Chapter

Tear Film – Physiology and Disturbances in Various Diseases and Disorders

Dorota Kopacz, Łucja Niezgoda, Ewa Fudalej, Anna Nowak and Piotr Maciejewicz

Abstract

The tear film is a thin fluid layer covering the ocular surface. It is responsible for ocular surface comfort, mechanical, environmental and immune protection, epithelial health and it forms smooth refractive surface for vision. The traditional description of the tear film divides it into three layers: lipid, aqueous and mucin. The role of each layer depends on the composition of it. Tear production, evaporation, absorption and drainage concur to dynamic balance of the tear film and leads to its integrity and stability. Nonetheless, this stability can be disturb in tear film layers deficiencies, defective spreading of the tear film, in some general diseases and during application of some general and/or topical medications. Dry eye disease is the result of it. In this review not only physiology of the tear film is presented. Moreover, we would like to discuss the influence of various diseases and conditions on the tear film and contrarily, spotlight tear film disorders as a manifestation of those diseases.

Keywords: tear film, dry eye, mucins, lipid layer, aqueous layer, ocular surface

1. Introduction

The tear film is a thin fluid layer covering the ocular surface; it is the interface of the ocular surface with the environment. It is responsible for ocular surface comfort, mechanical, environmental and immune protection, epithelial (both corneal and conjunctival) health and it forms smooth, refracting surface for vision [1, 2]. Tear production (about 1,2 microliters per minute, total volume 6 microliters, 16% turnover per minute), evaporation, absorption and drainage are responsible for dynamic balance of the preocular tear film [1, 3–5]. Homeostatic balance leads to stability of the tear film, that makes possible to realize its functions as lubrication, nutrition and protection of ocular surface [3, 6]. Nonetheless, this stability can be disturb in tear film layers deficiencies, defective spreading of the tear film, in some general diseases and during application of some systemic and/or topical medications and dry eye disease evolves as a consequence of it. These review focused on physiology of the tear film, it's meaning for the ocular surface stability and analyzed influence of various diseases and conditions on it.

2. Tear film structure and function

The traditional description of the tear film is three-layered structure: superficial-oily, middle - aqueous and mucous layer at the base [1–3]. A more recently proposed model consists of two layers: superficial – lipids and mucin/aqueous glycocalyx gel with decreasing mucin concentration from epithelium to lipid layer [1, 3, 7, 8]. Some authors says, that the tear film is a single unit that acts like a fluid shell [9] (**Table 1** and **Figure 1**).

Tear film layer	Function
Lipid layer (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 • Lubricate the ocular surface • Wash away foreign bodies and contaminations • Nourish the avascular cornea (oxygen, proteins, inorganic salts) • Include proteins (lysozyme, lactoferrin, lipocain), immunoglobulins, defensins and glycoproteins responsible for anti-microbial activity • Include growth factors, vitamins and electrolytes necessary for ocular surface health and epithelial integrity • Realign corneal microirregularities (refractive properties)
Mucous layer	• 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 1.
The function of tear film layers.

2.1 Lipids

The lipid layer is secreted by Meibomian glands, located within tarsal plates of upper and lower eyelids with some small contribution by Moll (modified apocrinic, sudoriferous) and Zeiss (modified subeceous) glands, located within superior and lower eyelids (connected with hair follicles) and possibly epithelial cells. The posterior, aqueous interface consists of polar lipids: ceramides, cerebrosides and phospholipids. The lipid-air interface is formed with nonpolar lipids: cholesterol esters, triglycerides and free fatty acids [1, 3, 7, 8, 10].

The main function of the lipid layer is to reduce evaporation of tears and improve the stability of them. Moreover, the lipid layer provides smooth refracting surface, limits contamination of ocular surface from particles (dust) and microorganisms, prevents tear contamination by skin lipids, limits aqueous layer surface tension and counteracts tears overflowing onto the skin. [1, 3, 7–14].

Regulation of lipid secretion supervenes through modulation of lipid synthesis or cell maturation. The Meibomian gland secretion is a subject of neuronal, hormonal

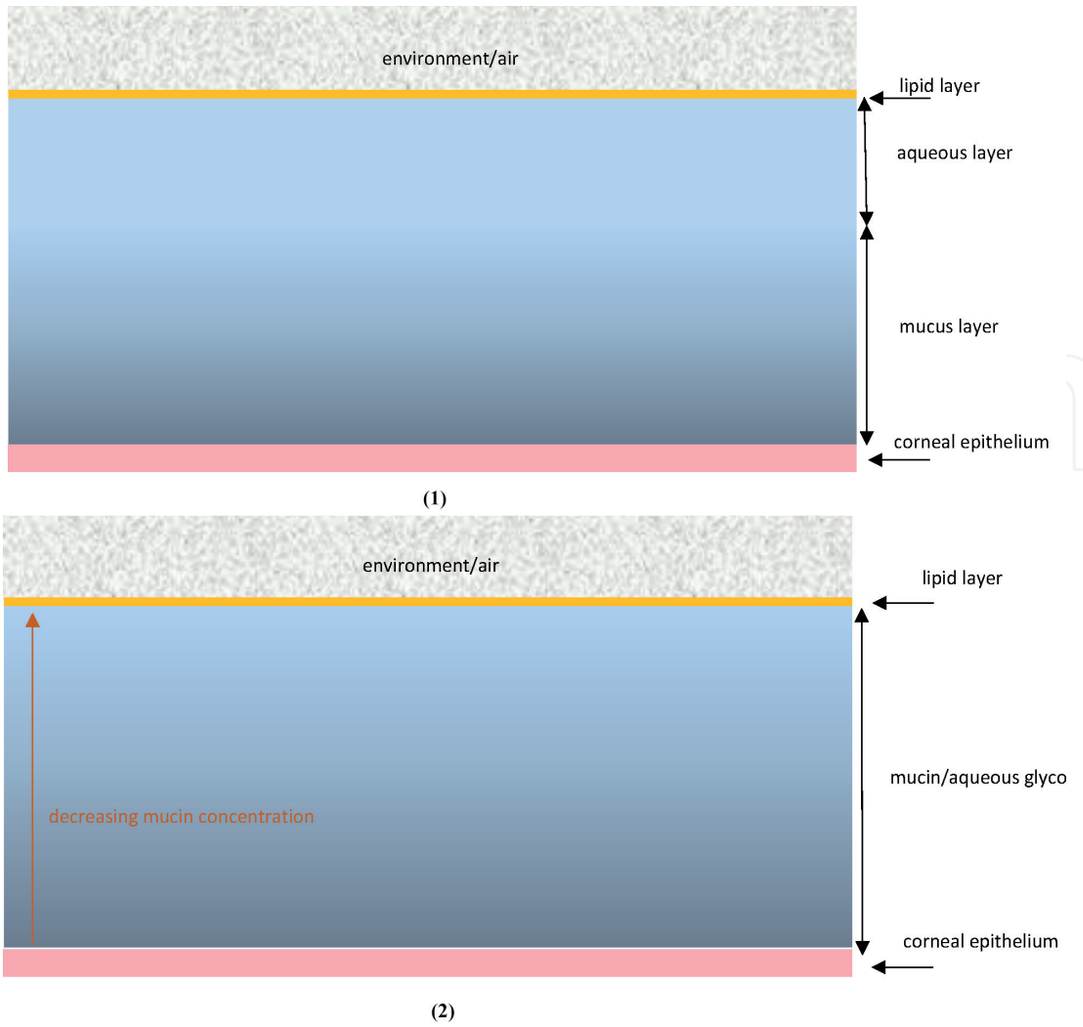

Figure 1.
Structure of the tear film: 1. Three layer conception. 2. Two layer conception.

and vascular influences. Androgen, estrogen and progesterone receptors have been identified in adult male and female rats, rabbits and humans. It is suggested that androgens stimulate and estrogens reduce Meibomian secretion [14–17]. Moreover, Meibomian gland function may be under direct neuronal (predominant parasympathetic, also sympathetic and sensory sources) or indirect vascular (vasoactive intestinal polypeptide VIP) influence to control lipid synthesis and/or excretion [2, 14, 15].

2.2 Aqueous component

The main non-reflex production of aqueous part of mucin/aqueous gel is from the Krauze and Wolfring glands (accessory lacrimal glands) located in the conjunctiva of superior eye lid and superior conjunctival fornix. The main lacrimal gland is responsible for aqueous tears production secondary to deleterious stimulation and plays important, though not entirely clear role in non-reflecting tearing (dry eye syndrome is noted in patients with damaged main lacrimal gland) [1, 7, 8, 11, 18]. The aqueous layer consists of water, electrolytes, proteins, cytokines, vitamins, immunoglobulins and peptide growth factors. Moreover, amino acids, bicarbonate, calcium, urea and magnesium were detected in tear film [15, 19].

The aqueous portion of the tear film is responsible for ocular surface lubrication, washing away foreign bodies or contaminations and nourishing avascular cornea (oxygen, inorganic salts, proteins, glucose) [3, 16, 20]. The soluble mucins decrease the surface tension, impact coherence of the aqueous layer, contribute to tear film

viscosity [14, 19]. Almost 500 different proteins have been extracted from the tear film [3, 21]. Lactoferrin, lysozyme, lipocalin, secretory immunoglobulin A(sIgA), immunoglobulin G(IgG), immunoglobulin M (IgM), albumin, transferrin, ceruloplasmin, defensins, tear specific prealbumin and glycoproteins participate in the ocular surface antimicrobial activity and defense [3, 15, 22]. Growth factors, vitamins, electrolytes, neuropeptides and protease inhibitors are necessary for retaining ocular surface health and epithelial integrity [1, 3, 23]. Retinol, secreted by the lacrimal gland, is necessary for maintenance of goblet cells and regulates corneal epithelium desquamation, keratinization and metaplasia [15, 24–26].

The lacrimal gland is affected by both nervous system and various hormones [1, 2, 7, 11, 15, 18, 23, 27]. The gland innervation comes from the first brunch of trigeminal nerve, the facial nerve and sympathetic fibers from the superior cervical ganglion [1, 11, 15, 28]. Stimulation of the ocular surface is the beginning of the main lacrimal gland production (reflexing tearing). The emotional tearing is also connected with this reflex loop (**Figure 2**). The meaning of the sympathetic part of innervation is thought to stimulate basal tearing but is still not completely understood. The accessory lacrimal glands are heavily innervated, but there is lack of parasympathetic part and most of the innervation is undefined [8, 15, 29].

Androgens and estrogens influence lacrimal gland production. Androgens lack is responsible for reversible degenerative changes of lacrimal gland, decreased volume of the tears, decreased level of proteins in tears. Estrogens remain controversial: some studies described estrogen deficiency linked to keratoconjunctivitis sicca (KCS) and lacrimal gland degeneration, other works have shown no changes in the lacrimal gland and tear film with decreased level of estrogens [15, 17, 30, 31]. Thyroid stimulating hormone (TSH) receptors (present in lacrimal gland) as well as thyroid

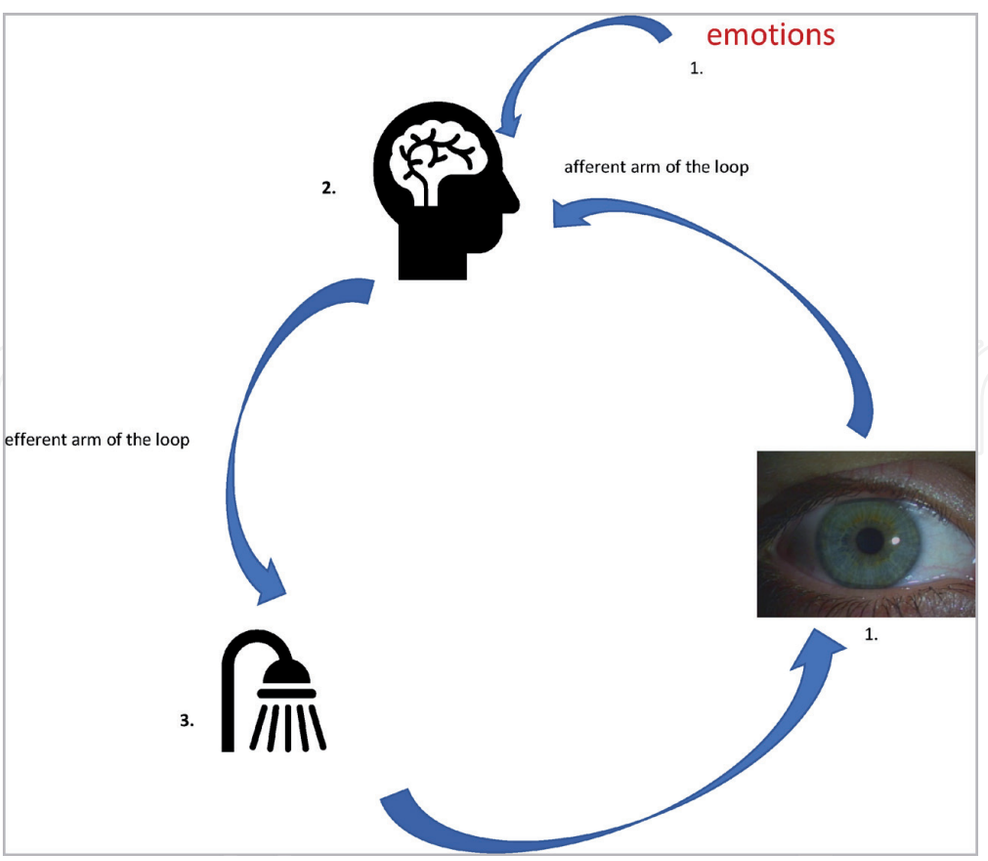

Figure 2.
Reflex loop of tearing: 1. Stimulants: - ocular surface and nasal mucosa - afferent arm of the loop (first branch of the fifth cranial nerve)- emotions, 2. brain - efferent arm of the loop (parasympathetic part of the seventh nerve), 3. lacrimal glands.

hormone and tissue interaction are necessary for lacrimal gland secretion. Adequate insulin level is important for lacrimal gland and ocular surface stability and function, because it is necessary for acinar cell and cornea epithelial cell proliferation [32].

2.3 Mucins

The mucous layer of the tear film is produced by both corneal and conjunctival epithelium and the lacrimal gland and conjunctival goblet cells [1, 3, 7, 11, 15, 33]. It is composed of secreted and transmembrane mucins, immunoglobulins, salts, urea, glucose, leukocytes, cellular debris and enzymes [1, 3, 15, 33–35].

Traditional description of the mucins role limits to secreted gel-forming mucins working as lubricating agents and clearing molecules. Current date indicate its role also as a barrier for corneal and conjunctival epithelium. We can find two kinds of the mucins: cell surface-associated and secreted [36].

Cell surface-associated mucins form a thick cell surface glycocalyx, providing through their O-glucans a disadhesive character to the apical surface of the corneal epithelium. That is why they assure boundary lubrication and prevent adhesion of corneal epithelium and tarsal conjunctiva during blinking and sleeping [36, 37]. Moreover, membrane-bound mucins take part in the maintenance of the mucosal barrier integrity to prevent the penetrance molecules onto ocular surface epithelia [36, 38]. Some recent studies have weighed up membrane-bound mucins as osmosensors in eukaryotic cells [36, 39, 40].

Secreted mucins have a capability to trap contaminations (e.g. allergens, debris, pathogens) in order to clearance them from mucosal surface. Gel-forming mucins retaining water, form highly hydrated gel to lubricate ocular surface and reduce shear stress during blinking or rubbing. Moreover, MUC 7 (detected in lacrimal gland), has potent antifungal and antimicrobial activity [34, 35, 37, 41–43].

Goblet cells may be stimulated for mucin secretion by histamine, antigen, immune complex, mechanical action (i.e. blinking), direct (muscarinic and α-adrenergic receptors on immature goblet cells) and indirect (sensory, sympathetic and parasympathetic innervation of conjunctiva surrounding goblet cells) neural control [15, 16, 44–46].

2.4 Tear film dynamics

Balanced tear film production and elimination is crucial for its integrity, stability and right osmolality [3]. Tear film production is a complex process, controlled by the various factors: main and accessory lacrimal glands, ocular surface structures (cornea, conjunctiva, eyelids with Meibomian gland) and interconnecting nerves (both sensory and motor) [3, 47, 48]. Ryc.1. Tears elimination proceeds as evaporation, drainage and absorption. Tear film interfaces with the environment; that is the reason of evaporation (about 1,4–39,3 x 10^{-7} g/cm^2/s) [5, 49]. Some environmental factors like humidity, temperature and air movements impact the rate of tear evaporation from the ocular surface [50]. Higher evaporation is the reason of tear film thinning and, because of that, instability and hyperosmolality [51]. Regardless of the recent date on evaporation, tears outflow through the lacrimal drainage system remains the main way of its elimination. With each blink, tears with contaminations (like cellular debris, toxins, inflammatory cells and other waste products) are moved towards the lacrimal puncta and next - due to the negative pressure created in lacrimal drainage system - to the lacrimal drainage tract [3, 52]. Some studies noted reduction of tears production in patients with impaired drainage that highlights the importance of this process in the model of tear dynamics [53–55]. At least absorption: process necessary for proper tear film dynamics, connected with cornea, conjunctiva and - mainly - nasolacrimal duct epithelium [56]. The equilibrium in

the tear film production, retention and elimination acts the crucial role in its proper functioning, thereby ocular surface health [3].

3. The influence of various diseases and conditions on the tear film

Tear film stability can be disturb in tear film layers deficiencies, defective spreading of the tear film, in some general diseases and during application of some general and/or topical medications. In the wake of it dry eye disease evolves [11, 36, 57] (**Tables 2** and **3**).

3.1 Lipid layer alteration

Deficiency of this layer is the reason of more rapid evaporation and in the absence of increased tear production activates evaporative form of dry eye disease [58].

The most common reason of lipid layer deficiency is obstruction of the Meibomian glands. Meibomian gland disfunction (MGD) may be provoked by various local and systemic conditions, e.g. atopic keratoconjunctivitis, chronic blepharitis [59, 60], generalized dysfunction of sebaceous glands (rosacea, seborrheic dermatitis), chemical agents such as turpentine, present in the sick building environment [36, 61]. Tobacco smokers are prone to development of MGD [62], the more severe course of MGD was observed in type 2 diabetes mellitus [63].

	Dry eye
Aqueous deficient dry eye (ADDE)	Evaporative dry eye (EDE)
Sjőgren syndrome dry eye (SSDE) Primary Secondary	Endogenous Meibomian gland dysfunction (MGD) Disorders of lids and lid aperture Low blinking Systemic medicines
Non- Sjőgren Syndrome dry eye Lacrimal deficiency Lacrimal gland duct obstruction Reflex block Systemic medicines	Exogenous Contact lens wear Ocular surface diseases Topical medicines Vitamin A deficiency

Table 2.
Dry eye classification [7, 23, 64–74].

	Dry eye disease
Signs	Symptoms
• Discomfort: itching, stinging, burning, "foreign body sensation" occasionally pain, photophobia • Visual fluctuations (especially during reading- blinking recover vision) • Tear film instability (potential damage of ocular surface)	• Eyelids: blepharitis posterior, Meibomian gland disfunction, trichiasis, symblepharon • Conjunctiva: hyperemia, keratonization, persistent inflammation, dyeing with the lissamine green(rose bengal) • Tear film: debris, reduced meniscus, instability(reduced break-up time), elevated osmolarity and level of inflammatory mediators • Cornea: epithelial defect (dyeing with the fluorescein), filaments, mucus clumping • Potential complications: persistent epithelial defect, keratomalacia, corneal perforation, corneal ulcer

Table 3.
Signs and symptoms of dry eye disease [1, 7, 23, 64].

Furthermore, the insufficient protein intake in bariatric patients negatively influences tear film lipids [75]. Also androgen deficiency (e.g. aging, anti-androgen therapy, congenital impairment or absence of the androgen receptor) hinders lipid production [76]. Incomplete blinking has been reported as the reason for lipid layer instability, because of inadequate lipid distribution [9, 77]. Some studies have revealed influence of medicines on the lipid layer: e.g. isotretinoin decreases Meibomian gland secretory ability [78], and on the contrary, botulinum neurotoxin A injections seem to increase lipid layer thickness [79].

3.2 Aqueous layer disturbances

Aqueous layer deficiency is the most common reason of dry eye and is classified into two groups: Sjögren Syndrome dry eye and non-Sjögren Syndrome dry eye [64, 65].

Sjögren's syndrome (SS) is a rheumatic autoimmune disease in which exocrine glands (salivary and lacrimal glands) are involved that results in clinical symptoms of dry mouth and dry eye. SS can be primary-pSS (without any other accompanying symptoms) or secondary-sSS (with other autoimmune diseases: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), polyarteritis nodosa, systemic sclerosis, granulomatosis with polyangiitis (GPA), primary biliary cholangitis (PBC), mixed connective tissue disease, occult thyroid eye disease) [64, 66]. Some studies demonstrated coincidence of dry eye disease (DED) and SS in 46.7% cases [64, 67].

In non-SS dry eye reduced tear secretion is a result of senile hyposecretion, lacrimal excision, lacrimal duct obstruction, immune lacrimal gland damage in sarcoidosis or lymphoma, sensory or motor reflex block, scarring conditions of the conjunctiva (pemphigoid, chemical burns, trachoma, chronic ocular Graft-versus-Host Disease) [11, 57, 64, 68, 69]. Corneal hypoesthesia and due to it dry eye can be result of corneal refraction surgery [70], contact lens wearing [71], herpetic keratitis or as a side effect after surgical trigeminal neuralgia management [72].

Increased electrolyte concentration, loss of growth factors, presence of proinflammatory cytokines result in changes in composition of the aqueous part of the tear film. Such a disturbances in connection with slow tear turnover are secondary to ocular surface damage [8, 47].

There are some medicines reported to exacerbate tear secretion, e.g. thiazide diuretics, tricyclic and tetracyclic antidepressants, ß-blokers, anticholinergics, benzodiazepines, antihistamines, antihypertensives and anti-Parkinson's drugs [8, 57, 73, 74].

3.3 Mucin layer deficiency

Disturbances of the mucin layer are connected with the goblet cell deficiency, which is observed in majority forms of dry eye [8, 80]. The leading reason of xerophthalmia connected with mucins the insufficiency of vitamin A is [8, 57, 81, 82]. The lack of vitamin A is usually connected with various forms of malnutrition or chronic malabsorption. Gastroenterological diseases (e.g. coeliac disease) impair vitamin A absorption [83–85]. Conditions affecting liver impair fat metabolism and decreases absorption of this fat-soluble vitamin [86, 87]. Pancreas insufficiency (e.g. cystic fibrosis) hinders vitamin A intake by its influence on fat digestion pathway [88, 89]. Alcoholism, restrictive diets (both in eating disorders and selective, like poor balanced vegans') and low-quality food consumption are the most common reasons of malnutrition and because of that vitamin A insufficiency [90–94].

There are some problems responsible for impairment of goblet cells function. Mucous membrane pemphigoid and its subtype – ocular cicatricial pemphigoid

via recurrent inflammation destroy goblet cells and promote subepithelial fibrosis, resulting in changes ranging from xerophthalmia to conjunctival keratinization and blindness [95–99]. Stevens-Johnson Syndrome, trachoma and severe burns (both thermal and chemical) impair mucin production by decreasing the number of active goblet cells [8, 100–103].

Moreover, some medications (e.g. mucolytics, antihistamines) and preservatives influence the ocular surface and modify mucous layer [8, 57, 104].

3.4 Multilayer disturbances

Although three layers of the tear film are investigated, all of them remain in strict dependence of each other and many conditions cause disturbances of the tear film as a whole. The most common problem impairing ocular surface is progression with age; decreased tear production, tantalic problems, hormonal changes, medications and other diseases affect tear production, its' ingredients and spreading over the ocular surface [8, 57, 105, 106]. Tantalic dry eye seems to be one of the most important conditions influencing all three layers: eyelid incongruency (entropion, ectropion, lid margin irregularities, exophthalmos), epitheliopathy (e.g. corneal scars) and evaporation are the reason of tear loss. Neurological problems (both afferent and efferent part of the reflex loop) directly affect tear secretion [8, 57, 105].

Hormonal changes (androgens, estrogens, prolactin, thyroid hormone, insulin resistance/deprivation, ACTH resistance, adrenal insufficiency, multiple endocrine deficiency) influence tear stability as well [105, 106]. Meanwhile, the newest meta-analysis revealed no correlation between hormonal replacement therapy or oral contraceptives and tear film – it seems to be speculative [107, 108]. Dry eye disease due to hormonal disorders often connect both aqueous tear deficient and evaporative mechanism. Thyroid associated diseases result usually in autoimmune condition (impaired thyroid hormone activity, autoantibodies against THS receptors present in lacrimal glands, autoantibodies against thyroid hormone and/or their receptors) but the final effect of dry eye is connected also with ocular surface disturbances due to enhanced environment exposure, lid mechanical impairment (reduced lipids secretion, eyelid retraction, eye globe proptosis, impaired blinking) and therapy (thyroid hormone replacement, iodine suppression, immunomodulators specific for orbit and ocular disease, local radiotherapy and surgical procedures) [106]. In patients with diabetes mellitus the frequency of dryness varies from 15.4 to 82%. The mechanism of dry eye disease in diabetic patients is multifactorial: insulin resistance or deprivation is responsible for lacrimal gland size reduction, histological and molecular changes of it, polyneuropathy and nerve-conduction abnormalities that reduce secretion. Peripheral microvascular disease and insulin reduced input in target tissues are the other reasons of lacrimal gland and ocular surface disorders. Tear film instability and higher osmolarity are probably the result of higher glucose and protein levels in the tears and changes in the protein profile [106, 109].

In literature there are examples of dry eye disease secondary to other hormonal imbalance (e.g. ACTH-triple A syndrome, multiple endocrine deficiency) [106, 110].

Some environmental factors (e.g. pollutions, visual display terminals, temperature, humidity) promotes dry eye disease, however the pathomechanism is still discussed [111, 112]. Contact lenses wear influences lipid layer, changes the dynamics of the whole tear film and is the reason of dry eye symptoms [113–115].

There are a lot of date on the influence of medications (both topical and systemic) on the tear film. Some samples: ß-blockers used for glaucoma therapy reduce test Shirmer I and break-up time values, long term general anesthesia decrease basal tear production, antihistamines block both goblet cells and lacrimal glands, topical glaucoma therapy reduces LLT, oral mucolytics modify mucous layer, systemic

	Causes of disturbances
Lipid layer	MGD: atopic local changes, chronic blepharitis, generalized dysfunction of the sebaceous glands, chemical agents, tabacco smokers, diabetes mellitus Insufficient protein intake (bariatric patients) Androgen deficiency: aging, anti-androgen therapy, congenital impairment or absence of the androgen receptor Incomplete blinking (inadequate lipid distribution) Medicins
Aqueous layer	• Sjőgren syndrome dry eye (SSDE) (primary, without other accompanying symptoms and secondary, with other autoimmune diseases) • Non- Sjőgren syndrome dry eye (nSSDE) (senile hyposecretion, lacrimal excision, lacrimal duct obstruction, immune lacrimal gland damage, sensor or motor reflex block, scarring condition of the conjunctiva, corneal hypoesthesia as a result of CL wearing, heretical keratitis or surgical procedures) • Medicines
Mucus layer	• Insufficiency of vitamin A: malnutrition or malabsorption (gastroenterological diseases, condition affecting liver, pancreas insufficiency, alcoholism, restrictive diets, low quality food) • Destruction of the goblet cells (cicatricial conjunctival changes: e.g. pemphigoid, Stevens-Johnson syndrome, trachoma, GVHD, severe thermal and chemical burns) • Medicines
Multilayer	• Aging: decreased tear production, tantalic problems (eyelid incongruency as entropion, ectropion, eyelid irregularities, exophthalmos, epitheliopathy; e.g. corneal scars) • Hormonal changes (androgens, estrogens, prolactin, ACTH, thyroid hormone) • Neurological problems (both afferent and efferent part of the reflex loop) • Environment (pollutions, ambient temperature, humidity) • Visual display terminals • Medicines (both topical and systemic) • Preservatives

Table 4.
The main causes of tear film deficiency [7, 58–125].

antidepressants, anticholinergics or antihypertensives increase risk of dry eye problems [56, 103, 116–122]. A comprehensive review of this problem with the list of medicines and herbs has been prepared by Askeroglu et al. [123]. Analyzing influence of medicines on the ocular surface and dry eye disease we have to remember that topical used multidose artificial tears and lubricants contain preservatives. The most common Benzalkonium chloride – BAK disrupts tear stability, causes corneal and conjunctival epithelium damage and induces inflammatory changes that depends on dose and time of use. Alternative preservatives (e.g. Polyquaternium-I: Polyquad®, Polyhexamethylene biguanide: PHMB, Sodium perborate: GenAqua®, Deqest®, stabilized Oxychlorocomplex SOC: Purite®, OcuPure®, ionic-buffered solution containing zinc chloride, borate, propylate glucol and sorbitol:Sofzia) are used in some artificial tears, lubricants or glaucoma drops. Published date on the ocular performance of them generally show they induce significantly less disturbances of the ocular surface than BAK [124, 125] (**Table 4**).

4. Conclusions

The ocular surface contacts with the environment by the tear film as interface. Thus, tear production, composition, dynamics and function is so important to prevent it healthy. There are many diseases and conditions (both systemic and

local) that may affect each layer of the tear film separately or all of them together. Moreover, tear film disorders can manifest systemic diseases and, sometimes, be necessary or even be the only clue to diagnosis. The commonness of tear film problems and wide spectrum of its different background seem to require to be considered in everyday medical, not only ophthalmological, practice. Those problems should be analyzed to plan and undertake proper therapy, especially in patients with eye dryness symptoms.

Author details

Dorota Kopacz[1,2*], Łucja Niezgoda[1], Ewa Fudalej[1], Anna Nowak[1] and Piotr Maciejewicz[1,2]

1 Medical University of Warsaw, Warsaw, Poland

2 Department of Ophthalmology, Infant Jesus Teaching Hospital, Warsaw, Poland

*Address all correspondence to: dr.dk@wp.pl

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