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Non invasive assessment of the human tear film dynamics

M.H. Ring[a,b,*], D.F. Rabensteiner[b], J. Horwath-Winter[b], I. Boldin[b], F. Schrödl[c,d], H. Reitsamer[c], T. Haslwanter[a]

[a] Department of Medical Engineering, University of Applied Sciences Upper Austria, Linz, Austria
[b] Department of Ophthalmology, Medical University of Graz, Graz, Austria
[c] Department of Ophthalmology and Optometry, Research Program for Ophthalmology and Glaucoma Research, Paracelsus Medical University, Salzburg, Austria
[d] Department of Anatomy, Paracelsus Medical University, Salzburg, Austria

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ABSTRACT

Dry eye disease, or keratoconjunctivitis sicca, is a multifactorial syndrome with altered tear film homeostasis leading to ocular irritations. These alterations cause discomfort and stress for the patient, but only a few objective parameters allow for proper differential diagnosis into different subtypes of this condition. The mostly invasively performed standard assessment procedures for tear film diagnosis are manifold, but often correlate quite poorly with the subjectively reported symptoms. Due to the inherent limitations, e.g. the subjectivity of the commonly performed invasive tests, a number of devices have been developed to assess the human tear film non-invasively. Since the production, delivery, distribution and drainage of the tear film is a dynamic process, we have focused our review on non-invasive methods which are capable of continuous or repetitive observations of the tear film during an inter-blink interval. These dynamic methods include (1) Interferometry, (2) Pattern Projection, (3) Aberrometry, (4) Thermography; and (5) Evaporimetry. These techniques are discussed with respect to their diagnostic value, both for screening and differential diagnostic of Dry Eye Disease. Many of the parameters obtained from these tests have been shown to have the potential to reliably discriminate patients from healthy subjects, especially when the tests are performed automatically and objectively. The differentiation into subtypes based solely on a single, dynamic parameter may not be feasible, but the combination of non-invasively performed procedures may provide good discrimination results.

1. Introduction

Some of the main functions of the tear film adjacent to the corneal epithelium are the maintenance of a proper homeostasis and the protection of the exposed ocular surface cells. To fulfill this function, the tear film is organized in three different layers: the innermost layer consists mainly of mucins secreted by the goblet and epithelial cells of the ocular surface. The middle layer provides the aqueous solution for proteins and electrolytes and is secreted primarily by the lacrimal glands. And the outermost layer consists mainly of non-polar and polar lipids and seals the tear film. It thereby prevents the aqueous compartments from hyperevaporation (Bron et al., 2004; Butovich, 2011; Tseng and Tsubota, 1997).

The diagnosis of an insufficient tear film is often referred to as Dry Eye Disease (DED) or keratoconjunctivitis sicca, which is a subgroup of ocular surface diseases (Lemp, 1984). It is defined as a "multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear instability with potential damage to the ocular surface. Dry Eye is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface" (International Dry Eye Workshop C.S., 2007).

Depending on the diagnostic criteria and the characteristics of the subject population, the prevalence of this condition varies within a range of 5.5% (McCarty et al., 1998) and 33.7% (Lin, 2003). These observations were undertaken within the Australian and Chinese population, respectively.

Abbreviations: DED, dry eye disease; ITBUT, invasive tear film break up time; NITBUT, non invasive tear film break up time; OSDI©, ocular surface disease index; CLST, corrected lipid layer stabilization time; SRI, surface regularity index; SAI, surface asymmetry index; RMS, root mean square; CCD, charged coupled device; HOA, higher order aberrations; ROC, receiver operating characteristic; CV, compactness value; TDV, temperature difference value; OCT, optical coherence tomography; MGD, meibomian gland dysfunction.

* Corresponding author at: University of Applied Sciences Upper Austria, Medical Engineering, Garnsionstraße 21, 4020 Linz, Upper Austria, Austria. Tel.: +43 0 732 7806 78412; fax: +43 0 732 7806 1822.
E-mail address: michael.ring@akh.linz.at (M.H. Ring).

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The growing relevance of DED for ophthalmologists is underlined by an increasing number of new patients affected: Moss et al. (2004) reported 322 new cases of 2414 initially healthy persons over a five years period, resulting in an incidence value of 13.3%. In addition Ellwein and Urato (2002) showed a 57.4% increase in prevalence from 1991 to 1998 (from 1.22 to 1.92 per 100 Fee-for-Service Medicare Beneficiaries). These high numbers have led to the development of a battery of tests in order to assess the performance of the pre-ocular tear film.

The standard assessment procedures for tear film diagnosis are manifold: questionnaires to assess the subjectively reported symptoms (Schiffman et al., 2000; Begley et al., 2002; Schaumberg et al., 2003); investigations of ocular surface damage via staining techniques (Goren and Goren, 1988); the Invasive Tear Film Break Up Time (ITBUT) as determined with fluorescein (Abelson et al., 2002; Lemp and Hamill, 1973), which represents the time span from a blink to the first signs of tear film collapse; and the lacrimal gland production capacity via the Schirmer test (Lucca et al., 1990; Farris et al., 1981). However, it has been shown that these clinical investigations correlate quite poorly with the subjectively reported symptoms and vice versa (Begley et al., 2003). This can be explained by the highly dynamic characteristics of the tear film, its sensitivity to the surrounding environment such as, e.g. temperature and humidity and air circulation, and by the inherent drawbacks of these investigations: questionnaires reflect the self-reported symptoms and therefore show limitations e.g. for patients with suppressed corneal sensitivity; staining techniques represent a semi-quantitative method to assess the extent of DED according to a grading scheme, which may be interpreted differently according to the experience of the investigator; the ITBUT measurement may be influenced by different procedures of fluorescein instillation; and reflex tearing is also induced by the Schirmer test (Clinch et al., 1983).

Due to these constraints a number of non-invasive techniques have been introduced. Here we refer to “non- invasive” as investigations, carried out without the installation of any substance and physical contact with the tear fluid, the corneal surface or the orbit. The aim of this paper is to summarize recent non-invasive methods for the assessment of human tear film parameters. While the tear film itself is a dynamic structure, we focus on parameters which reflect the temporal changes of the tear film during an interblink interval, either by repeated or continuous evaluation of tear film parameters. Since the differential diagnosis of DED is still a challenging task, the parameters will be discussed with respect to their diagnostic value for the discrimination between different subtypes of this disease. We appreciate that nevertheless it is difficult to directly compare the merits of the individual investigations. The deficiencies of the human tear film have multifactorial causes, leading to different inclusion criteria and study protocols for the individual studies presented below. We have therefore decided to mention not only the results of the individual studies, but also the number of subjects and the inclusion criteria.

2. Methods

This section is organized into five chapters: the first introduces devices based on the physical principle of interferometry; the second chapter deals with methods based on the projection of patterns on the tear film; the third chapter gives an overview over methods which assess tear film quality through aberrometry; the fourth chapter describes methods to assess the change of the ocular temperature during an inter-blink interval; and the fifth chapter provides information on tear film evaporimetry measurements. An overview of the methods and their relationship to the assessed dynamic biophysical parameters of the tear film can be seen in Table 1.

Table 1
Overview of non-invasive methods and the assessed dynamic biophysical characteristics of the tear film.

Principle	Information content	Information form
Interferometry	Local and dynamic thickness (tearfilm; lipid layer) irregularities	Direct measurement of external tear film surface irregularities
Pattern projection	Irregularities, (NITBUT)	Direct measurement of external tear film surface irregularities
Aberrometry	Irregularities, (NITBUT)	Indirect measurement of tear film irregularities
Thermography	Ocular surface temperature	Indirect measurement of tear film evaporation
Evaporimetry	Total evaporation rate	Direct measurement of tear film evaporation

2.1. Interferometry

Since the tear film consists of three layers, each with different optical properties, the tear film can be visualized through the reflection patterns induced by these layers. Some wavelengths thereby show in-phase reflections from the front and back surfaces of the individual layers, reaching a maximum of reflections, whereas other reflections that are out of phase yield a minimum. These extrema alternate in the spectrum and give rise to spectral oscillations. These oscillations create a certain visible pattern, referred to as interferometry patterns, comparable to patterns that are caused by an oily layer on a wet road. Purposes of the superficial oily tear film layer include the prevention of the underlying aqueous compartments from hyperevaporation and the formation of an optically smooth corneal surface (Bron et al., 2004). The lipids are mainly produced by the meibomian glands, located in the upper and lower tarsal plate, and the subsequent delivery of the lipids to the tear film mainly occurs during the up-phase of the blink (Knop et al., 2011). The lipids thereby usually distribute dynamically from the inferior to the superior part of the ocular surface and stabilize after a short period of time (Yokoi et al., 2008).

Since the thickness of any layer can be estimated based on the reflection patterns, the first parameters extracted when applying interferometry were related to the thickness. Olsen (1985) were among the first to estimate the thickness of the tear film lipid layer through a slit-lamp photometer by measuring the reflectivity of two distinct wavelengths. They reported a thickness of the lipid layer of about 40 nm.

Since then, a number of studies have measured the thickness of the tear film based on single wavelength interferometry (King-Smith et al., 1999; Lu et al., 2014), whereby some studies have refined the technique to extract the interblink thinning rates for the pre-corneal tear film. Nichols et al. (2005) then applied this technique in order to investigate the dynamic behavior of the pre-contact lens and pre-corneal tear film. They recorded the invasive tear film break-up and the tear film lipid layer images simultaneously, whereby 85 subjects, both healthy and with DED, were measured.

In principle, the dynamic process of tear film thinning can be attributed to three mechanisms:

(1) The flow of water in and out of the corneal epithelial or surface of the contact lens.
(2) The evaporation of water into the surrounding air.
(3) Tangential flow of the tear film parallel to the underlying surface.