Chapter

Etiology of Dry Eye

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Abstract

The scope of this chapter is to provide insights into the classification based on the significant factors causing dry eye. The etiological causes of dry eye have been classified broadly into two primary arms. The first arm, aqueous deficient dry eye (ADDE), illustrates malfunction of normal lacrimal secretion causing tear hyposecretion. ADDE is subdivided into Sjogren's and the non-Sjogren's syndrome. The former exclusively includes systemic autoimmune characteristics, while the latter comprises age-related disorders, genetic disorders, denervation in the lacrimal gland, and obstruction in tear secretion. The second arm, evaporative dry eye (EDE), explains the excessive loss of aqueous from the tear film despite the normal lacrimal secretion. Extrinsic EDE is with ocular surface pathology caused by vitamin A deficiency, contact lens wear, use of topical drugs with preservatives, and ocular surface diseases (allergic eye disease). The intrinsic EDE encompasses abnormalities in the meibomian lipid deficiency, low blink rate, and poor lid congruity. In brief, clinical tests to investigate the corneal epithelium integrity and the tear film have been discussed. This chapter aims to highlight the main etiologies of dry eye disease (DED) and current updates on techniques involved in diagnosing DED to help clinical practice.

Keywords: dry eye, etiology, tear film, tear hyperosmolarity, ocular surface

1. Introduction

Dry eye disease (DED) is associated with a chronic inflammatory condition of the ocular surface comprising tear hyperosmolarity and disorder of the lacrimal functional unit (LFU) [1]. LFU contains the lacrimal glands, ocular surface (cornea, conjunctiva, and meibomian glands), and the sensory and motor nerves that connect them to form an integrated system known as a "Reflex arc" [2]. LFU plays a significant role in maintaining the tear film in a regulated manner. Environmental, endocrinological, and cortical influence the functionality of LFU. Its function is to preserve the integrity of the tear film and the corneal transparency [2, 3]. There are two compartments of tears at the surface of the open eye. The first lies in the fornices and the spaces behind the lids, and the second is called the pre-ocular tears that comprise the tear menisci and the tear film. The tear film is about 3 μm thick layer [4]. The lipid layer hinders the evaporation of tear film surfaced on the top of the tear film, derived from the meibomian glands. The lacrimal gland mainly contributes to the aqueous component of the tear film lying below the surface lipid layer. The conjunctival goblet cells contribute to the mucin layer that lies over the corneal surface [5]. The mucin forms like a gel layer over the corneal surface and protects to keep up the moisture of

the normal ocular surface. These three layers of the tear film help protect the exposed ocular surface from desiccation. Lacrimal secretion is at its minimum during sleep [6]. When the eyes are open in the waking state, the lacrimal secretion is determined by the sensory stimuli to increase the tear flow rate. A functional Reflex arc is the key to controlling the tear flow and maintaining the homeostasis of tear osmolarity. The Reflex arc comprises the afferent and the efferent limb, while the former is contributed from the trigeminal innervation of the ocular surface (cornea) [7]. The trigeminal neurons synapse in the superior salivatory nucleus in the brainstem. This is the nervus intermedius of the VIIth cranial nerve, carrying the region where the efferent limb of the reflex arc arises. These parasympathetic nerve fibers synapses with the other neuronal connections, help supply to the glandular tissues, and aid in their secretion function. The reflex arc functions as a "feedback loop" [2, 3] and can be influenced by humidity, airflow, temperature, and blink rate. Damage to the afferent sensory nerves or the efferent autonomic and motor nerves will lead to dysfunction in the tear-secreting glands. This causes an alteration in the function of LFU, leading to tear film instability and ocular surface disease, mainly dry eye. Inflammation in the ocular surface accompanying chronic alteration in tear secretion due to reduced corneal sensation results in tear film instability [8]. Therefore, dysfunction of LFU has been identified to be prominent in the development of various forms of dry eye. There are two major divisions of dry eye (discussed later in this chapter): 1. Aqueous-deficient dry eye and 2. Evaporative dry eye. Both lead to tear hyperosmolarity.

1.1 Ocular surface homeostasis and hyperosmolarity

Homeostasis in the ocular surface is correlated with the tear hyperosmolarity influenced by the sensory stimulation to the lacrimal gland via the LFU. In evaporative dry eye, the lacrimal gland is healthy to stimulate secretory response and compensate for the tear volume with a rise in tear osmolarity. However, this is accountable for a high-volume dry eye with increased tear secretion in patients suffering from meibomian gland dysfunction, which causes a deficiency of the tear film lipid layer [9]. On the contrary, the aqueous-deficient dry eye with dysfunction in the lacrimal gland is characterized by tear hyperosmolarity associated with low tear volume [10]. Of note, excessive reflex stimulation of the lacrimal gland may induce cytokine responses in the gland, initiating a cascade of autoantigen expression and T-cell activation with the release of inflammatory mediators into the tears [3]. "Lacrimal exhaustion" may also be induced due to intense reflex stimulation of the lacrimal gland [11].

Hyperosmolarity is regarded as the central mechanism for various forms of dry eye as a response to reduced tear flow or increased tear evaporation. Tear film instability and thinning of the tear film with excessive aqueous evaporation are the events that influence tear hyperosmolarity. Tear hyperosmolarity stimulates a sequence of inflammatory events in the ocular surface epithelium, involving NF-kB signaling and MAP kinases pathways [12] with the secretion of inflammatory cytokines (IL-1α, IL-1β, and TNF-α) and matrix metalloproteinases (e.g., MMP9) [13]. The cytokines activate inflammatory cells at the ocular surface [14], cause apoptosis of the surface epithelium, and reduced expression of glycocalyx mucins, eventually leading to the loss of goblet cells [15]. Damage to the epithelium or apoptosis is fundamental for ocular surface staining in a dry eye. Additionally, a loss of protective barrier (glycocalyx mucins) will aid in the dye (fluorescein) entry in comparison to the normal lubricated ocular surface with an intact ocular surface barrier [10]. Goblet cell loss is a phenomenon investigated in dry eye [16, 17], demonstrated by conjunctival

biopsy and impression cytology that show reduced levels of the gel mucin MUC5AC [18]. Tear hyperosmolarity and inflammatory mediators in tear causes discomfort, especially during blinking, due to the loss of goblet cell mucin that helps maintain the ocular surface's lubrication. Ocular surface damage, mainly with the loss or damage to the epithelial glycocalyx, leads to insufficient lubrication, tear film instability, and progressive shortening of the tear film break-up time [19]. In the presence of a shorter break-up time, an increase in the level of hyperosmolarity is expected. Ocular surface damage, caused by osmotic stress and inflammatory events, will result in the reflex stimulation of the lacrimal gland. This is responsible for increasing the blink rate and increasing lacrimal tear secretion. Patients with meibomian gland dysfunction were diagnosed with the high-volume dry eye with increased tear secretion [9]. Experimental models suggest that intense reflex stimulation of the lacrimal gland may induce an inflammatory response in the gland. This will lead to a cascade of events, such as autoantigen expression in the gland, T-cell activation, and the release of inflammatory mediators into the tears [3, 20]. Reports have indicated to induce a state of "lacrimal exhaustion," which may need further evidence to test this hypothesis [21]. Tear Hyperosmolarity attained at the eye surface gives rise to a vicious cycle of events that results not only in symptoms and compensatory responses but also in ocular surface damage and mediating inflammatory responses. Eventually, it drives into a self-perpetuated disease.

1.2 The role of the environment in dry eye

Dry eye is susceptible to environmental conditions that can increase tear evaporation and osmolarity. These conditions may aggravate various forms of dry eye or trigger its onset in predisposed patients. The term environment can be broadly divided into (a) physiological variation between the individuals that include low natural blink rate [22], variations in the palpebral aperture [23], and sex hormones [24, 25]. (b) ambient conditions an individual encounters include environmental factors that increase tear evaporation, such as lower relative humidity, high wind velocity, air conditioning, air travel, or exposure to another artificial environment [26]. This influences tear hyperosmolarity induced by prolonged blink interval or with widened palpebral aperture, which is common during extended usage of a video display terminal, microscopy, reading, and the performance of challenging visual tasks, which reduce the blink rate or more extended periods with the eyes held up in gaze [27]. The other factors include the use of systemic drugs, which reduce lacrimal secretion, causing tear hyperosmolarity and may be listed as a risk factor for dry eye [28]. A correlation between activities of daily living the dry eye disease symptoms has been explored [29]. Awareness of such influences may allow preventative measures to be implemented.

1.3 The role of corneal sensitivity

A phenomenon of increased corneal sensory excitability was reported in dry patients [30]. This is expected to increase pain and compensatory lacrimal response in dry eye patients. Interestingly, in dry eye, morphological changes have been recorded via confocal microscopy that showed a reduction in the subbasal nerve plexus bundles in the cornea [31]. These results relate to observations made in several reports suggesting impaired corneal sensitivity in chronic dry eye disease [32]. With advancing dry eye disease, sensory loss at the ocular surface is evident, which reduces the sensory drive and stimulation to the lacrimal gland. Therefore, tear hyperosmolarity would increase

with reduced lacrimal secretion, eventually leading to a fall in tear volume and tear film thickness. Furthermore, a slowing of tear film lipid layer spreading [33], with an increase in tear evaporation, is observed. Overall, ocular surface changes during dry eye are negatively affected by a reduction in corneal sensitivity and a loss of sensory drive.

2. Major etiological causes of dry eye

The leading etiological causes of dry eye have been portrayed as etiopathogenic classification developed by the subcommittee presented in the National Eye Institute (NEI) industry workshop report with a current understanding of DED (**Figure 1**).

As stated earlier in the 1995 report, the term keratoconjunctivitis sicca (KCS) is regarded as synonymous with the term dry eye. As illustrated in **Figure 1**, there are two major classes of dry eye: (1) aqueous tear-deficient dry eye (ADDE) and (2) evaporative dry eye (EDE). ADDE refers to mainly the failure of lacrimal secretion, while EDE has been subdivided to differentiate the causes that are dependent on intrinsic conditions of the eyelids and ocular surface and those that arise from extrinsic influences. It is recognized that disease initiated in one significant division may coexist with or even progress to dry eye by another considerable mechanism. This is part of a vicious cycle of interactions that can enhance the severity of dry eye. Overall, consequences of dry eye include goblet cell loss, which will contribute to loss of tear film stability, ocular surface damage and evaporative water loss, and symptoms resulting from a failure of ocular surface lubrication and inflammation.

The major groups and subgroups of dry eye are described below.

2.1 Aqueous tear-deficient dry eye (tear deficient dry eye)

Dysfunction in the lacrimal gland leads to the aqueous-deficient dry eye that reduces lacrimal tear secretion and volume [34]. Tear-deficient dry eye causes tear hyperosmolarity. Reduced lacrimal secretion may be due to 1 Sjogren syndrome, 2
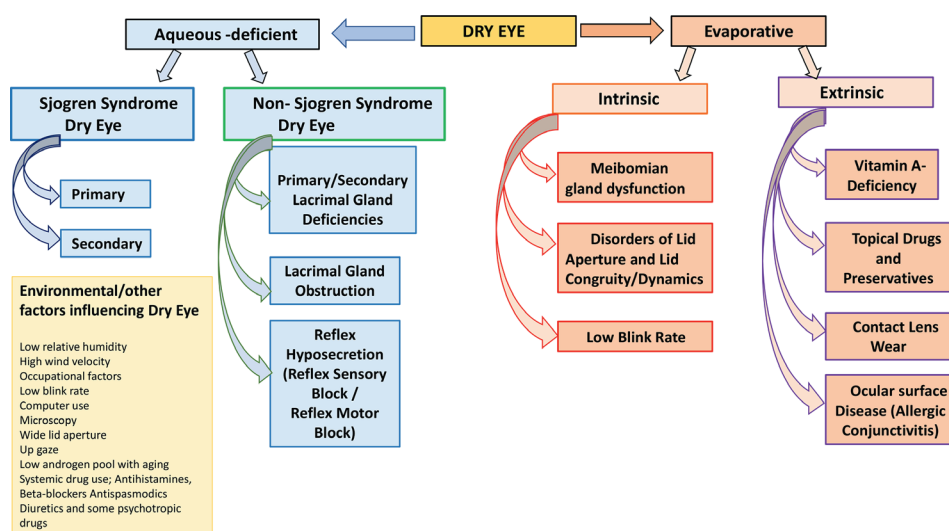

Figure 1.
Etiological classification of dry eye.

obstruction to its outflow, and 3 an intervention with the homeostatic mechanism. A reflex sensory blockade may be caused due to topical anesthesia, and efferent blockade may be due to damage in the pterygopalatine ganglion and third-order neurons [35]. Additionally, lacrimal secretion may be pharmacologically inhibited by certain systemic drugs [36]. Tear film hyperosmolarity causes an increase in osmolarity of the ocular surface epithelium and stimulates a cascade of inflammatory events involving MAP kinases and NFkB signaling pathways [12, 37] and the secretion of inflammatory cytokines (interleukin (IL)-1A; -1B; tumor necrosis factor (TNF)-A); and matrix metalloproteinases (MMP-9) [13]. During lacrimal dysfunction due to lacrimal gland infiltration and inflammation, inflammatory mediators generated in the gland may find their way into the tears and be delivered to the ocular surface. The inflammatory mediators are detected in tears and can be derived from the lacrimal gland or the ocular surface (conjunctiva and cornea). Studies have reported that the tear film lipid layer in ADDE has a delayed spreading of the lipid layer in the interblink [38, 39]. In severe ADDE, spreading may be undetectable by interferometry, suggesting significant damage to the tear film lipid layer. Delayed improper spreading of the tear film may increase an aqueous loss from the tear film. ADDE can be divided into two major subgroups, Sjogren syndrome dry eye (SSDE) and non-Sjorgen syndrome dry eye.

2.1.1 Sjogren syndrome dry eye (SSDE)

Sjogren syndrome is an exocrinopathy that involves the lacrimal and salivary glands targeted by an autoimmune process. Immune cell infiltration, mainly the activated T cells, occurs in the lacrimal and salivary glands, which causes acinar and ductular cell death. This leads to the hyposecretion of tears or saliva. The inflammatory process in the glands leads to the expression of autoantigens in the epithelium of the ocular surface [40] with the homing of tissue-specific CD4 and CD8 T-cells [41]. Th1 cells and cytokines as INF-ϒ were considered to be the main components of tissue damage, with new evidence of the major role played by Th-17 cells (T follicular (Tf), Th22, and Treg cells—the IL-17 axis) and the cytokines, especially IL-17, in the salivary and lacrimal glands [42, 43]. A neurosecretory block influences the hyposecretion of the tears due to the effects of immune cell influx and secretion of inflammatory cytokines or the presence of circulating antibodies (e.g., anti-M3 antibody) directed against muscarinic receptors within the glands [44, 45].

There are two forms of SSDE:

a. Primary SSDE consists of ADDE integrated with symptoms of dry mouth, reduced salivary secretion, and autoantibodies [46, 47].

b. Secondary SSDE consists of the features of primary SSDE along with the characteristics of an autoimmune connective disease, such as rheumatoid arthritis, systemic lupus erythematosus, Wegener's granulomatosis, primary biliary sclerosis, polyarteritis nodosa, systemic sclerosis, or mixed connective tissue disease.

It is essential to note the risk factors of SSDE, which include genetic profile [48], androgen status [49], and exposure to environmental agents. For instance, a study investigated from a mouse model of ocular HSV-1 infection showed that the lacrimal gland was affected by the immune cell influx (CD4 and CD8 T cells), causing reduced tear volume [50]. Additionally, nutritional deficiency in omega-3, Vit C, and other unsaturated fatty acids has also been reported in patients with SSDE [51]. Environmental

factors causing increased evaporative water loss from the eye may trigger inflammatory events at the ocular surface via a hyperosmolar mechanism. A defective tear film lipid layer is identified to contribute to dry eye leading to evaporation [52]. This can be correlated to high rates of meibomian gland dysfunction in SSDE patients when compared to the average population [52]. Overall, the ocular dryness in SSDE is due to hyposecretion in the lacrimal glands associated with the characteristic inflammatory changes within the gland in the presence of inflammatory mediators in tears [53].

2.1.2 Non-Sjogren syndrome dry eye

Non-Sjogren syndrome dry eye is a type of ADDE caused due to lacrimal dysfunction but not with the characteristics of systemic autoimmunity; age-related dry eye is the most common. The different types of NSSDE are briefly discussed below.

2.1.2.1 Primary lacrimal gland deficiencies

i. Age-related dry eye (ARDE): A significant age-related correlation for tear evaporation, volume, flow, and osmolarity, was reported by Mathers et al. [54]. Still, no correlation was noted by Craig and Tomlinson [55] or in other reports concerning tear turnover [56] and lipid layer [57]. With increasing age in an average population, an increase in ductal pathology has been reported that may promote lacrimal gland dysfunction by its obstructive effect [58, 59]. The ductal pathology included periductal fibrosis, interacinar fibrosis, periductal blood vessel loss, and acinar cell atrophy [58, 59]. Lymphocytic immune cell infiltrates in 70% of lacrimal glands were studied and identified as the basis of fibrosis [58]. However, it appeared to be less severe when compared to Sjogren syndrome.

ii. Congenital alacrima: Congenital alacrima is reported to be a rare cause of dry eye in youth [60]. It is also part of the autosomal recessive, triple A syndrome (Allgrove syndrome), in which congenital alacrima is accompanied by achalasia of the cardia, Addison's disease, central neurodegeneration, and autonomic dysfunction [61]. It is caused by harmful mutations in the gene encoding the protein ALADIN and is involved in RNA and protein trafficking between the nucleus and cytoplasm [62, 63].

iii. Familial dysautonomia: Familial dysautonomia (Riley Day syndrome) is an autosomal recessive disorder associated with lacrimal dysfunction. Consequences include a generalized insensitivity to pain by a marked lack of emotional and reflex tearing within a multisystem condition. This is accompanied by developmental and progressive neuronal abnormality of the lacrimal gland's cervical sympathetic and parasympathetic innervations and a defective sensory innervation of the ocular surface. This affects both small myelinated (AD) and unmyelinated (C) trigeminal neurons [64, 65]. The mutation mainly affects the gene encoding an IKB kinase-associated protein.

2.1.2.2 Secondary lacrimal gland deficiencies

Inflammatory infiltration of the lacrimal gland is known to cause dysfunction in tear secretion.

i. Sarcoidosis: Lacrimal gland infiltration by sarcoid granulomata causes dry eye [66].

ii. Lymphoma: Infiltration of the lacrimal gland by lymphomatous cells causes dry eye [67].

iii. AIDS: Dry eye may be caused by T-cell infiltration in the lacrimal gland. However, in AIDS-related dry eye, unlike SSDE, CD8 suppressor cells are predominant rather than CD4 helper cells [68].

iv. Graft versus host disease (GVHD): Dry eye is a frequently observed complication of GVHD disease. It may typically occur around six months after hematopoietic stem cell transplantation. The leading cause of this is infiltration of both CD4 and CD8 T-lymphocytes, which colocalizes with antigen-presenting fibroblasts in the periductal area of the glands leading to lacrimal gland fibrosis [69, 70].

v. Lacrimal gland ablation: Dry eye may be caused by partial or complete ablation of the palpebral and/or main lacrimal gland. However, this effect can be rescued by the accessory gland and conjunctival secretion [34]. In some species (primates), it is shown that the ablation of the main lacrimal gland may reduce basal and reflex tear secretion levels but does not lead to dry eye [71].

vi. Lacrimal gland denervation: Parasympathetic denervation of the human lacrimal gland may cause dry eye [72]. As reported in some animal model experiments, it has been shown that lacrimal gland denervation causes reduced tear flow and decreased lacrimal protein secretion associated with inflammatory changes in the gland [71].

2.1.2.3 Obstruction of the lacrimal gland ducts

Obstructing the principal, palpebral, and accessory lacrimal gland ducts lead to aqueous-deficient dry eye. Additionally, deformity in the eyelid influences uneven tear film spreading. Specific conditions are discussed below.

i. Trachoma: Trachoma comprises corneal opacity leading to blindness. It is caused by tarsal and conjunctival scarring, trichiasis, and a cicatrizing meibomian gland obstruction. A dry eye may be caused resulting from lacrimal duct obstruction, lid mal-apposition, and a deficient tear film lipid layer [73].

ii. Cicatricial pemphigoid and mucous membrane pemphigoid: This is a mucocutaneous disorder characterized by skin blistering and blistering in the mucous membranes, leading to severe conjunctival scarring. Dry eye may also be caused by an obstruction in the lacrimal gland, cicatricial MGD, and/or poor lid apposition [74, 75].

iii. Erythema multiforme: This is an acute, self-limited mucocutaneous condition usually precipitated by drugs, infection, or malignancy. Dry eye may be caused due to conjunctival scarring [76].

iv. Chemical and thermal burns: Burns that are diffuse may cause much scarring to cause dry eye [46].

2.1.2.4 Reflex hyposecretion

2.1.2.4.1 Reflex sensory block

Tear secretion in the waking state is induced by trigeminal sensory input arising from the nasolacrimal passages and the eye. When the eyes are open, an increased reflex sensory drive is stimulated from the exposed ocular surface. A depletion in the sensory movement from the ocular surface may play a role in the cause of dry eye in two routes, first, by reducing reflex-induced lacrimal tear secretion and, second, by lowering the blink rate and, thereby, increasing evaporative loss [47]. It is evident from the reports that experiment conducted on the rabbit models has shown that trigeminal denervation alters the regulation of lacrimal protein secretion [77].

i. *Contact lens wear*: Extended contact lens wear has been reported to reduce sensitivity in the cornea, and this can happen in individuals who wear hard and extended-wear contact lenses. Experimental evidence from the rabbit model showed trigeminal denervation to increase tear film osmolarity and cause morphological changes in the ocular surface characteristic of dry eye [78]. When studies were conducted on patients wearing contact lenses, elevated tear osmolarity levels were recorded, leading to dry eye symptoms [79, 80]. Therefore, this has promoted to advance of LASIK surgery in patients. However, some patients' neurotrophic deficiency or neuralgic disorder was reported post-LASIK surgery [30, 81].

ii. *Diabetes:* It is evident from the research reports that diabetes mellitus has been studied as a risk factor for dry eye [82–84]. The prevalence of dry eye symptoms was evident in 18.1% of diabetics compared to 14.1% of non-diabetics in the Beaver Dam study [83, 84]. Interestingly, reports also suggested the frequency of use of ocular lubricants in people with diabetes (20.6%) when compared to non-diabetics (13.8%) [82]. This study also investigated a correlation between abnormal glycemic levels (as indicated by serum HbA1C) and frequency of ocular lubricant use. In diabetic patients, neuropathic disorders could be hypothesized to influence tear volume levels/tear secretion from the lacrimal glands. Goebbels et al. reported lower levels of reflex tears tested by the Schirmer's test in people with diabetes with no change in the basal tear flow or the tear film break-up time tested by a fluorophotometer. A study found a reduction in reflex tearing (Schirmer test) in insulin-dependent diabetics but no difference in tear film break-up time or basal tear flow by fluorophotometry [85].

iii. *Neurotrophic keratitis*: Neurotrophic keratitis is the hallmark of the herpes ocular infection, mainly involving damage to the sensory nerves in the cornea, bulbar and palpebral conjunctiva. Sensory denervation in the ocular surface will lead to characteristic features of dry eye such as tear instability, loss of mucin-secreting goblet cells, the appearance of diffuse punctate keratitis, and occurrence of ulcerative keratitis, which may lead to perforation [86, 87]. Damage to the sensory nerves results in a reduced blink rate and lacrimal secretion of tears [88]. Furthermore, it has been proposed that sensory loss in the ocular surface will lead to the loss of trophic support with the deficiency in the expression of nerve growth factor and substance P [89–92].

2.1.2.4.2 Reflex motor block

The VII cranial nerve nervus intermedius carries postganglionic, parasympathetic nerve fibers (of pterygopalatine ganglion origin) to the lacrimal gland. Significant damage to the VII cranial nerve leads to dry eye due to loss of lacrimal secretomotor function and lacrimal hyposecretion. Additionally, incomplete lid closure with multiple neuromatosis has also been reported as a characteristic of dry eye [93]. Several studies have reported a correlation between dry eye and reduced lacrimal tear secretion with systemic drug agents such as beta-blockers, antispasmodics, diuretics, and antihistamines [84]. On the contrary, no relationship was found with calcium channel blockers or cholesterol-lowering drugs [84].

2.2 Evaporative dry eye

Evaporative dry eye is caused due to increased water loss (evaporation) from the tear film in the presence of normal lacrimal secretory function. The tear film lipid layer is the main barrier to evaporation from the ocular surface. The loss of the tear film lipid layer due to meibomian gland dysfunction (MGD) is the leading cause of evaporative dry eye. Nevertheless, evaporation may also be increased by a prolonged blink interval or a widened palpebral aperture [9]. Of note, tear hyperosmolarity is also observed as an elevated characteristic feature due to evaporative water loss from the tear film. Evaporative dry eye can be distinguished further concerning the intrinsic disease affecting lid structures or dynamics or extrinsic, where the ocular surface disease occurs due to various irrelevant exposure such as topical drugs, contact lenses, and others (discussed in Section 2.2.2).

2.2.1 Intrinsic causes

2.2.1.1 Meibomian gland dysfunction (MGD)

MGD is a condition with meibomian gland dysfunction and posterior blepharitis, the leading and common cause of evaporative dry eye [94]. MGD is associated with the obstruction in the gland hindering lipid secretion. Other observations are noted in experimental models, including glandular cyst formation and meibomian duct keratinization [95, 96]. MGD can be distinguished as simple or cicatricial, primary or secondary. In simple MGD, the orifices of the gland remain located within the eyelid skin (anterior to the mucocutaneous junction). In cicatricial MGD, the orifices of the duct are drawn posteriorly onto the tarsal mucosa and the lid. This makes it incapable of delivering lipids to the tear film. Criteria for diagnosis are based on morphologic features of the gland acini and duct orifices. Methods are developed to grade the degree of MGD [97], measure the degree of gland dropout (meibography) [98, 99], and measure the levels of lipid in the lid margin reservoir (meibometry) [100]. MGD is correlated with the deficiency in the tear film lipid layer leading to an increase in tear evaporation with a higher risk of the occurrence of evaporative dry eye. An exciting finding showed the importance of meibomian lipid composition and its effect on tear film lipid layer stability. Variations in meibomian lipid composition were investigated in different individuals; for instance, one group of subjects had low levels of cholesterol esters and esters of unsaturated fatty acids, while the other group had high levels of these fractions [101]. Intriguingly, it was studied that the eyelid commensals (coagulase-negative staphylococci [CoNS], Propionibacterium acnes, and S aureus) play a role in releasing

esterases, lipases fatty acids, mono- and diglycerides into the tear film [102]. The study also showed that the subjects who had a high commensal load on the eyelid margin had meibomian lipid composition rich in cholesterol when compared to the issues with low levels of cholesterol in the meibomian lipid [103]. Therefore, microbial load on the lid margin may influence the development of blepharitis.

2.2.1.2 Disorders of lid aperture and lid/globe congruity or dynamics

An increase in palpebral fissure width exposes the tear film to greater evaporation with a risk of desiccation in the ocular surface and tear hyperosmolarity [19, 104]. Desiccation of the ocular surface occurs due to poor lid apposition or lid deformity, leading to improper tear film resurfacing [19]. In Graves' disease, the effect of proptosis on exposure is compounded by lid retraction, incomplete blinking, or lid closure, by restriction of eye movements, which plays a part in tear spreading [105]. Increased ocular surface exposure and evaporation also occur in up gaze [106]. Desiccating stress in the ocular surface may also occur in the workplace through activities such as snooker, where, while aiming, the head is inclined downward, and the eyes are in the extreme up gaze [107].

2.2.1.3 Low blink rate

A complete blinking is essential to replenish the tear film by evenly distributing the aqueous tears (lacrimal glands) and lipids (from meibomian glands) over the ocular surface. Aqueous tears evaporate from the tear film during the interval between each blink. Hence, reduced or low blinking will result in dryness of the ocular surface, leading to increased evaporative loss and dry eye.

Ocular surface desiccation may be due to a reduced blink rate, which increases the blink interval time and extends the period for tear evaporation before the next blink [108, 109]. Reduced blink rate may occur during tasks involving increased concentration, especially while working at video terminals [27], with video games, at microscopes, and when the eyes are in a downgaze, as in reading. This phenomenon may also occur in the extrapyramidal disorder Parkinson's disease (PD) due to a reduction in the dopaminergic neurons of the substantia nigra [110]. Additionally, reduced reflex tearing in PD has been associated with autonomic dysfunction, considering the presence of sympathetic and peripheral parasympathetic ganglia and Lewy bodies in the substantia nigra [111]. Other contributing factors in PD include impaired meibomian oil delivery, decreased reflex tearing due to autonomic dysfunction, and the effects of androgen deficiency on the lacrimal and meibomian glands [112]. Overall, it can be summarized from these studies that there are multiple causes of dry eye in PD.

Of note, a common extrinsic risk factor for dry eye in today's world is increased digital screen time, for example, smartphone, tablet, laptop, and computer use. Studies have reported a relationship between digital screen use and dry eye, affecting the blinking dynamics and leading to ocular dryness [113]. Furthermore, a relationship between increased digital screen use and ocular surface metrics involving tear volume and tear-break-up time status has been studied, affecting the aqueous component of the tear film [114]. Blink rates during reading tasks on digital screens have been found to reduce compared to rest conditions [27, 115]. Intriguingly, reading hard-copy material also decreases the blink rate like reading on a digital screen [116, 117]. A resurgence in digital screen use during the COVID-19 pandemic led to an increased risk factor for DED in the individuals staying home with an incentive to learn, work, and socialize remotely [118].

Digital screen use is part of everyday life and is a risk factor for DED. A valid explanation to relate digital screen use and DED is the reduced blink rate and increased percentage of incomplete blinks during the digital screen. This may lead to ocular surface dryness, eventually leading to the development of DED with chronic use of the digital screen for extended periods. Hence, the prevention of DED may involve the following:

i. Deliberately blinking the eyes.

ii. Allowing natural blinking of the eyes.

iii. Incorporating environmental modifications aimed at reducing tear evaporation from the ocular surface and compensating for tear film instability.

2.2.2 Extrinsic causes

A disease of the ocular surface disorder may lead to poor surface wetting, early tear film break-up, tear hyperosmolarity, and eventually dry eye conditions. Extrinsic causes include mainly vitamin A deficiency and the effects of extensively applied topical anesthetics and preservatives. Additionally, contact lenses may be responsible for an increased risk of dry eye.

2.2.2.1 Vitamin A deficiency

Deficiency in vitamin A may cause dry eye (xerophthalmia) through a decrease in several functional conjunctival goblet cells with reduced expression of glycocalyx mucins [119]. Vitamin A is reported to be essential for both the development of goblet cells in mucous membranes and the presentation of glycocalyx mucins [119, 120]. In patients with xerophthalmia, lacrimal acinar damage is diagnosed that may have a lacrimal, aqueous tear-deficient dry eye featured with unstable tear film [121]. Vitamin A is found to be crucial for inducing mucin gene expression, mucin production, and the maintenance of mucin [122, 123]. Retinoids have been shown to play a role in regulating mucin gene expression *In-vivo*. The reports have indicated the importance of vitamin A via studies conducted in vitamin A-deficient humans and rat models. The study reported reduced conjunctival goblet cells with keratinization in the conjunctival epithelium [124]. Therefore, vitamin A deficiency is known to cause alteration in mucin production by the ocular epithelium leading to dry eye conditions.

2.2.2.2 Topical drugs and preservatives

Topical drug components can induce a toxic and inflammatory response from the ocular surface. Topical drug (eye drop) formulations with preservatives are the most common offenders, such as benzalkonium chloride (BAC). Preservative components in the eye drop cause ocular surface epithelial cell damage leading to punctate epithelial keratitis, which interferes with the tear film stability and ocular surface lubrication (surface wettability). The effects of preservative, especially BAC, in the eye drops is a significant cause of dry eye symptoms in glaucoma patients [125]. This condition was rescued by using preservative-free eye drops [125]. Using eye drops with preservatives on a long-term basis must be avoided. The use of topical anesthesia causes ocular surface drying. It reduces lacrimal secretion by lowering the sensory

drive to the lacrimal gland [126] and also reduces the blink rate. Chronic use of topical anesthetics may cause neurotrophic keratitis-inducing corneal perforation [127, 128].

2.2.2.3 Contact lens wear

Contact lens wear is prominent in the developed world. There were 35 million wearers cited in the USA in the year 2000 [129]. Therefore, it is essential to study the causes of contact lens-related symptoms and intolerance experienced in the wearers. The main reason for contact lens intolerance is dryness and discomfort in the eye [130, 131]. Long-term use of contact lens wear may induce corneal epithelial changes [132] and the expression of inflammatory surface markers (HLA-DR and ICAM-1) [133]. Several studies have indicated its effect on conjunctival goblet cell density [134] and mucin expression [133, 135]. Women report dry eye symptoms more frequently than men [80]. Dry eye symptoms in contact lens wearers are associated with a higher tear osmolarity [80]. Poor lens wettability may also play a role in the increased evaporation rate.

2.2.2.4 Ocular surface disease

Reports have indicated that chronic ocular surface disease causes tear film instability with dry eye symptoms. Allergic eye disease will provide an excellent example to discuss the phenomenon of dry eye [136].

Several forms of allergic conjunctivitis can be listed as follows: (a) seasonal allergic conjunctivitis, (b) vernal keratoconjunctivitis, and (c) atopic keratoconjunctivitis. A common mechanism that occurs during allergic conjunctivitis is the exposure to antigens inducing the release of inflammatory cytokines via degranulation of IgE-primed mast cells. A Th2 response is activated first in the conjunctiva and later in the corneal epithelium. During this process, a loss of surface membrane mucins is observed with damage to the conjunctival and corneal epithelium [137]. Damage to the ocular surface with the release of inflammatory mediators will lead to allergic symptoms and reflex stimulation of the lacrimal gland. Inflammatory changes are observed in the case of vernal keratoconjunctivitis and atopic keratoconjunctivitis. Corneal surface irregularities (punctate epithelial keratitis) and conjunctival goblet cell defects can lead to tear film instability and, eventually, to dry eye symptoms in allergic eye disease. This condition may be augmented during meibomian gland dysfunction, intensifying the ocular surface drying [138]. In atopic keratoconjunctivitis, lid apposition and tear film spreading are interfered with, thus, exacerbating the dry eye.

3. Brief overview of novel diagnostic technologies for dry eye

There are several newer diagnostic techniques for dry eye. There will be a few commonly used techniques that will be highlighted in this chapter.

i. Tear osmolarity: tear hyperosmolarity is one of the major hallmarks of dry eye. A device named "Tearlab" is commercially available to measure the osmolarity of tears. A tear collection strip is designed by the Tearlab so that the capillary action can collect along the Tearlab strip. The Tearlab strip can then be inserted into the instrument to measure tear osmolarity. This test's sensitivity was better compared to traditional techniques to test dry eye, especially in mild to moderate

cases. Nevertheless, it is recommended to test the tear film break-up time in severe dry eye cases.

ii. Tear film interferometry: this technique uses infrared light interference patterns to yield a tear lipid layer image. More advanced technology is available to measure the thickness of the tear lipid layer and the tear film break-up time via inbuilt software. It will benefit the patients undergoing tests using fluorescein [139, 140].

iii. Meibography: this technique is used for imaging meibomian glands via transillumination or infrared devices. However, in patients with atrophied meibomian glands, a direct clinical identification such as notching in the eyelid will be more promiscuous than using meibography [141].

4. Conclusion

This chapter has provided insights into factors associated with dry eye disease. They have been distinguished into their primary forms, aqueous deficient and evaporative dry eye. Ocular surface abnormalities and tear hyperosmolarity are both equally essential in the mechanism of dry eye. However, water loss is the common etiological factor in both forms of dry eye disease. Etiological triggers and causes outlined in this chapter form the basis for framing diagnostic and therapeutic approaches. It is essential to consider a standardized approach for diagnosing dry eye. A standard testing regimen will be good to practice that includes tests for tear film break-up time (TBUT), Schirmer test, and corneal staining status with fluorescein. More advanced testing can lead to successful treatment strategies.

Conflict of interest

The author declares no conflict of interest.

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