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Evaluating tear clearance rate with optical coherence tomography

Izabela K. Garaszczuk[a,*], Maryam Mousavi[b], Alejandro Cervino Exposito[a], Maciej M. Bartuzel[b], Robert Montes-Micó[a], D. Robert Iskander[b]

[a] Department of Optics, Optometry and Vision Sciences, University of Valencia, Spain
[b] Department of Biomedical Engineering, Faculty of Fundamental Problems of Technology, Wroclaw University of Science and Technology, Poland

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ABSTRACT

Purpose: To assess the early-phase of tear clearance rate (TCR) with anterior segment optical coherence tomography (OCT) and to determine the association between TCR and other clinical measures of the tear film in a group of young subjects with different levels of tear film quality.

Methods: TCR was classified as the percentage decrease of subject's inferior tear meniscus height 30 s after instillation of 5 µl 0.9% saline solution. Fifty subjects (32F and 18M) aged (mean ± standard deviation) 25.5 ± 4.3 years volunteered for the study. It consisted of a review of medical history, Ocular Surface Disease Index (OSDI) questionnaire, tear film osmolarity measurements, slit lamp examination and TCR estimation based on dynamic measurements of the lower tear meniscus with OCT. Estimates of TCR were contrasted against subject age and tear film measures commonly used for dry eye diagnosis, which includes OSDI score, fluorescein tear film break-up time (FBUT), tear meniscus height (TMH), blinking frequency, tear film osmolarity and corneal staining.

Results: The group mean TCR was 29 ± 13% and 36 ± 19% respectively after 30 and 60 s margin after saline solution instillation. Statistically significant correlations were found between TCR and FBUT ($r^2 = 0.319$, $p < 0.001$), blinking frequency ($r^2 = 0.138$, $p < 0.01$), tear film osmolarity ($r^2 = 0.133$, $p < 0.01$) and subject's age ($r^2 = 0.095$, $p < 0.05$).

Conclusions: Anterior segment optical coherence tomography allows following changes of tear meniscus morphology post saline solution instillation and evaluating the TCR. OCT based TCR might be used as additional measure of the lacrimal functional unit.

1. Introduction

Tear turnover or tear clearance is described as a global measure of the integrity of the lacrimal functional unit [1–3] and tear exchange on the ocular surface. Tear turnover rate (TTR), a temporal measure of tear turnover is proportional to the sum of the effects of tear secretion by the glands, fluid transudation through the conjunctiva, tear drainage through nasolacrimal duct, evaporation and conjunctival and corneal permeability [2,3] and was shown to be an indirect measure of ocular surface irritation (regardless of reduced or normal aqueous tear production) [4–7], severity of the ocular surface disease [6,7], Meibomian gland dysfunction [6,7] and decreased ocular surface sensitivity [2,5–11]. Also, factors connected with age (conjunctivochalasis, lid laxity, tear flow functional obstruction, blink abnormalities) may all contribute to delayed tear turnover [5,6,12]. Tear Clearance Rate (TCR) is also proven to be reduced in symptomatic dry eye subjects [1,13–15] and in contact lens associated papillary conjunctivitis [16]. Delay in tear clearance can lead to prolonged exposure to topical medications and their preservatives on the ocular surface, thus affected subjects have higher chance to develop ocular surface medication toxicity [5].

The most popular techniques of tear turnover assessment are based on following the elution of tracer molecule added to the tear film with the means of electromagnetic spectrum. This family of methods include fluorophotometry [3,6,12,14,17–27] and lacrimal gamma scintigraphy [28–31]. Fluorophotometry is considered the *gold standard* in tear turnover and tear flow assessment [27,32]. Standardized procedure, following instillation of 1 µl of 2 % sodium fluorescein into the lower conjunctival sac with a micropipette, lasts up to 30 min [10], when scans are performed every two minutes [1,18] with a commercially available fluorophotometer. In vivo fluorophotometry can be directed to marginal strip [12,18,21] or precorneal tear film [1,3,17–19,21,23–25,33]. The change in rate of fluorescence decay is calculated and tear turnover rate is defined as percentage of fluorescence decay per minute.

* Corresponding author at: Department of Optics, Optometry & Vision Sciences, University of Valencia, Calle del Doctor Moliner, 50 - 46100 Burjassot, Spain.
E-mail address: Izabela.garaszczuk@uv.es (I.K. Garaszczuk).

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Fluorophotometry has some limitations. It requires considerable skill to perform and expensive equipment which lowers its clinical utility. Also extensive period of time is required to obtain results. Due to these limitations, it has been mostly confined to research settings. The aperture of the photometric microscope is larger than the tear film, which is the cause of low spatial resolution of the device [19] that does not allow to measure the fluorescence coming from a thin layer of the tear film without including a portion of the cornea and together with the corneal permeability to sodium fluorescein [3,17,19,25] leads to errors in TTR assessment. Other factors that may contribute to errors in TTR estimation are connected with too high concentrations of fluorescein being instilled [19,21] and counting saturation of the device's electronics [33]. Pearce et al. [24] also pointed out that reduction in blink rate, as well as nonconfluence of the tear film during scans and reflex tearing caused by excessive facial illumination may also contribute to errors in TTR calculation [19,24].

The DEWS I report from 2007 [34] mentioned TTR assessment with fluorophotometry as one of the additional measures of tear film used to diagnose and monitor dry eye disease and addressed the need to develop cheaper and less time consuming methodologies. Recently, a new method for observing tear meniscus morphology by anterior segment optical coherence tomography (AS-OCT) was proposed by Zheng et al. to study the tear clearance as a function of age [35]. Measurements of tear meniscus morphology including tear meniscus height (TMH), depth (TMD), and tear meniscus cross-section area (TMA) have a wide range of applications [36–39]. OCT ensures good repeatability and allows following changes of tear meniscus morphology after fluid instillation [40,41]. In Zheng's study the tear meniscus height, depth and cross-sectional area were measured based on a single scan with in-build OCT software and measurements were repeated 3 times with an interval of at least 15 min between them. In the study presented here, a custom-written algorithm was developed for more precise, automatic estimation of tear meniscus parameters following a blink to simplify the procedure [42]. The aim was to assess the early-phase TCR, utilising an anterior segment OCT and newly-developed software and to compare TCR with tear film measures most commonly used clinically in dry eye diagnosis, to test OCT-based measurements of TCR have potential as a clinically applicable diagnostic method.

2. Methodology

Fifty healthy subjects (32F and 18M) aged (mean ± standard deviation) 25.5 ± 4.3 years (from 20 to 37) have been recruited for the study. Study adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects after the nature and possible consequences of the procedures were explained. Subjects were advised to refrain from wearing contact lenses and instilling ophthalmic solutions at least one week before commencing the study. Exclusion criteria included subjects with signs and symptoms of eye dryness or inflammation, recovering after surgery or with any known tear flow impairment. Slit lamp examination was performed with strong emphasis on sings of lid malformations (entropion or ectropion), conjunctivochalasis (LIPCOF > 1.0) and lacrimal puncta obstruction to ensure that the subjects meet the inclusion criteria.

The study protocol in a chronological order consisted of review of medical history, Ocular Surface Disease Index (OSDI) questionnaire, tear film osmolarity measured with TearLab Osmolarity System (Tear Lab Corp., San Diego, CA, US), slit lamp examination, tear meniscus height, TCR estimation based on inferior tear meniscus height dynamics assessed with anterior segment spectral optical coherence tomography (SOCT Copernicus, Optopol Ltd., Poland), fluorescein tear film break-up time (FBUT) and corneal staining.

The temperature in the laboratory was stable and monitored. The mean temperature was 24.5 ± 1.2 [°C] and mean humidity was 32.2 ± 4.8 [%RH]. Following the evidence that TCR could vary with the daytime [21] measurements were only performed in the morning.

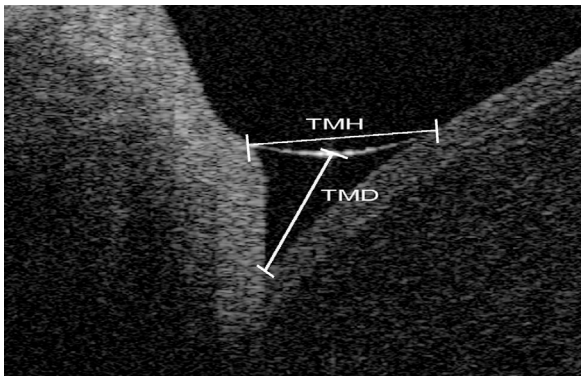

Fig. 1. An exemplary B-scan of the inferior tear meniscus (the image was cropped and resized to show the area of interest), TMH – tear meniscus height, TMD – tear meniscus depth.

OCT measurements were taken in mesopic conditions to ensure good contrast of the acquired images.

2.1. The assessment of tear meniscus dynamics

All measurements were performed on the left eye of each of the subjects. Following the procedure presented by Zheng et al. in [35], spectral OCT was used to record the dynamic changes of the inferior tear meniscus. The scanning angle and width was set to 90° and 4 mm, respectively. The B-scan plane, with a maximum of 1800 A-scans, was central (with respect to the iris outline) to the posterior region of the eye-eyelid junction and normal to the eyelid. The maximum possible number of 90 B-scans allowed in that setting was set.

The subject was asked to look straight ahead and refrain from movements. To make sure that the sequence capture the blink period, right after the sequence was initialised, the subject was asked to blink once and then refrain from blinking for the sequence to be finished. Each sequence comprised of 90 frames which corresponds to 3.75 s and can be divided into blink and post-blink intervals. Fig. 1 presents an exemplary B-scan from a sequence.

Baseline tear meniscus morphology of each subject was assessed at the beginning of the procedure, which will be later marked as 'Baseline' (BL) measurement. Subsequently, 5 µl of 0.9% room-temperature saline solution was instilled into the subjects' left eye with a micropipette. Then, shortly after instillation, another sequence was obtained (which is marked as the zero minutes). To follow changes in the tear meniscus morphology over time, the same procedure was repeated after 30 s, 1 min and every minute up to 5 min after the first post-instillation sequence. The TCR was estimated as a percentage decrease in TMH after $t = 30$ [s]. The reduction in the TMH during the first 30 s post instillation was proven to be the most significant [35].

2.2. Tear clearance rate calculation

Custom-written algorithm was developed [42] to more precisely estimate the tear meniscus height. After a blink the tear meniscus parameters stabilises and it is possible to distinguish frames that correspond to the post-blinking interval. In this interval, the mean value of the inferior TMH was automatically assessed and calculated. Fig. 2 presents all the TMH values from a single 90 B-scan sequence obtained from one of the subjects. With this method one can avoid the influence of post-blink tear meniscus morphology nonconfluence on the acquired data, giving a more precise estimate of the tear meniscus parameters after blink. The software can calculate tear meniscus height, tear meniscus depth and the area of the tear meniscus cross-section. TMH, which was shown to have better clinical utility than tear TMD [35] was used to assess TCR.