniscus area, the tear volume at this location will increase. LIPCOF have been described as a sub-type of conjunctivochalasis that might represent a mild stage.[35] This hypothesis may be supported by the finding that the cross-sectional area of LIPCOF tissue appeared to be much smaller than that of conjunctivochalasis, and that even after conjunctivochalasis treatment the remaining tissue is still commonly much larger than LIPCOF.[23] However, with an increasing LIPCOF grade, an increase in cross-sectional TMA was found for the temporal location. This seems to be conflicting with the findings of a reduced TMA in conjunctivochalasis. From this it may be

hypothesised that a small amount of conjunctival tissue that protrudes into the meniscus results in an increase in volume, while a large amount of tissue results in a decrease of tear volume at this location. So it is likely that there is a turning point at which an increasing cross-sectional area of conjunctival tissue in the meniscus induces a decreasing tear volume.

Furthermore, it might be concluded that even if conjunctivochalasis and LIPCOF both interfere with the meniscus, they have different impacts on the distribution of tear fluid along the lower eyelid.

However, in the existing studies on LIPCOF and conjunctivochalasis, tear meniscus parameters were observed in the lid area from limbus to limbus, which represents approximately 12 mm of the total lid length of about 25 mm. Consequently the impact of conjunctival folds on the total tear meniscus, and therefore on the overall tear meniscus volume, remains unknown. There is only one report in the literature in which TMH measured in the nasal and temporal areas 3 mm from the nasal and temporal canthi was found to be lower than central TMH, but it was not noted whether conjunctival folds were present in this study.[13]

In summary, using OCT tear meniscus parameters, it was possible to investigate the influence of LIPCOFs on TMH, TMR and for the first time on TMA at the central and paracentral position of the lower lid. The presence of LIPCOFs results in an irregularity of the tear meniscus along the lid length, and it is also associated with a variation in the relationship between tear volume and tear meniscus height or radius.

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Tables

Table 1. Optimized Grading Scale of LIPCOF.[14, 25]

Table 2. Mean values and standard deviations for the tear meniscus parameters and LIPCOF grades at the different locations along the lower eyelid.

Table 3. Predicted tear volume for typical values of TMH and TMR at the different location along the lower eyelid.

Figures

Figure 1. Anterior segment 5 lines raster of the Cirrus HD-OCT, showing the observer's view and the alignment targets at the three locations along the lower lid.

Figure 2A. Tear meniscus height (TMH) measured on the optical coherence tomography (OCT) image using the straight-line tool in ImageJ.

Figure 2B. Tear meniscus radius (TMR) measured on the optical coherence tomography (OCT) image using the 3-point line-fit technique in ImageJ.

Figure 2C. Tear meniscus cross-sectional area (TMA) measured on the optical coherence tomography (OCT) image using the segmented-line tool in ImageJ.

Figure 3. Slit lamp image of LIPCOF grade 3 at the temporal position.

Figure 4. Linear regression to describe the relationship between measured TMH and tear volume at the different locations.

Figure 5. Linear regression to describe the relationship between measured TMR and tear volume at the different locations.

Figure 6. Examples of tear meniscus cross-sectional areas (TMA) and LIPCOF grades at the different locations.