ABSTRACT
The tear film consists of multiple layers, traditionally categorized as three separate units (the outermost lipid layer, the middle aqueous layer and the innermost mucins). Each building substance of the tear film has a specific role in its proper functioning and is prone to certain disturbances caused by both local and general disorders. A systematic review of the recent literature was conducted, with data obtained via PubMed. The authors focused on tear film disorders as a manifestation of various diseases and conditions, with consideration of the current classification and diagnostic approaches. The elaborate composition of the ocular surface results in the diversity of problems affecting it. Bearing in mind the extentiveness of the subject, the most common and clinically important defects were selected. Defining the etiology of some disturbances can be very complex, but it is crucial for proper diagnosis and treatment.

KEYWORDS: ocular surface, tear film, tear dysfunction, tear film alterations.

INTRODUCTION
The external part of the eye is constantly exposed to the environment. Therefore, it is protected by the ocular surface (OS) – a unit consisting of the cornea, conjunctiva (bulbar, tarsal), lacrimal glands and lids (definition suggested by Thoft and Friend in 1979) [1]. The tear film fills the conjunctival sac and hydrates the OS [2].

The tear film consists of three main components. Traditionally, they are categorized as three separate units: the outermost oily layer, the middle aqueous layer and the innermost mucins [2, 3]. More recent articles postulate a two-layer model (the lipid and the muco-aqueous phase) [4], while some authors go as far as stating that the tear film is a single unit that acts like a fluid shell [5].

The role of the tear film includes cleansing, lubrication and nourishment of the OS, creating a smooth, refractive surface for the light to pass freely and physical and immunological protection against infections [6-25] (Table I).

The tear film is a dynamic unit that washes over the eye surface and can be described by its four main characteristics, i.e. secretion, evaporation, drainage and absorption. Secreted elements – under control of the lacrimal unit – are distributed over the OS by the lids during blinking and hover in the lipid and aqueous phase in the interblink. There, because of the direct exposure to the environment, its evaporation occurs, carefully restrained by the lipids. In time, tears are drained by the canaliculi and puncta and absorbed mostly by the epithelial cells of the nasolacrimal duct [26, 27]. Any disruption in this dynamic process can lead to tear film instability, which can be investigated by measuring the tear film breakup time (TBUT). This test is performed either after fluorescein instillation or with non-invasive methods [28], among which lateral shearing interferometry seems most promising [29].

The functions of the ocular surface, tear secretion and blinking rate are regulated by the nervous, endocrine, immune and circulatory systems [30], in order to assure even distribution of tears over the OS.

The prevalence of tear film disorders varies depending on population, sex, and age [31]. Many risk factors are being investigated: diabetes, dyslipidemia, autoimmune disorders, ophthalmic surgery, the use of certain medications, air pollution, sleep quality, and allergies [32-37]. As of now, it is generally agreed that the population at highest risk are older women [38]. In Western China, a study reported a 27.8% dry eye disease incidence [39], while in Spain it is estimated as 18.4% [40] and in the USA as 6.8% [41]. Data from Poland are to be collected.

This review aims to focus on the importance of the tear film in proper functioning of the OS and to highlight the role of its disorders as the manifestation of various diseases.

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Tear film disorders as a manifestation of various diseases and conditions

CONDITIONS AFFECTING TEAR FILM LAYERS

Each layer of the tear film can be affected by different diseases and conditions, thereby causing its instability. Because of the wide spectrum of the problems that may interfere with proper functioning of the tear film, diagnosis of particular disturbances may be challenging. The results of the most common tests may be quite similar in different disorders and further, more specific examinations are required.

The lipid layer

Damage to the outermost layer manifests itself primarily as a change of its thickness (lipid layer thickness – LLT). It can be measured by optical reflectometry using a slit lamp or single-wave interferometry, both of which are non-invasive techniques [42]. Interferometry of the tear film also allows for assessment of kinetic stability of the lipid phase [43]. From the available diagnostic tools only meibometry provides quantitative assessment of the lipid reservoir [44]. Increase in the tear film evaporation rate has been reported to be strongly correlated with lipid layer impairment, but its great dependence on extrinsic conditions decreases its diagnostic value [28]. Moreover, in normal conditions the tear surface tension is maintained by the lipids, so its rise may serve as a diagnostic clue. The higher proportion of branched fatty acid chains in Meibomian gland excreta also serves as a marker of lipid layer dysfunction [45]. Ring et al. introduced a promising novel parameter called corrected lipid layer stabilization time; however, further trials are needed before it can be recognized as a standard procedure [46].

Meibomian gland dysfunction (MGD) directly affects the composition and stability of the lipid layer, as those structures are almost exclusively responsible for lipid excretion to the tear film [47]. It can result from both hyper- and hyposecretion. Also, androgen deficiency, which occurs in patients on anti-androgen therapy and with aging, hinders lipid production [48]. Various local and systemic conditions may provoke obstructive defect to the glands, e.g. chronic blepharitis and atopy [49, 50]. The more severe course of MGD is associated with type 2 diabetes mellitus [51, 52]. Insufficient protein intake in bariatric patients also negatively influences tear film lipids [53]. Furthermore, it has been reported that incomplete blinking may be the reason for lipid layer instability, because of inadequate lipid distribution [5, 54]. Moreover, tobacco smokers are prone to development of MGD [55]. Demodiconis is another condition that should be named as a contributing factor. Demodex spp. can be found in eyelashes, with prevalence in healthy individuals ranging from 18% (age group of 21-35 years old) to 33% (> 65 years old) [56]. Otherwise harmless, mites are associated with marginal blepharitis and chalazion as a result of gland penetration [57]. Interestingly, a link between the number of mites and disease severity has been reported [58]. Recently, a small study presented a new in-office technique for infestation confirmation in patients with cylindrical dandruff [59].

There are some studies on medications, both topical and systemic, that may cause distortions specific to the lipid layer. Isotretinoin, used for acne treatment, decreases Meibomian gland secretory ability [60, 61]. In contrast, botulinum neu-

<table>
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<th>Tear film layer</th>
<th>Function</th>
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| Lipids (meibum) | – Form the outer layer of the tear film  
|                  | – Minimize the evaporation of water from the eye surface  
|                  | – Isolate ocular surface from the environment  
|                  | – Improve the stability of tear film  
|                  | – Provide smooth refracting surface  
|                  | – Limit contamination of ocular surface from particles (dust) and microorganisms  
|                  | – Prevent tear contamination by skin lipids  
|                  | – Limit aqueous layer surface tension  
|                  | – Counteract tears overflowing onto the skin |
| Aqueous phase    | – Constitutes roughly 90% of the tear film volume  
|                  | – Lubricates the ocular surface  
|                  | – Washes away foreign bodies and contaminations  
|                  | – Nourishes the avascular cornea (oxygen, proteins, inorganic salts)  
|                  | – Includes proteins (lysozyme, lactoferrin, lipocalin), immunoglobulins, defensins and glycoproteins responsible for anti-microbial activity  
|                  | – Includes growth factors, vitamins and electrolytes necessary for ocular surface health and epithelial integrity  
|                  | – Realigns corneal microirregularities (refractive properties) |
| Mucins           | – Form a glycocalyx over the ocular epithelium that prevents pathogen adhesion  
|                  | – Bind water to hydrate and lubricate the ocular surface  
|                  | – Reduce friction during blinking  
|                  | – Clear the surface of pathogens and debris  
|                  | – Contribute to tear stability  
|                  | – Take part in regulation of epithelial growth  
|                  | – Might be involved in cellular signaling |

### Table I. The function of tear film layers

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rotoxin A injections for blepharospasm and hemifacial spasm seem to increase LLT [62].

The aqueous layer

Examination of the middle, aqueous layer can be performed using various diagnostic tools. The tear meniscus assessment is of significant value [63], as it is a simple method for visualizing the tear film volume. A traditional, popular test for assessing tear secretion is the Schirmer I test, which can be performed with or without anesthesia. However, its results can be altered by the globe movements and eye position [64]. Another test that can describe the aqueous phase is the tear film osmolarity – its increase suggests a deficit of the aqueous compound [11, 65].

A dysfunction of the lacrimal glands leads to aqueous deficient dry eye. The diagnosis is established by the presence of subjective complaints and objective evidence of dry eye symptoms. Aqueous deficient dry eye can be classified into two groups: Sjögren syndrome dry eye and non-Sjögren syndrome dry eye [66].

Patients with Sjögren syndrome (SS) are a heterogeneous group of patients, among whom two common symptoms can be identified – keratoconjunctivitis and xerostomia [67]. Brito Zenon et al. showed in their cohort study that sicca manifestations occur in up to 98% of SS cases [68]. In addition to clinical presentation, biomarkers characteristic for SS include anti-Ro/SSA and anti-La/SSB autoantibodies [69]. The pathophysiology of Sjogren syndrome is of a dual origin. The primary SS occurs when symptoms from the lacrimal and saline glands are isolated, whereas the secondary SS is accompanied by connective tissue diseases such as rheumatoid arthritis (20-32%), systemic lupus erythematosus (15-36%), and progressive systemic sclerosis (11-24%) [70]. In both types, the gland tissues are infiltrated by activated T-lymphocytes [71].

In the non-SS dry eye, we can distinguish lacrimal deficiency, lacrimal gland duct obstruction and reflex block [72]. In this type of eye dryness, the basal tear production is hindered. Many of the non-SS eye dryness cases are idiopathic, but some of the factors responsible for this disorder include: age-related atrophy and/or fibrosis of the lacrimal gland [73], Mikulicz disease (IgG4-positive plasmocytes infiltration) [74], other autoimmuneological diseases (such as systemic lupus erythematosus, rheumatoid arthritis, autoimmune thyroiditis and chronic ocular graft versus host disease [75].

Moreover, keratoconjunctivitis sicca is linked to corneal hypoesthesia, occurring after corneal refraction surgery [76] and in patients wearing contact lenses [77]. Damage to the V cranial nerve may manifest as neurotrophic keratitis – it is observed in some patients with Herpes zoster keratitis (12.8%), in 6% of herpetic keratitis cases and as a side effect of surgical trigeminal neuralgia management (2.8%) [78].

Aqueous layer stability can also be affected by medications – some antidepressants (escitalopram, venlafaxine, duloxetine) have been shown to reduce the values of the Schirmer I test [79] and depression has been linked to a higher probability of developing eye dryness [80]. Hydrochlorothiazide has also been reported to decrease tear production [81]. Retinoic acids, although often associated with aqueous deficiency, do not decrease water secretion [82, 83].

The mucin layer

The state of the mucin layer, which is directly adherent to the cornea, can be tested using various diagnostic techniques. Tear film osmolarity demonstrates the strongest correlation with disease severity, but results obtained using different measurement means may vary [28, 84]. Also, tear wash levels of myeloperoxidase and metalloproteinases increase in mucous disorders [85]. Examination of the epithelial surface, i.e. conjunctival impression cytology, reveals lower goblet cell densities per millimeter compared to healthy subjects. Tear ferning is present in affected patients, which can be estimated with the ocular ferning test, but unfortunately unequivocal agreement on its interpretation is still lacking [86, 87]. It is worth bearing in mind that very often patients suspected of problems with the mucin layer suffer from vitamin A deficiency, detectable in blood plasma.

The leading cause of xerophthalmia associated with mucins is related to insufficient vitamin A levels [88, 89]. This avitaminosis manifests itself in various ways and can be observed in the course of several illnesses and syndromes. Night blindness should be regarded as the most common symptom mentioned by the patients, apart from dry eye. In the direct eye examination Bitot’s spots can be visible in the conjunctiva, along with xerosis and corneal scarring and even ulcers [90]. It is also characterized by the loss of goblet cells, whose growth strongly depends on vitamin A [91]. Generally, lack of vitamin A is associated with different forms of malnutrition or chronic malabsorption [92-94]. Some gastroenterological diseases such as celiac disease may serve as examples of the latter [92]. Moreover, any condition affecting the liver, hence challenging the fat metabolism, decreases the absorption rate of this fat-soluble vitamin [95, 96]. The pancreas is closely involved in the fat digestion pathway and its insufficiency, such as in cystic fibrosis, hinders vitamin A intake [97, 98]. Alcoholism is the major cause of malnutrition [99, 100], along with restrictive diets, both in eating disorders and a selective, e.g. poorly balanced, vegan diet, and consumption of low-quality food [101-103].

The second most common disease associated with mucin layer defects is mucous membrane pemphigoid (MMP) and its subtype ocular cicatricial pemphigoid (OCP), which affects the conjunctiva exclusively [104]. A recurrent inflammatory process destroys the mucous cells and promotes subepithelial fibrosis, resulting in conditions ranging from xerophthalmia to total conjunctival keratinization and blindness [105-108].

There are some other conditions affecting mucin production. Steven-Johnson syndrome, being a manifestation of adverse drug reactions, impairs the mucin layer of the tear film [109]. Its pathomechanism involves metaplasia of the conjunctiva and hence a decrease in the number of the goblet cells [110, 111]. Severe burns, both chemical and thermal, can affect the conjunctival mucin production by decreasing the number of functioning goblet cells [112]. Of the pharmaco-
logic factors, ambroxol, a popular oral mucoactive drug, has been found to modify the mucous layer [113].

CONDITIONS AFFECTING MULTIPLE LAYERS

Tear film layers remain in strict dependence on each other – in terms of both the functionality on the molecular level and the regulation of its secretion. Therefore, some conditions affect tear film as a whole, causing disturbances to each of its layers. The most common and definitely unavoidable condition impairing the ocular surface is progression in age, which hinders each step of tear production and secretion, although to a variable extent. Notably, it also influences other tear film impairing factors, mentioned below. Tantalic dry eyes, in all three subtypes, may seem to be the most obvious condition affecting all three layers – lid-eye incongruity, epitheliopathy and evaporation being the reasons for tear loss. Also, the neurologic cause should not be missed, as it directly affects tear secretion. Hormonal regulation, mainly by estrogens, androgens and prolactin, acts likewise [114-116].

As regards environmental factors, use of visual display terminals promotes dry eye disease, but the actual pathomechanism is still being discussed [117, 118]. Contact lens wear, even though influencing mainly the lipid layer, changes the dynamics of the tear film as a whole, as reported in the Mann et al. report [119], and very often causes dry eye symptoms [120, 121].

Multiple layers of the tear film may also be affected by various medications, for instance, topical beta-blockers used by glaucomatous patients – studies report the decrease of Schirmer I test values and fluorescein break up time, and an increase in eye surface staining results [122, 123]. Moreover, there have been reports that topical glaucoma therapy significantly lowers LLT [124]. Additionally, the basal tear production decreases under long-term general anesthesia, causing perioperative dry eye syndrome [125]. The side effect of hindering both the goblet cells and lacrimal glands is associated with H1 antihistamines [126]. An extensive review and list of medications were presented by Askeroglu et al. [127]. Surprisingly, based on the latest metaanalysis, the negative effect of hormonal replacement therapy and oral contraceptives on the tear film seems to be rather speculative [128, 129].

CONCLUSIONS

The problem of tear film disorders can overwhelm with its extensivity. Our review focused on selected aspects, which were chosen on the basis of clinical importance and prevalence. The broad spectrum of diseases and conditions that may affect each layer of the tear film impedes comprehensive depiction of them all. Defining the etiology and pathophysiology of some disturbances can be very complex, and represents clinical and therapeutic challenge. Notably, tear film disorders can manifest other systemic diseases and sometimes be the sole clue to diagnosis, so the subject should be considered as of great importance not only to ophthalmologists, but also to physicians of other specialties. Furthermore, the commonness of tear film instability and wide spectrum of its different backgrounds call for incorporating its general state evaluation into daily medical practice. If a patient has eye dryness symptoms, these complaints should also be taken into consideration when planning treatment. If a certain drug has been proven to cause tear film disturbance, a different substance should be considered. We believe that questions about eye problems should be a part of every medical history taken, and diagnostic tests, which assess the tear film function, should be a part of every ophthalmic examination.

DISCLOSURE

The authors declare no conflict of interest.

References

163


