

Aging and dry eye disease

Meiling Xie¹, Ruihan Yang¹, Jian Zhu², Jian Sima¹ (✉)

¹Laboratory of Aging Neuroscience and Neuropharmacology, School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing 210009, China

²Department of Psychology, Eastern Illinois University, Charleston, IL 61920, USA

Received: 22 January 2024 | Revised: 24 February 2024 | Accepted: 29 February 2024

ABSTRACT

Dry eye disease (DED) is an eye condition that primarily affects up to 30% of adults aged 50 years and older, impacting visual function and quality of life. The prevalence of the condition increases with age. Common symptoms of dry eye include dry eyes, redness, a sensation of having a foreign object in the eye, eye pain, sensitivity to light, increased eye discharge, eye itching, and visual fatigue. In this paper, we systematically review the primary pathological mechanisms of dry eye, the impact of aging on dry eye, and current strategies for clinical treatment.

KEYWORDS

aging, dry eye disease (DED), meibomian gland, lacrimal gland

1 Introduction

Tears are essential for maintaining the health of the ocular surface and normal vision. Several internal and external factors can have a negative impact on the composition, integrity, and stability of the tear film, leading to dry eye disease (DED). It is considered one of the most common eye conditions that prompt patients to seek eye care. Although DED may be asymptomatic, symptomatic patients often report a gritty or foreign body sensation, discomfort, dryness, photophobia, irritation, burning, stinging, pain, and blurred vision in the eye. The stages of DED can range from mild, temporary eye discomfort to chronic, severe pain with deteriorating visual function. It imposes a significant burden on patients and society in terms of economic and medical resource utilization and quality of life [1–11]. TFOS DEWS II 2017 [12] defines DED as a multifactorial condition characterized by the loss of homeostasis *in vivo*. This involves tear film instability and hyperosmolarity, ocular surface inflammation and injury, and neurosensory abnormalities, all of which contribute to the vicious cycle of DED. The Asian Dry Eye Society has proposed an alternative definition: "Dry eye is a multifactorial disease characterized by instability of the tear film, which can lead to a variety of symptoms and/or visual impairment, often accompanied by damage to the ocular surface" [13]. There are two types of dry eye: aqueous deficiency and evaporative. The former is due to decreased tear production from the lacrimal gland, while the latter is

mainly caused by the meibomian gland dysfunction (MGD). Evaporative dry eye has been shown to have a strong positive correlation with aging [14]. In fact, aging is one of the primary risk factors for dry eye [15]. The prevalence of DED and its associated morbidity is expected to increase as the elderly population grows [16]. The Epidemiology Subcommittee of the Dry Eye Workshop (DEWS) conducted a meta-analysis, which showed that the overall prevalence of the combination of signs and symptoms ranged from 8.7% to 30.1% [17]. Studies show that 14.4% of the population over the age of 50 suffers from dry eye, and indicate that it is particularly prevalent among women [18]. Therefore, this review will focus on the impact of aging on dry eye research and the corresponding treatment strategies.

2 Pathological mechanism of DED

2.1 Inflammation

Ocular surface and lacrimal gland inflammation are the primary causative factors of DED. Ocular surface stress, including environmental factors, infections, endogenous stress, antigens, and genetic factors, has been postulated as the pathogenic trigger mechanism. Studies have shown that patients with DED can detect a significant infiltration of lymphocytes in the ocular surface and lacrimal gland tissues. This is accompanied by a decrease in lactoferrin secretion and an increase in cellular inflammatory factors, which further

exacerbates the inflammation. Ocular surface inflammation is both the primary cause and the subsequent result of DED [19]. The initiation and resolution of inflammation on the surface of the eye, when the body is exposed to external stimuli or when homeostasis is imbalanced, is typically controlled by immunoregulatory processes. A sustained inflammatory response will enhance the activity of multipotent adult progenitor cells (mAPCs), as well as the production and recruitment of CD4⁺ Th cells on the ocular surface. When immune regulation is inadequate to eliminate inflammation, effector T cell activity will become dysregulated, primarily through increased release of pro-inflammatory cytokines, leading to further inflammation and injury. New inflammation and injury then reinitiate the innate immune response, creating a vicious cycle [20]. Throughout the inflammatory response, immune cells release pro-inflammatory cytokines and chemokines, which recruit more immune cells and ultimately lead to a vicious cycle of

inflammation (Fig. 1). Current studies on inflammatory mediators associated with DED include IL-1 α , IL-1 β , IL-1R, IL-2, IL-4, IL-6, CCR2, CCR6, CCR7, CX3CL1, CXCL9, ICAM-1, IFN- γ , MMP-1, MMP-3, MMP-9, TNF- α [21].

Throughout the inflammatory response, immune cells release pro-inflammatory cytokines and chemokines, which recruit more immune cells and ultimately lead to a vicious cycle of inflammation.

The signaling pathway that triggers the inflammatory cascade in cells on the ocular surface is shown in Fig. 2. The signals are detected by cell surface receptors that can detect various stimuli such as pathogen-associated molecular pattern (PAMP), danger-associated molecular pattern (DAMP), or reactive oxygen species (ROS), which initiate a pathway of downstream effects that activate nuclear factor- κ B (NF- κ B) or other transcription factors [22–25]. NF- κ B controls the transcription of a number of genes that are involved in inflammatory responses, including proinflammatory

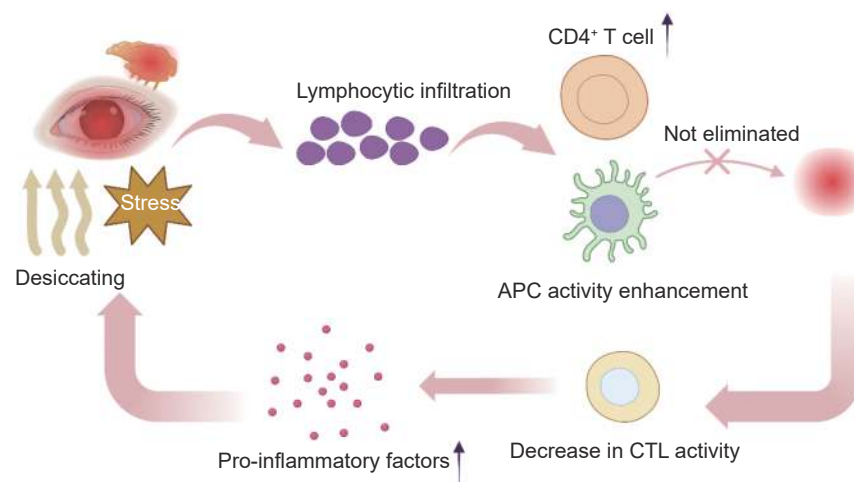


Figure 1 The vicious cycle of inflammation in dry eye.

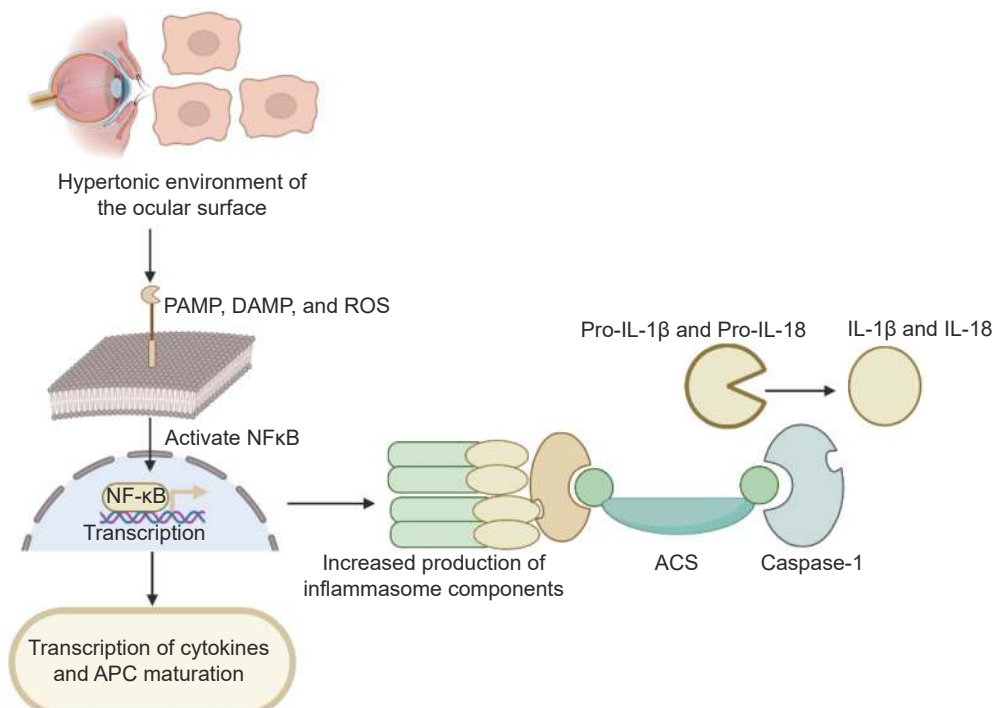


Figure 2 The signaling pathway that triggers the inflammatory cascade in cells on the ocular surface.

cytokines. This pathway further promotes APC maturation and initiates the inflammatory cascade.

NF- κ B also regulates the transcription of inflammatory vesicle components in response to extracellular stimuli, such as high osmolarity. Activation of the inflammasome pathway is thought to be a key initiating stage of epithelial inflammation [26]. Essentially, inflammasomes are multiprotein structures that assemble in the cytoplasm of epithelial cells in response to extracellular signals. Once assembly is activated, the central protein (NLRP3) recruits the apoptotic speck-like protein (ASC) to the junction. The ASC is activated and cleaves procaspase to caspase-1. The active caspase-1 then cleaves the pro-inflammatory cytokines prointerleukin-1 β and prointerleukin-18 to their active forms, IL-1 β and IL-18. Inflammasome activation also leads to cell death through plasma membrane rupture, followed by the release of intracellular components that release active cytokines and initiate an immune response.

Inflammasomes are molecular platforms, assembled from eight proteins – these vary with the specific inflammasome type, but the central protein is always a member of the protein family NLRP (NOD-, LRR-, and pyrin domain-containing protein). Studies suggest NLRP3 is the key inflammasome protein in DED, via the ROS-NLRP3-IL-1 β signaling axis [26–29], although NLRP6 inflammasomes have also been observed in models of DED [26].

Throughout the inflammatory response, the NF- κ B pathway is activated, resulting in increased transcription of pro-inflammatory factors, and the NF- κ B pathway leads to the assembly of inflammatory vesicles, which further activates ACS and caspase-1.

2.2 Hyperosmolarity

Tear hyperosmolarity (THO) is common to all subtypes of DED and is considered a central factor driving the pathophysiology of DED [30]. THO causes morphological changes, such as apoptosis in the conjunctiva and cornea, and triggers an inflammatory cascade response that leads to additional cell death [31]. The presence of THO alone is sufficient to disrupt neuroimmune homeostasis in the mouse ocular surface, leading to many subclinical cases of DED. THO activates the NF- κ B signaling pathway in the conjunctival epithelium, reduces the recruitment and maturation of dendritic cells, and activates memory T cells in the ocular lymph nodes (Fig. 3). Furthermore, THO reduces the density of nerve endings in the corneal epithelium and

makes the ocular surface more sensitive to hyperosmolarity. Overall, THO appears to be a key initiating factor in the development of DED [32].

THO activates the NF- κ B signaling pathway in the conjunctival epithelium, reduces the recruitment and maturation of dendritic cells, and activates memory T cells in the ocular lymph nodes.

2.3 Meibomian gland dysfunction

The meibomian glands are sebaceous glands with a tubular-vesicular structure and a fully secretory function. They are located in the upper and lower eyelid margins. The meibomian glands secrete meibum, which is composed of polar lipids (phospholipids) and nonpolar lipids (cholesterol, cholesteryl esters). Meibum is delivered to the ocular surface where it coats the aqueous layer and provides tear film stability and protects against microbial agents and organic matter [33]. Several risk factors for MGD include aging, oxidative stress, androgen depletion, changes in the microbiome, and wearing contact lenses.

MGD is the most common cause of evaporative DED. MGD is characterized by obstruction of the terminal ducts and/or changes in the quality or quantity of meibomian gland secretion, which is a component of the lipid layer of the tear film [12]. Displacement, obstruction, and/or inflammation of the lacrimal gland can result in the accumulation of tears within the gland and the growth of bacteria and mites, including staphylococci. Bacterial growth increases the production of lipase and esterase enzymes, which degrade lipids, leading to an increase in the viscosity of tear fluid and a decrease in its secretion on the surface of the tear film. A tear film deficient in lipids promotes increased tear evaporation, hyperosmolarity, and inflammation. This leads to the subsequent keratinization of the lacrimal gland orifice, which further obstructs and atrophies the lacrimal gland, contributing to the development of DED [34]. It is the changes in the lacrimal gland that connect the two vicious cycles of MGD and DED (Fig. 4). The changes in the lacrimal gland connect the two vicious cycles of MGD and DED (Fig. 4). The absence of normal meibomian glands reduces the lipid content of the tear film, initiating a vicious cycle in DED. The reduced lipid content leads to increased tear evaporation, hyperosmolarity, and inflammation, further exacerbating evaporative dry eye.

In a cross-sectional study involving 177 subjects aged 21–93 years, a significant association between abnormalities in the

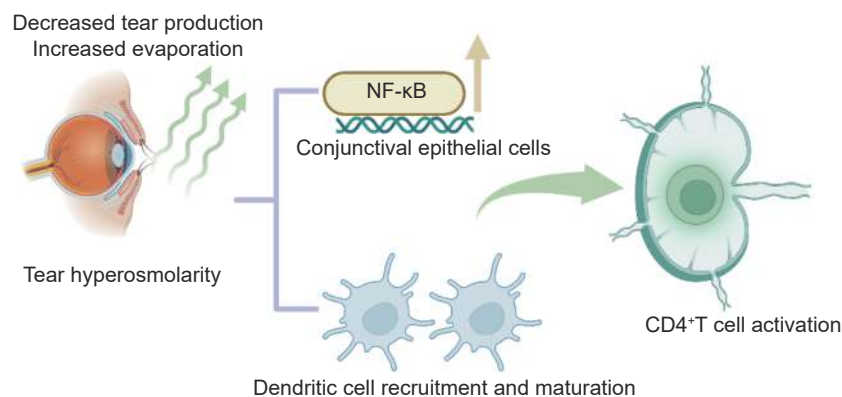


Figure 3 Tear hyperosmolarity in the pathological mechanism of dry eye.

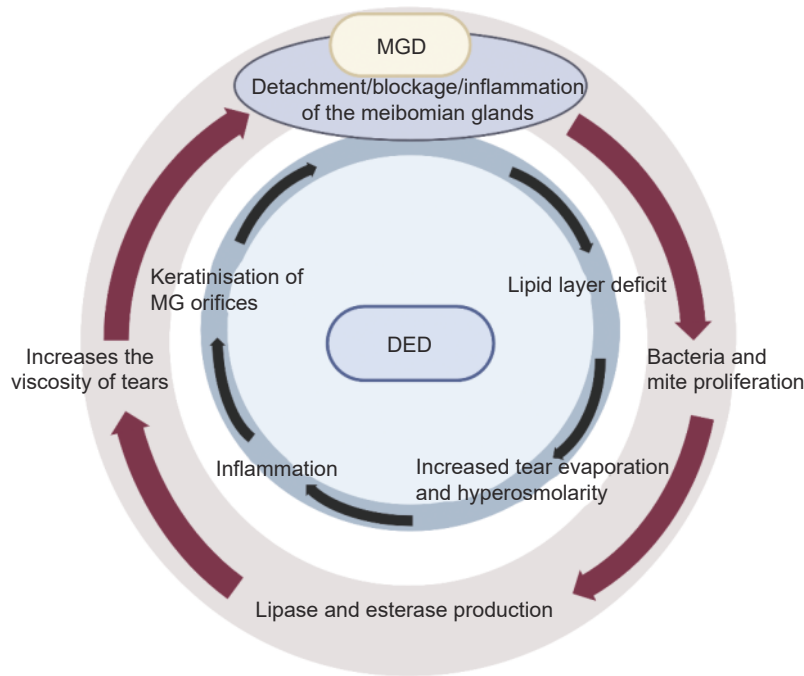


Figure 4 Importance of meibomian gland dysfunction in the vicious circle of the pathology of DED.

lid margin or meibomian glands and aging is observed [14]. Another cross-sectional study of 80 subjects aged 5–87 years found that lid margin vascularity, cutaneous hyperkeratinization and meibomian gland orifice narrowing increased with age [35]. The number of active meibomian glands also decrease by half from 20 to 80 years [36] and gland dropout is visible at old age [37]. Histology of 83 human meibomian gland samples from 17 to 87 years at autopsy reveals acini atrophy, cystic dilatation of acini and/or ducts and basement membrane thickening of acini [38]. In one report, older mice (12 and 24 months) exhibited less lipid content and atrophy of vesicular tissue compared to younger mice (2 and 6 months) [39].

Changes in the lacrimal gland connect the two vicious cycles of MGD and DED.

Sexual or gender diversity is a key variable that affects the functioning of every organism in the biological world. Ocular surface physiology is no exception. It is a well-established fact that women are more likely to develop DED than men [40]. The Women's Health Study, a large health survey conducted in North America, reported a prevalence of DED as high as 9.5% among women over the age of 75 [41]. The same research group assessed the prevalence of DED in men using a similar methodology, and showed that the prevalence of DED was 70% higher in women than in men in the age group of 50 years and older [42]. The prevalence of DED in women was also found to be higher than in men in the age group of 50 years and older. Of the 1174 Australian participants who were examined for dry eye and completed the dry eye questionnaire, and women had a higher frequency of dry eye symptoms [43]. Next, we will discuss the unique effects of sex hormones on ocular surface structure.

2.3.1 Androgens and meibomian gland dysfunction

Androgens promote lipid synthesizing activity in sebaceous gland cells and leptomeningeal cells. Androgen receptors are expressed in both sebaceous gland cells and leptomeningeal

cells [44, 45]. Androgens regulate the expression of leptomeningeal genes and lipid production [46]. In particular, androgens stimulate genes in the lipid synthesis pathway of the mouse leptomeningeal glands [47]. One of these genes is the sterol regulatory element-binding protein (SREBP), which is the most important transcription factor known to be involved in the process of lipogenesis [48]. Scd-1 is an important enzyme in fatty acid metabolism, and sebaceous glands and sebaceous glands in mice deficient in Scd-1 are severely atrophied [49]. This suggests that androgens promote genes that are critical for normal blepharoplasts. Thus, age-related declines in androgens [50, 51] may lead to impaired lipid synthesis by the meibomian gland cells, which may lead to senile blepharoconjunctivitis.

2.3.2 Estrogen and meibomian gland dysfunction

Estrogen and progesterone receptors are present in a wide variety of ocular surface structures, including the cornea, conjunctiva, meibomian glands and lacrimal glands, as well as many ocular surface structures [52, 53]. As such, it regulates key cellular events on the ocular surface. In contrast to androgens, estrogens appear to have antagonistic effects on the physiology of the meibomian glands. In animal experiments, 17 β -estradiol stimulates genes involved in the catabolism of lipids and fatty acids and downregulates genes involved in lipid synthesis [54]. Injection of estrogen leads to sebaceous gland atrophy, decreased activity, and reduced lipid synthesis in humans and many other species [55]. The loss of androgen trophic support for the meibomian gland is more critical to the worsening of tear film instability and other DED symptoms in older women than the reduction in estrogen support [56].

The mechanism of the age-related increase in MGD is not known. In fact, as discussed above, very few studies have been conducted on MGD in the context of aging at the mechanistic level. Previous studies have shown that age-related MGD appears to be primarily caused by a decrease in the number of

differentiated lacrimal gland cells [57]. PPAR- γ (peroxisome proliferator-activated receptor) is a key regulator of lacrimal gland cell differentiation and function. The transition of PPAR- γ from cytoplasmic to nuclear localization during aging is a significant event in the development of MGD [39]. Furthermore, the buildup of reactive oxygen species as individuals age may contribute to the development of MGD [58]. These mechanisms may underlie MGD in the elderly population.

2.4 Neurosensory abnormalities

Some DED patients show little or no ocular surface findings but report major ocular pain or ocular dysesthesia. These patients are typically diagnosed as neuropathic DED and may demonstrate corneal nerve abnormalities and altered corneal sensitivity [59]. This fact was acknowledged by the updated DEWS II definition for DED that includes “neurosensory abnormalities” as a pathophysiological event [12].

Tear hyperosmolality itself may lead to a reduction of intraepithelial corneal nerves and endings [60]. In a mouse model of chronic DED, the reduction in tear production and the development of corneal inflammation is accompanied by a reduction in intraepithelial corneal nerve endings. Studies have shown that corneal sensitivity and nerve density decrease with age in mice [61]. The cornea is extensively innervated by trigeminal ganglion cold thermoreceptor neurons that express transient receptor potential melastatin 8 (TRPM8). These neurons respond to cooling, hyperosmolality, and wetting of the corneal surface. TRPM8 was significantly elevated in the ocular branch of the trigeminal ganglion in a mouse model of severe dry eye associated with corneal cold hypersensitivity [62]. The dysregulated balance between TRPM8-expressing endings ultimately determines the changes in tear quality and quantity observed in elderly patients with DED, as well as the appearance of the accompanying unpleasant dryness [63].

3 The effects of aging on dry eye

3.1 Lacrimal gland malfunction in aging

The incidence of dry eye increases with age, and it is estimated that nearly 15% of people over 65 years old suffer from dry eye [64]. As individuals age, the typical tissue structure of the human lacrimal gland undergoes changes, including lacrimal gland lobular fibrosis, lobular atrophy, diffuse fibrosis, diffuse atrophy, periductal fibrosis, and lymphocytic infiltration, along with elevated levels of IL-1 β and TNF- α protein expression [65]. Periductal fibrosis, interlobular expansion, and interlobular duct hyperplasia were not observed in glands from 3-, 8-, or 12-month-old mice, but these tissue changes were observed in glands from 24- and 32-month-old animals [66].

Lipofuscin-like inclusions are part of a group of age-related pigments that are composed of polymeric polymers resulting from the oxidation of lipids and proteins [67]. These inclusions accumulate in the lysosomes of post-mitotic cells over time [68]. No accumulation of lipofuscin was observed in 3-month-old animals. Lipofuscin-like inclusion bodies appeared in the cytoplasm of the glandular vesicle cells of animals aged 8–12 months. As the animals aged (24 and 32 months), large cytoplasmic granules of lipofuscin-like

inclusion bodies appeared in many glandular vesicle cells, in contrast to the glands of young animals. This further suggests a strong correlation between aging and the accumulation of lipofuscin-like inclusion bodies in the lacrimal gland [66].

Chronic inflammation can be observed in the aging lacrimal glands of various mammals, including humans [69]. Experimental studies have found that mast cells in the lacrimal glands of 3-month-old mice are restricted to the interlobular connective tissue and are positioned around blood vessels. Mast cells were observed infiltrating the interlobular space in the glands of animals aged 8 to 12 months. The presence of degranulated mast cells was also observed in 12-month-old mice. An increased number of mast cells were observed in the glands of 24- and 32-month-old mice. It was further demonstrated that there is a strong correlation between aging and the infiltration of mast cells in the lacrimal gland [66].

3.2 MGD in aging

Age-related changes in the meibomian glands have been studied in humans and mice [70, 71]. Structural changes in the human meibomian glands involve a decrease in gland density and diameter, while rates of gland detachment and obstruction increase with age [71]. These changes were also observed in healthy mice aged 2–24 months, showing a decrease in alveolar tissue with age [39]. In both humans and mice, the number of Ki67-positive cells decreases with age and is significantly negatively correlated with increasing age [71]. Age-related changes in human and mouse sebaceous glands also affect the expression of peroxisome proliferator-activated receptor (PPAR) γ in meiotic cells [72]. Nuclear staining for PPAR γ was similar in meiotic cells between young and old mice, but the distribution of PPAR γ staining in the cytoplasm was observed only in young mice [71]. Overall, these findings suggest that the aging process of the meibomian glands leads to MGD, resulting in tear film instability that may contribute to evaporative dry eye.

3.3 Ocular surface inflammation in aging

In humans and mice, fluorescein corneal and conjunctival staining increases with age, indicating greater corneal irregularity and permeability, and consequently reduced epithelial barrier function [73]. The number of cupped cells decreases with age in mice and humans [74]. The structure of cupped cells changes with age, especially in mice [75], but such changes are not observed in humans as they age [76]. Furthermore, research has shown that corneal sensitivity and nerve density decrease with age in mice [61]. The infiltration of antigen-presenting cells on the mouse ocular surface also significantly increases with age [77]. With advancing age, there is an increase in the infiltration of CD4 $^{+}$ T cells in the conjunctiva of both humans and mice, while the infiltration of CD8 $^{+}$ T cells remains unchanged. This led to a significant increase in the CD4/CD8 ratio. In addition, the expression of Th1 and Th17-related cytokines (such as IFN- γ and IL-17) increased with age in the mouse conjunctiva. Both human and mouse conjunctival epithelium exhibited elevated levels of various pro-inflammatory cytokines and chemokines [78].

Anatomic changes, such as conjunctival tenderness and laxity of the eyelids, are more common in older adults. Studies

have shown that these changes in the ocular surface are associated with symptoms of dry eye and abnormalities in tear production. Conjunctival softening is characterized by a relaxed, redundant, non-edematous conjunctiva, typically located between the eyeball and the lower eyelid. It is a significant factor contributing to ocular discomfort and instability of the tear film. The condition can affect the nasal, central, and temporal regions of the lower eyelid and usually occurs bilaterally [79]. It has been found that tear film stability is significantly reduced in patients with conjunctival chondromalacia. Additionally, it has been observed that lesions in the medial and nasal areas interfere with tear film stability more than lesions in the temporal area [80]. The eyelids are known to play an important role in maintaining the dynamics of a healthy tear film. Previous studies have shown that under normal blinking conditions, the lipid film spreads within the eyelid. If the eyelids are lax, it can lead to extremely severe ocular surface symptoms. Previously reported risk factors for eyelid laxity include older age, weight gain, male gender, and obstructive sleep apnea [81].

3.4 Autoimmune diseases in aging

Aging, as a universal biological phenomenon, is an inevitable tendency throughout life and has a close impact on the immune system. Aging induces a decline in the function of the immune system, a process known as immunosenescence, which affects the composition, number, and function of immune organs, immune cells, and cytokines [82]. According to previous studies and reports, autoimmune diseases are important contributors to the development of DED. DED is seen in about 10%–95% of patients with immune-related diseases; 38%–47% of rheumatoid arthritis (RA) patients have DED, compared to 13.4%–39.5% for systemic lupus erythematosus (SLE), 95% for Sjögren's syndrome (SS), and 37%–79% for systemic sclerosis (SSc) [83].

3.4.1 SS and DED

Primary SS is a complex systemic autoimmune disease that primarily affects exocrine glands, including the salivary and lacrimal glands. Of the various types of autoimmune rheumatic diseases (ARDs) [84], primary SS is most closely associated with dry eye. Destruction of exocrine glands and infiltration of lymphocytes play an important role in the pathogenesis of SS. SS is usually accompanied by symptoms of dry eyes and dry mouth at the time of presentation. It has been emphasized that patients often describe not only ocular discomfort but also visual disturbances.

In patients with SS, activated T cells target the lacrimal gland, leading to cell death and inadequate tear production,

which triggers aqueous-deficient dry eye (ADDE); however, MGD may also be involved [85]. This leads us to recognize that EDE also plays an important role in SS. When the meibomian glands fail to secrete the oil layer that covers the tear film, evaporation of the aqueous layer is accelerated, leading to EDE. These mucins make up the mucus layer of the tears and play a role in stabilizing the tear film on the ocular surface [86]. Studies have also emphasized that an unstable tear film is more prone to evaporation, which can exacerbate the symptoms of DED [87].

3.5 Metabolic diseases in aging

The prevalence of dry eye may be higher in patients with diabetes than in the healthy population [88]. About one in five patients with type 2 diabetes mellitus (T2DM) has been reported to suffer from dry eye, which reduces the patient's quality of life [89]. The prevalence of dry eye in patients with T2DM has been reported to be higher than in the healthy population. The tear film is the interface between the surface of the eye and the external environment, and it contains a tightly controlled amount of water, proteins, and lipids. Normal secretion of proteins and fluids in the tear film is essential for maintaining the health of the ocular surface. Diabetes impairs tear secretion and induces lacrimal gland (LG) changes. Early studies found that insulin was involved in LG disturbances such as impaired secretion and decreased protein secretion [90]. Subsequent studies confirmed that lipid accumulation in the LG spine layer increased with age in a nonobese diabetic (NOD) mouse model. This change is accompanied by lymphocytic infiltration and destruction of the spines [91].

4 Treatment strategies for aging-related dry eye

As the lacrimal system undergoes numerous changes with age, it is important to first assess which part of the system is dysfunctional and to treat it according to the location of the dysfunction. The initial treatment for patients with DED starts with protecting the ocular surface using artificial tears, of which there are many products available. In addition, numerous emerging therapies have been developed for the treatment of DED, as treatments are continuously updated (Table 1). Starting with anti-inflammatory approaches, as well as other mechanisms in combination, are described.

4.1 Anti-inflammatory therapy

Omega-3 essential fatty acids have been shown to reduce inflammation in older patients with dry eye [92]. Diets rich in

Table 1 Emerging therapies for the treatment of DED

Therapy name	Mechanism of action	Ocular condition or disease
Omega-3	Anti-inflammatory	DED
SkQ1 (Visomitin)	Antioxidant	DED
Thermal pulsation therapy	Improves meibomian gland function	DED associated with meibomian gland dysfunction
Intense pulsed light therapy	Improves meibomian gland function	DED associated with meibomian gland dysfunction
Intranasal tear nerve stimulator	Increase tear volume	DED
Hormonal and calorie restriction	Anti-aging	DED associated with aging

omega-3 fatty acids, such as tuna, or omega-3 supplements like fish oil, have been reported to reduce the risk of chronic dry eye disease (DED) and improve signs and symptoms [93]. The omega-3 fatty acid EPA and the omega-6 fatty acid arachidonic acid (AA) competitively act as substrates for cyclooxygenase and 5-lipoxygenase. The anti-inflammatory effect is believed to result from the synthesis of prostaglandin E3 and leukotriene B5 (LTB5) by EPA, which inhibits the conversion of AA to the potentially harmful inflammatory mediators prostaglandin E2 and leukotriene B4. Studies have found improvements in tear film stability, lid margin inflammation, expression of meibomian glands, and Schirmer's test results in patients with DED who take oral omega-3 supplements [94]. Additionally, the use of omega-3 fatty acid supplementation reduced the expression of human leukocyte antigen-DR (HLA-DR), a marker of conjunctival inflammation, and may contribute to the improvement of DED symptoms [95].

4.2 Anti-oxidative stress

Oxidative stress is believed to be a contributing factor in the development of DED, leading to episodes of inflammation and increased angiogenesis. Recent advancements in DED research indicate that inflammation and injury to the ocular surface play a causative role, with inflammation being a central mechanism in the development of DED. Therefore, investigating the connection between ROS production, lipid peroxidation-related membrane damage, and inflammatory processes in DED may lead to an effective treatment for DED [96].

SkQ1 (Visomitin) is a novel synthetic antioxidant that penetrates the cell and accumulates in the inner mitochondrial membrane. It reduces the damage caused by the overproduction of mitochondrial ROS by switching between reduced and oxidized forms [97]. The protective effect of SkQ1 enhances the clinical condition of the ocular surface by inhibiting apoptotic and pre-necrotic changes in the corneal epithelium. The potential mechanism involves inhibiting oxidative stress by stimulating intrinsic antioxidant activity and antioxidant enzymes, particularly glutathione peroxidase and glutathione reductase, in the cornea. In addition, SkQ6 enhances the antioxidant activity and stability of the tear film and exerts anti-inflammatory effects, as indicated by a decrease in TNF- α and IL-10 levels in the tear fluid and a notable increase in IL-1 [98].

According to clinical trials, SkQ1 demonstrated a reduction in tear film instability and an improvement in the functional status of the cornea. Through its antioxidant mechanism of action, SkQ1 appears to significantly improve symptoms in patients with mild to moderate DED [97].

4.3 Treatment of blepharoplasty dysfunction

Intense pulsed light (IPL) treatments are performed using devices such as the Lumenis OPT M22 (Lumenis, Yokneam, Israel), E-Eye (E-Swin, Gambais, France), and DermaMed Quadra 4 IPL (DermaMed, Lenni, PA, USA). These devices provide high-intensity visible light across a broad spectrum (wavelengths ranging from 500 to 1200 nm) as a non-coherent, multi-color light source. These wavelengths of light stimulate melanin and hemoglobin in the skin, leading to the

coagulation and ablation of blood vessels. In 2008, IPL therapy became commonly used to treat dermatological conditions [99]. Early clinical studies applying this therapy to patients with MGD suggest that it may be beneficial in improving signs and symptoms of this disease, such as eyelid erythema and capillary dilation [100].

Several hypotheses exist regarding how IPL may improve various aspects of DED, including enhancing lid quality by increasing periocular skin temperature, disrupting periocular capillary dilation rich in pro-inflammatory mediators, eliminating bacteria, inhibiting inflammatory cytokines (IL-6, tumor necrosis factor (TNF)- α), and reducing reactive oxygen species. One study demonstrated that intense pulsed light reduced inflammatory mediators in tears [101].

4.4 Treatment of LG dysfunction

The eye contains ocular surface sensory reflexes and blink reflexes that involve the functional units of the lacrimal gland. Additionally, there is a nasal tear reflex, in which the afferent pathway begins in the sensory receptors of the nasal mucosal epithelium and travels to the superior salivary nucleus (SSN) of the brainstem via the anterior ethmoid sinus nerve and the ophthalmic branch of the trigeminal nerve. From there, preganglionic fibers travel along the median nerve to reach the pterygopalatine ganglion, where they innervate the lacrimal gland, cupula, and meibomian glands [102]. The nasolacrimal reflex originates from the SSN in the same efferent pathway that innervates the lacrimal functional unit (LFU) [30].

Recently published preclinical studies have utilized nerve stimulators implanted in the nasal cavity or near the lacrimal nerve to stimulate the anterior ethmoidal nerve for 3 minutes at frequencies ranging from 30 to 90 Hz. The results of these studies showed that electrical stimulation increased tear production and decreased tear concentration [103]. The intranasal tear nerve stimulator device has recently been approved by the US Food and Drug Administration (FDA) for use in adults. Preclinical studies have shown statistically significant improvements in lacrimal gland dysfunction, cupped cell density, and tear production. TrueTear (Allergan, Parkway Parsippany, NJ, USA) has been discontinued from the market, but iTEAR100 (Olympic Ophthalmology, Issaquah, WA, USA) is still available [104].

4.5 Treatment of ocular surface changes

Previously reported risk factors for eyelid laxity include advanced age, weight gain, male gender, and obstructive sleep apnea. The prevalence of laxity is higher with increased severity of the disease [105]. Palliative treatments, such as eyelid coverings, eyelid taping, nocturnal lubrication, topical steroids, and eyelid scrubs, have been utilized [106]. However, their discomfort and impracticality, particularly the risks and dangers associated with topical steroid use, have led to a shift in treatment towards surgical interventions aimed at tightening the eyelid. These interventions include total wedge resection, lateral/medial eyelid folding, and medial sub lid stripping [107].

Conjunctival softening, characterized by excessive conjunctival folds, is another anatomical abnormality that disrupts tear film integrity and can lead to symptoms of DED. Patients with conjunctival softening exhibit tear film

abnormalities, such as decreased Schirmer scores, increased detachment of meibomian glands, and heightened eyelid vascularity [108]. Artificial tears and/or topical anti-inflammatory medications are typically used as the initial treatment for symptomatic relief. If pharmacologic treatment is ineffective, excision or thermal cautery of the excess conjunctiva may be considered [93].

4.6 Advanced ocular surface reconstruction

Advanced ocular surface remodeling methods, such as lacrimal gland regeneration or transplantation of bioengineered lacrimal tissue, may also be used after the above treatments have failed to improve symptoms in patients with DED. In the case of partial damage to the lacrimal gland and other components of the functional unit of the lacrimal gland, the therapeutic strategy is to take regenerative measures to the residual cells or tissues. In cases of complete damage to the lacrimal gland and other components of the functional unit of the lacrimal gland, *in vitro* reconstruction of the lacrimal gland or bioengineering of the lacrimal gland are the only options [109].

4.7 Treatment of autoimmune disease-related DED

Treatment options for DED range anywhere from eliminating the risk factors and environmental factors to surgical approaches. The same approach also applies to autoimmune disease-related DED. Recently, lifitegrast ophthalmic solution 5% (Xiidra™) has been FDA approved in the USA. Lifitegrast works by inhibiting the binding of lymphocyte function-associated antigen-1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1), and appears to impact the T cell-mediated immune response and inflammation associated with DED [110]. Physician-prescribed topical corticosteroids or topical prochlorperazine for a limited period of time are among the prescription medications that can also be used to treat autoimmune-related dry eye. In conclusion, the cooperative treatment of multiple systems plays an important role in elderly patients with dry eye.

4.8 Treatment of diabetes-related DED

The treatment strategy for diabetes-related dry eye is a combination of systemic interventions and targeted ocular therapy. For patients with aqueous-deficient dry eye, the effect of real-time blood glucose concentrations on tear film stability is significant and rapid; therefore, effective control of blood glucose concentrations should be emphasized in such dry eye patients. Because the effect of high blood glucose concentrations on patients with hyper-evaporative dry eye is slow and gradual, these dry eye patients should pay attention to eyelid margin cleaning in addition to controlling blood glucose concentrations. Dietary and lifestyle control as well as modification of systemic disease therapy will greatly improve dry eye symptoms in diabetic patients.

In addition, we should cooperate with endocrinologists to regularly assess the ocular surface status of diabetic patients, so as to achieve early prevention, diagnosis, and treatment of diabetes-related dry eye, and ultimately to realize a good quality of life and visual quality of patients with diabetes-related dry eye.

4.9 Anti-aging treatment

The incidence of dry eye increases with age due to systemic changes [111]. While medication is the primary treatment for dry eye, addressing environmental factors and adjusting daily habits are also crucial for treating and preventing the disease. Age is a risk factor for the disease [112]. As we age, tear production decreases, leading to a significant reduction in the amount of tears in patients with dry eye [113].

Aging is a long-term cumulative process, primarily characterized by the effects of oxidative stress that accumulate over time and the simultaneous decrease in the body's defense capacity. During the aging process, the formation of reactive oxygen species resulting from various reactions impacts molecular, mitochondrial, cellular, and organ levels, ultimately contributing to systemic aging [114]. The molecular-level approach has not been satisfactorily observed at the systemic level. After antioxidant supplementation, hormonal regulation and calorie restriction are two potential approaches to counteract and slow down the aging process.

5 Conclusion

In conclusion, the changes that occur in the lacrimal gland, Meibomian gland, and ocular surface with aging are likely to underlie the connection between aging and dry eye. With the growing number of people affected by dry eye and extensive research on the pathogenesis of the condition, it has been demonstrated that dry eye is an ocular disease caused by multiple systemic and local factors with complex and diverse origins and clinical presentations. Therefore, the treatment of dry eye is no longer limited to simple lubrication and moisturizing therapy. It is more important to consider the benefits and risks of each dry eye therapy and to adjust the treatment accordingly. In addressing dry eye treatment in the elderly, lifestyle interventions, such as dietary therapy and anti-aging approaches, may complement clinically based treatment strategies to effectively manage dry eye symptoms.

Conflict of interests

The authors declare no competing interests.

References

- [1] Nelson, J. D., Helms, H., Fiscella, R., Southwell, Y., Hirsch, J. D. A new look at dry eye disease and its treatment. *Advances in Therapy*, **2000**, 17(2): 84–93. <https://doi.org/10.1007/BF02854841>
- [2] de Pinho Tavares, F., Fernandes, R. S., Bernardes, T. F., Bonfioli, A. A., Soares, E. J. C. Dry eye disease. *Seminars in Ophthalmology*, **2010**, 25(3): 84–93. <https://doi.org/10.3109/08820538.2010.488568>.
- [3] Latkany, R., Miller, D., Zeev, M. S. B. Diagnosis of dry eye disease and emerging technologies. *Clinical Ophthalmology*, **2014**, 8: 581. <https://doi.org/10.2147/ophth.s45444>.
- [4] Rahman, M. Q., Chuah, K. S., MacDonald, E. C. A., Trusler, J. P. M., Ramaesh, K. The effect of pH, dilution, and temperature on the viscosity of ocular lubricants—Shift in rheological parameters and potential clinical significance. *Eye*, **2012**, 26(12): 1579–1584. <https://doi.org/10.1038/eye.2012.211>.
- [5] Dana, R., Bradley, J. L., Guerin, A., Pivneva, I., Stillman, I. Ö., Evans, A. M., Schaumberg, D. A. Estimated prevalence and incidence of dry eye disease based on coding analysis of a large, all-age United States health care system. *American Journal of Ophthalmology*, **2019**, 202: 47–54. <https://doi.org/10.1016/j.ajo.2019.01.026>.
- [6] Barabino, S., Labetoulle, M., Rolando, M., Messmer, E. M.

- Understanding symptoms and quality of life in Patients with dry eye syndrome. *The Ocular Surface*, **2016**, 14(3): 365–376. <https://doi.org/10.1016/j.jtos.2016.04.005>.
- [7] Messmer, E. M. The pathophysiology, diagnosis, and treatment of dry eye disease. *Deutsches Ärzteblatt International*, **2015**, 112(5): 71. <https://doi.org/10.3238/arztebl.2015.0071>.
 - [8] McDonald, M., Patel, D. A., Keith, M. S., Snedecor, S. J. Economic and humanistic burden of dry eye disease in Europe, North America, and Asia: A Systematic literature review. *The Ocular Surface*, **2016**, 14(2): 144–167. <https://doi.org/10.1016/j.jtos.2015.11.002>.
 - [9] Wan, K. H., Chen, L. J., Young, A. L. Depression and anxiety in dry eye disease: A systematic review and meta-analysis. *Eye*, **2016**, 30(12): 1558–1567. <https://doi.org/10.1038/eye.2016.186>.
 - [10] Zheng, Y. J., Wu, X. H., Lin, X. M., Lin, H. T. The prevalence of depression and depressive symptoms among eye disease patients: A systematic review and meta-analysis. *Scientific Reports*, **2017**, 7: 46453. <https://doi.org/10.1038/srep46453>.
 - [11] Gomes, J. A. P., Santo, R. M. The impact of dry eye disease treatment on patient satisfaction and quality of life: A review. *The Ocular Surface*, **2019**, 17(1): 9–19. <https://doi.org/10.1016/j.jtos.2018.11.003>.
 - [12] Craig, J. P., Nichols, K. K., Akpek, E. K., Caffery, B., Dua, H. S., Joo, C. K., Liu, Z. G., Nelson, J. D., Nichols, J. J., Tsubota, K. et al. TFOS DEWS II definition and classification report. *The Ocular Surface*, **2017**, 15(3): 276–283. <https://doi.org/10.1016/j.jtos.2017.05.008>.
 - [13] Tsubota, K., Yokoi, N., Shimazaki, J., Watanabe, H., Dogru, M., Yamada, M., Kinoshita, S., Kim, H. M., Tchah, H. W., Hyon, J. Y. et al. New perspectives on dry eye definition and diagnosis: A consensus report by the Asia dry eye society. *The Ocular Surface*, **2017**, 15(1): 65–76. <https://doi.org/10.1016/j.jtos.2016.09.003>.
 - [14] Den, S., Shimizu, K., Ikeda, T., Tsubota, K., Shimmura, S., Shimazaki, J. Association between meibomian gland changes and aging, sex, or tear function. *Cornea*, **2006**, 25(6): 651–655. <https://doi.org/10.1097/01.icc.0000227889.11500.6f>.
 - [15] Schaumberg, D. A., Nichols, J. J., Papas, E. B., Tong, L., Uchino, M., Nichols, K. K. The international workshop on meibomian gland dysfunction: Report of the subcommittee on the epidemiology of, and associated risk factors for, MGD. *Investigative Ophthalmology & Visual Science*, **2011**, 52(4): 1994. <https://doi.org/10.1167/iovs.10-6997e>.
 - [16] Schaumberg, D. A. Hormone replacement therapy and dry eye syndrome. *JAMA*, **2001**, 286(17): 2114. <https://doi.org/10.1001/jama.286.17.2114>.
 - [17] Song, P. G., Xia, W., Wang, M. L., Chang, X. L., Wang, J. P., Jin, S., Wang, J. W., Wei, W., Rudan, I. Variations of dry eye disease prevalence by age, sex and geographic characteristics in China: A systematic review and meta-analysis. *Journal of Global Health*, **2018**, 8(2): 020503. <https://doi.org/10.7189/jogh.08.020503>.
 - [18] Gipson, I. K. Age-related changes and diseases of the ocular surface and cornea. *Investigative Ophthalmology & Visual Science*, **2013**, 54(14): ORSF48. <https://doi.org/10.1167/iovs.13-12840>.
 - [19] Baudouin, C. The pathology of dry eye. *Survey of Ophthalmology*, **2001**, 45: S211–S220. [https://doi.org/10.1016/s0039-6257\(00\)00200-9](https://doi.org/10.1016/s0039-6257(00)00200-9).
 - [20] Periman Laura, M., Perez Victor, L., Saban Daniel, R., Lin Meng, C., Piergiorgio, N. The immunological basis of dry eye disease and current topical treatment options. *Journal of Ocular Pharmacology and Therapeutics: the Official Journal of the Association for Ocular Pharmacology and Therapeutics*, **2020**, 36(3): 137–146. <https://doi.org/10.1089/jop.2019.0060>.
 - [21] Yu, L. F., Yu, C. J., Dong, H., Mu, Y. N., Zhang, R., Zhang, Q. S., Liang, W., Li, W. J., Wang, X., Zhang, L. J. Recent developments about the pathogenesis of dry eye disease: Based on immune inflammatory mechanisms. *Frontiers in Pharmacology*, **2021**, 12: 732887. <https://doi.org/10.3389/fphar.2021.732887>.
 - [22] Guzmán, M., Keitelman, I., Sabbione, F., Trevani, A. S., Giordano, M. N., Galletti, J. G. Desiccating stress-induced disruption of ocular surface immune tolerance drives dry eye disease. *Clinical and Experimental Immunology*, **2016**, 184(2): 248–256. <https://doi.org/10.1111/cei.12759>.
 - [23] Luo, L. H., Li, D. Q., Corrales, R. M., Pflugfelder, S. C. Hyperosmolar saline is a proinflammatory stress on the mouse ocular surface. *Eye & Contact Lens: Science & Clinical Practice*, **2005**, 31(5): 186–193. <https://doi.org/10.1097/01.icl.0000162759.79740.46>.
 - [24] Luo, L. H., Li, D. Q., Doshi, A., Farley, W., Corrales, R. M., Pflugfelder, S. C. Experimental dry eye stimulates production of inflammatory cytokines and MMP-9 and activates MAPK signaling pathways on the ocular surface. *Investigative Ophthalmology & Visual Science*, **2004**, 45(12): 4293. <https://doi.org/10.1167/iovs.03-1145>.
 - [25] Pellegrino, F. S. A., Pflugfelder, S. C., De Paiva, C. S. Low humidity environmental challenge causes barrier disruption and cornification of the mouse corneal epithelium via a c-Jun N-terminal kinase 2 (JNK2) pathway. *Experimental Eye Research*, **2012**, 94(1): 150–156. <https://doi.org/10.1016/j.exer.2011.11.022>.
 - [26] Chi, W., Hua, X., Chen, X., Bian, F., Yuan, X. Y., Zhang, L. L., Wang, X. R., Chen, D., Deng, R. Z., Li, Z. J. et al. Mitochondrial DNA oxidation induces imbalanced activity of NLRP3/NLRP6 inflammasomes by activation of caspase-8 and BRCC36 in dry eye. *Journal of Autoimmunity*, **2017**, 80: 65–76. <https://doi.org/10.1016/j.jaut.2017.02.006>.
 - [27] Niu, L. L., Zhang, S. J., Wu, J. H., Chen, L., Wang, Y. Upregulation of NLRP3 inflammasome in the tears and ocular surface of dry eye patients. *PLoS One*, **2015**, 10(5): e0126277. <https://doi.org/10.1371/journal.pone.0126277>.
 - [28] Zheng, Q. X., Ren, Y. P., Reinach, P. S., She, Y. J., Xiao, B., Hua, S. S., Qu, J., Chen, W. Reactive oxygen species activated NLRP3 inflammasomes prime environment-induced murine dry eye. *Experimental Eye Research*, **2014**, 125: 1–8. <https://doi.org/10.1016/j.exer.2014.05.001>.
 - [29] Zheng, Q. X., Ren, Y. P., Reinach, P. S., Xiao, B., Lu, H. H., Zhu, Y. R., Qu, J., Chen, W. Reactive oxygen species activated NLRP3 inflammasomes initiate inflammation in hyperosmolarity stressed human corneal epithelial cells and environment-induced dry eye patients. *Experimental Eye Research*, **2015**, 134: 133–140. <https://doi.org/10.1016/j.exer.2015.02.013>.
 - [30] Bron, A. J., de Paiva, C. S., Chauhan, S. K., Bonini, S., Bonini, S., Gabison, E. E., Jain, S., Knop, E., Markoulli, M., Ogawa, Y. et al. TFOS DEWS II pathophysiology report. *Ocul Surf*, **2017**, 15(3): 438–510. <https://doi.org/10.1016/j.jtos.2017.05.011>.
 - [31] Baudouin, C., Aragona, P., Messmer, E. M., Tomlinson, A., Calonge, M., Boboridis, K. G., Akova, Y. A., Geerling, G., Labetoulle, M., Rolando, M. Role of hyperosmolarity in the pathogenesis and management of dry eye disease: Proceedings of the OCEAN group meeting. *The Ocular Surface*, **2013**, 11(4): 246–258. <https://doi.org/10.1016/j.jtos.2013.07.003>.
 - [32] Yazici, A., Sari, E. S., Sahin, G., Kilic, A., Cakmak, H., Ayar, O., Ermis, S. S. Change in tear film characteristics in visual display terminal users. *European Journal of Ophthalmology*, **2015**, 25(2): 85–89. <https://doi.org/10.5301/ejo.5000525>.
 - [33] Chhadv, P., Goldhardt, R., Galor, A. Meibomian gland disease: The role of gland dysfunction in dry eye disease. *Ophthalmology*, **2017**, 124(11S): S20–S26. <https://doi.org/10.1016/j.ophtha.2017.05.031>.
 - [34] Baudouin, C., Messmer, E. M., Aragona, P., Geerling, G., Akova, Y. A., Benítez-del-Castillo, J., Boboridis, K. G., Merayo-Llves, J., Rolando, M., Labetoulle, M. Revisiting the vicious circle of dry eye disease: A focus on the pathophysiology of meibomian gland dysfunction. *British Journal of Ophthalmology*, **2016**, 100(3): 300–306. <https://doi.org/10.1136/bjophthalmol-2015-307415>.
 - [35] Hykin, P. G., Bron, A. J. Age-related morphological changes in lid margin and meibomian gland anatomy. *Cornea*, **1992**, 11(4): 334–342. <https://doi.org/10.1097/00003226-199207000-00012>.
 - [36] Norn, M. Expressibility of meibomian secretion. Relation to age, lipid precorneal film, scales, foam, hair and pigmentation. *Acta Ophthalmologica*, **1987**, 65(2): 137–142. <https://doi.org/10.1111/j>

- 1755-3768.1987.tb06991.x.
- [37] Arita, R., Itoh, K., Inoue, K., Amano, S. Noncontact infrared meibography to document age-related changes of the meibomian glands in a normal population. *Ophthalmology*, **2008**, 115(5): 911–915. <https://doi.org/10.1016/j.ophtha.2007.06.031>.
 - [38] Obata, H. Anatomy and histopathology of human meibomian gland. *Cornea*, **2002**, 21(Supplement 2): S70–S74. <https://doi.org/10.1097/01.icc.0000263122.45898.09>
 - [39] Nien, C. J., Paugh, J. R., Massei, S., Wahlert, A. J., Kao, W. W., Jester, J. V. Age-related changes in the meibomian gland. *Experimental Eye Research*, **2009**, 89(6): 1021–1027. <https://doi.org/10.1016/j.exer.2009.08.013>.
 - [40] Hashemi, H., Khabazkhoob, M., Kheirkhah, A., Emamian, M. H., Mehravaran, S., Shariati, M., Fotouhi, A. Prevalence of dry eye syndrome in an adult population. *Clinical & Experimental Ophthalmology*, **2014**, 42(3): 242–248. <https://doi.org/10.1111/ceo.12183>.
 - [41] Schaumberg, D. A., Sullivan, D. A., Buring, J. E., Dana, M. R. Prevalence of dry eye syndrome among US women. *American Journal of Ophthalmology*, **2003**, 136(2): 318–326. [https://doi.org/10.1016/s0002-9394\(03\)00218-6](https://doi.org/10.1016/s0002-9394(03)00218-6).
 - [42] Schaumberg, D. A. Prevalence of dry eye disease among US men. *Archives of Ophthalmology*, **2009**, 127(6): 763. <https://doi.org/10.1001/archophthmol.2009.103>.
 - [43] Chia, E. M., Mitchell, P., Rochtchina, E., Lee, A. J., Maroun, R., Wang, J. J. Prevalence and associations of dry eye syndrome in an older population: The Blue Mountains Eye Study. *Clinical & Experimental Ophthalmology*, **2003**, 31(3): 229–232. <https://doi.org/10.1046/j.1442-9071.2003.00634.x>.
 - [44] Luderschmidt, C., Eiermann, W., Jawny, J. Steroid hormone receptors and their relevance for sebum production in the sebaceous gland ear model of the Syrian hamster. *Archives of Dermatological Research*, **1983**, 275(3): 175–180. <https://doi.org/10.1007/BF00510049>.
 - [45] Rocha, E. M. Identification of androgen receptor protein and 5alpha-reductase mRNA in human ocular tissues. *British Journal of Ophthalmology*, **2000**, 84(1): 76–84. <https://doi.org/10.1136/bjo.84.1.76>.
 - [46] Krenzer, K. L., Reza Dana, M., Ullman, M. D., Cermak, J. M., Tolls, D. B., Evans, J. E., Sullivan, D. A. Effect of androgen deficiency on the human meibomian gland and ocular Surface'. *The Journal of Clinical Endocrinology & Metabolism*, **2000**, 85(12): 4874–4882. <https://doi.org/10.1210/jcem.85.12.7072>.
 - [47] Schirra, F., Richards, S. M., Sullivan, D. A. Androgen influence on cholesterologenic enzyme mRNA levels in the mouse meibomian gland. *Current Eye Research*, **2007**, 32(5): 393–398. <https://doi.org/10.1080/02713680701316674>.
 - [48] Rosignoli, C., Nicolas, J. C., Jomard, A., Michel, S. Involvement of the SREBP pathway in the mode of action of androgens in sebaceous glands in vivo. *Experimental Dermatology*, **2003**, 12(4): 480–489. <https://doi.org/10.1034/j.1600-0625.2003.00014.x>
 - [49] Miyazaki, M., Man, W. C., Ntambi, J. M. Targeted disruption of stearoyl-CoA Desaturase1 gene in mice causes atrophy of sebaceous and meibomian glands and depletion of wax esters in the eyelid. *The Journal of Nutrition*, **2001**, 131(9): 2260–2268. <https://doi.org/10.1093/jn/131.9.2260>.
 - [50] Feldman, H. A., Longcope, C., Derby, C. A., Johannes, C. B., Araujo, A. B., Coviello, A. D., Bremner, W. J., McKinlay, J. B. Age trends in the level of serum testosterone and other hormones in middle-aged men: Longitudinal results from the Massachusetts male aging study. *The Journal of Clinical Endocrinology & Metabolism*, **2002**, 87(2): 589–598. <https://doi.org/10.1210/jcem.87.2.8201>.
 - [51] Morley, J. E., Kaiser, F. E., Perry, H. M. III, Patrick, P., Morley, P. M. K., Stauber, P. M., Vellas, B., Baumgartner, R. N., Garry, P. J. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. *Metabolism*, **1997**, 46(4): 410–413. [https://doi.org/10.1016/s0026-0495\(97\)90057-3](https://doi.org/10.1016/s0026-0495(97)90057-3).
 - [52] McKay, T. B., Priyadarsini, S., Karamichos, D. Sex hormones, growth hormone, and the cornea. *Cells*, **2022**, 11(2): 224. <https://doi.org/10.3390/cells11020224>.
 - [53] Erdem, U., Ozdegirmenci, O., Sobaci, E., Sobaci, G., Göktolga, U., Dagli, S. Dry eye in post-menopausal women using hormone replacement therapy. *Maturitas*, **2007**, 56(3): 257–262. <https://doi.org/10.1016/j.maturitas.2006.08.007>.
 - [54] Suzuki, T., Schirra, F., Richards, S. M., Jensen, R. V., Sullivan, D. A. Estrogen and progesterone control of gene expression in the mouse meibomian gland. *Investigative Ophthalmology & Visual Science*, **2008**, 49(5): 1797. <https://doi.org/10.1167/iov.07-1458>.
 - [55] Schäfer, G., Krause, W. The effect of estradiol on the sebaceous gland of the hamster ear and its antagonism by tamoxifen. *Archives of Dermatological Research*, **1985**, 277(3): 230–234. <https://doi.org/10.1007/BF00404322>.
 - [56] Sriprasert, I., Warren, D. W., Mircheff, A. K., Stanczyk, F. Z. Dry eye in postmenopausal women: A hormonal disorder. *Menopause*, **2016**, 23(3): 343–351. <https://doi.org/10.1097/GME.0000000000000530>.
 - [57] Jester, J. V., Parfitt, G. J., Brown, D. J. Meibomian gland dysfunction: Hyperkeratinization or atrophy. *BMC Ophthalmology*, **2015**, 15(1): 156. <https://doi.org/10.1186/s12886-015-0132-x>.
 - [58] Ibrahim, O. M. A., Dogru, M., Matsumoto, Y., Igarashi, A., Kojima, T., Wakamatsu, T. H., Inaba, T., Shimizu, T., Shimazaki, J., Tsubota, K. Oxidative stress induced age dependent meibomian gland dysfunction in Cu, Zn-superoxide dismutase-1 (Sod1) knockout mice. *PLoS One*, **2014**, 9(7): e99328. <https://doi.org/10.1371/journal.pone.0099328>.
 - [59] Galor, A., Moein, H. R., Lee, C., Rodriguez, A., Felix, E. R., Sarantopoulos, K. D., Levitt, R. C. Neuropathic pain and dry eye. *The Ocular Surface*, **2018**, 16(1): 31–44. <https://doi.org/10.1016/j.jtos.2017.10.001>.
 - [60] Guzmán, M., Miglio, M., Keitelman, I., Shiromizu, C. M., Sabbione, F., Fuentes, F., Trevani, A. S., Giordano, M. N., Galletti, J. G. Transient tear hyperosmolarity disrupts the neuroimmune homeostasis of the ocular surface and facilitates dry eye onset. *Immunology*, **2020**, 161(2): 148–161. <https://doi.org/10.1111/imm.13243>.
 - [61] De Silva, M. E. H., Hill, L. J., Downie, L. E., Chinnery, H. R. The effects of aging on corneal and ocular surface homeostasis in mice. *Investigative Ophthalmology & Visual Science*, **2019**, 60(7): 2705. <https://doi.org/10.1167/iov.19-26631>.
 - [62] Messmer, E. M. Pathophysiology of dry eye disease and novel therapeutic targets. *Experimental Eye Research*, **2022**, 217: 108944. <https://doi.org/10.1016/j.exer.2022.108944>.
 - [63] Alcalde, I., Íñigo-Portugués, A., González-González, O., Almaraz, L., Artime, E., Morenilla-Palao, C., Gallar, J., Viana, F., Merayo-Llves, J., Belmonte, C. Morphological and functional changes in TRPM8-expressing corneal cold thermoreceptor neurons during aging and their impact on tearing in mice. *Journal of Comparative Neurology*, **2018**, 526(11): 1859–1874. <https://doi.org/10.1002/cne.24454>.
 - [64] Schaumberg, D. A., Sullivan, D. A., Dana, M. R. Epidemiology of dry eye syndrome. In: *Advances in Experimental Medicine and Biology*. Boston: Springer US, **2002**: 989–998. https://doi.org/10.1007/978-1-4615-0717-8_140
 - [65] de Souza, R. G., Yu, Z. Y., Hernandez, H., Trujillo-Vargas, C. M., Lee, A., Mauk, K. E., Cai, J. Y., Alves, M. R., de Paiva, C. S. Modulation of oxidative stress and inflammation in the aged lacrimal gland. *The American Journal of Pathology*, **2021**, 191(2): 294–308. <https://doi.org/10.1016/j.ajpath.2020.10.013>.
 - [66] Ríos, J. D., Horikawa, Y., Chen, L. L., Kublin, C. L., Hodges, R. R., Dartt, D. A., Zoukhri, D. Age-dependent alterations in mouse exorbital lacrimal gland structure, innervation and secretory response. *Experimental Eye Research*, **2005**, 80(4): 477–491. <https://doi.org/10.1016/j.exer.2004.10.012>.
 - [67] Sohal, R. S., Marzabadi, M. R., Galaris, D., Brunk, U. T. Effect of ambient oxygen concentration on lipofuscin accumulation in cultured rat heart myocytes—a novel *in vitro* model of

- lipofuscinogenesis. *Free Radical Biology and Medicine*, **1989**, 6(1): 23–30. [https://doi.org/10.1016/0891-5849\(89\)90155-x](https://doi.org/10.1016/0891-5849(89)90155-x).
- [68] Terman, A., Brunk, U. T. Ceroid/lipofuscin formation in cultured human fibroblasts: The role of oxidative stress and lysosomal proteolysis. *Mechanisms of Ageing and Development*, **1998**, 104(3): 277–291. [https://doi.org/10.1016/s0047-6374\(98\)00073-6](https://doi.org/10.1016/s0047-6374(98)00073-6).
- [69] Draper, C. E., Adegate, E. A., Singh, J., Pallot, D. J. Evidence to suggest morphological and physiological alterations of lacrimal gland acini with ageing. *Experimental Eye Research*, **1999**, 68(3): 265–276. <https://doi.org/10.1006/exer.1998.0605>.
- [70] Borchman, D., Ramasubramanian, A., Foulks, G. N. Human meibum cholesteryl and wax ester variability with age, sex, and meibomian gland dysfunction. *Investigative Ophthalmology & Visual Science*, **2019**, 60(6): 2286. <https://doi.org/10.1167/jovs.19-26812>.
- [71] Yoon, C. H., Ryu, J. S., Hwang, H. S., Kim, M. K. Comparative analysis of age-related changes in lacrimal glands and meibomian glands of a C57BL/6 male mouse model. *International Journal of Molecular Sciences*, **2020**, 21(11): 4169. <https://doi.org/10.3390/ijms21114169>.
- [72] Nien, C. J. Effects of age and dysfunction on human meibomian glands. *Archives of Ophthalmology*, **2011**, 129(4): 462. <https://doi.org/10.1001/archophthalmol.2011.69>.
- [73] Kitazawa, K., Inomata, T., Shih, K., Hughes, J. W. B., Bozza, N., Tomioka, Y., Numa, K., Yokoi, N., Campisi, J., Dana, R. et al. Impact of aging on the pathophysiology of dry eye disease: A systematic review and meta-analysis. *The Ocular Surface*, **2022**, 25: 108–118. <https://doi.org/10.1016/j.jtos.2022.06.004>.
- [74] Wei, A. J., Hong, J. X., Sun, X. H., Xu, J. J. Evaluation of age-related changes in human palpebral conjunctiva and meibomian glands by *in vivo* confocal microscopy. *Cornea*, **2011**, 30(9): 1007–1012. <https://doi.org/10.1097/ico.0b013e31820ca468>.
- [75] Abdel-Khalek, L. M., Williamson, J., Lee, W. R. Morphological changes in the human conjunctival epithelium. I. in the normal elderly population. *British Journal of Ophthalmology*, **1978**, 62(11): 792–799. <https://doi.org/10.1136/bjo.62.11.792>.
- [76] Vujkovic, V., Mikac, G., Kozomara, R. Distribution and density of conjunctival goblet cells. *Medicinski Pregled*, **2002**, 55(5-6): 195–200. <https://doi.org/10.2298/mpns0206195v>.
- [77] Jung, Y. H., Ryu, J. S., Yoon, C. H., Kim, M. K. Age-dependent distinct distributions of dendritic cells in autoimmune dry eye murine model. *Cells*, **2021**, 10(8): 1857. <https://doi.org/10.3390/cells10081857>.
- [78] Bian, F., Xiao, Y. Y., Barbosa, F. L., de Souza, R. G., Hernandez, H., Yu, Z. Y., Pflugfelder, S. C., de Paiva, C. S. Age-associated antigen-presenting cell alterations promote dry-eye inducing Th1 cells. *Mucosal Immunology*, **2019**, 12(4): 897–908. <https://doi.org/10.1038/s41385-018-0127-z>.
- [79] Di Pascuale, M. A. Clinical characteristics of conjunctivochalasis with or without aqueous tear deficiency. *British Journal of Ophthalmology*, **2004**, 88(3): 388–392. <https://doi.org/10.1136/bjo.2003.025460>.
- [80] Le, Q. H., Cui, X. H., Xiang, J., Ge, L., Gong, L., Xu, J. J. Impact of conjunctivochalasis on visual quality of life: A community population survey. *PLoS One*, **2014**, 9(10): e110821. <https://doi.org/10.1371/journal.pone.0110821>.
- [81] Karger, R., White, W., Park, W., Rosales, A., McLaren, J., Olson, E., Woog, J. Prevalence of floppy eyelid syndrome in obstructive sleep apnea–hypopnea syndrome. *Ophthalmology*, **2006**, 113(9): 1669–1674. <https://doi.org/10.1016/j.ophtha.2006.02.053>.
- [82] Pawelec, G. Age and immunity: What is “immunosenescence”. *Experimental Gerontology*, **2018**, 105: 4–9. <https://doi.org/10.1016/j.exger.2017.10.024>.
- [83] Kemeny-Beke, A., Szodoray, P. Ocular manifestations of rheumatic diseases. *International Ophthalmology*, **2020**, 40(2): 503–510. <https://doi.org/10.1007/s10792-019-01183-9>.
- [84] Yu, K., Bunya, V., Maguire, M., Asbell, P., Ying, G. S. Systemic conditions associated with severity of dry eye signs and symptoms in the dry eye assessment and management study. *Ophthalmology*, **2021**, 128(10): 1384–1392. <https://doi.org/10.1016/j.ophtha.2021.03.030>.
- [85] Kuklinski, E., Asbell, P. A. Sjogren’s syndrome from the perspective of ophthalmology. *Clinical Immunology*, **2017**, 182: 55–61. <https://doi.org/10.1016/j.clim.2017.04.017>.
- [86] Vehof, J., Utheim, T. P., Bootsma, H., Hammond, C. J. Advances, limitations and future perspectives in the diagnosis and management of dry eye in Sjögren’s syndrome. *Clinical and Experimental Rheumatology*, **2020**, 38(4): 301–309.
- [87] Mavragani, C. P., Moutsopoulos, H. M. Sjögren syndrome. *CMAJ*, **2014**, 186(15): E579–E586. <https://doi.org/10.1503/cmaj.122037>.
- [88] De Freitas, G. R., Ferraz, G. A. M., Gehlen, M., Skare, T. L. Dry eyes in patients with diabetes mellitus. *Primary Care Diabetes*, **2021**, 15(1): 184–186. <https://doi.org/10.1016/j.pcd.2020.01.011>.
- [89] Su, Y. C., Hung, J. H., Chang, K. C., Sun, C. C., Huang, Y. H., Lee, C. N., Hung, M. J., Lai, C. C., Shao, S. C., Lai, E. C. C. Comparison of sodium-glucose cotransporter 2 inhibitors vs glucagonlike peptide-1 receptor agonists and incidence of dry eye disease in patients with type 2 diabetes in Taiwan. *JAMA Network Open*, **2022**, 5(9): e2232584. <https://doi.org/10.1001/jamanetworkopen.2022.32584>.
- [90] Dias, A. C., Batista, T. M., Roma, L. P., Módulo, C. M., Malki, L. T., Dias, L. C., Alves, M., Reinach, P. S., Carneiro, E. M., Rocha, E. M. Insulin replacement restores the vesicular secretory apparatus in the diabetic rat lacrimal gland. *Arquivos Brasileiros De Oftalmologia*, **2015**, 78(3): 158. <https://doi.org/10.5935/0004-2749.20150041>.
- [91] Wu, K. J., Joffe, C., Li, X. D., MacVeigh-Aloni, M., Hom, M., Hwang, J., Ding, C. Q., Gregoire, S., Bretillon, L., Zhong, J. F. et al. Altered expression of genes functioning in lipid homeostasis is associated with lipid deposition in NOD mouse lacrimal gland. *Experimental Eye Research*, **2009**, 89(3): 319–332. <https://doi.org/10.1016/j.exer.2009.03.020>.
- [92] Foulks, G. N. Pharmacological management of dry eye in the elderly patient. *Drugs & Aging*, **2008**, 25(2): 105–118. <https://doi.org/10.2165/00002512-200825020-00003>.
- [93] Ezuddin, N. S., Alawa, K. A., Galor, A. Therapeutic strategies to treat dry eye in an aging population. *Drugs & Aging*, **2015**, 32(7): 505–513. <https://doi.org/10.1007/s40266-015-0277-6>.
- [94] Olenik, A., Jiménez-Alfaro, A., Alejandro, M., Mahillo-Fernández, A. A randomized, double-masked study to evaluate the effect of omega-3 fatty acids supplementation in meibomian gland dysfunction. *Clinical Interventions in Aging*, **2013**: 1133. <https://doi.org/10.2147/cia.s48955>.
- [95] Brignole-Baudouin, F., Baudouin, C., Aragona, P., Rolando, M., Labetoulle, M., Pisella, P. J., Barabino, S., Siou-Mermet, R., Creuzot-Garcher, C. A multicentre, double-masked, randomized, controlled trial assessing the effect of oral supplementation of omega-3 and omega-6 fatty acids on a conjunctival inflammatory marker in dry eye patients. *Acta Ophthalmologica*, **2011**, 89(7): e591–e597. <https://doi.org/10.1111/j.1755-3768.2011.02196.x>.
- [96] Wei, Y., Troger, A., Spahiu, V., Perekhvatova, N., Skulachev, M., Petrov, A., Chernyak, B., Asbell, P. The role of SKQ1 (visomitin) in inflammation and wound healing of the ocular surface. *Ophthalmology and Therapy*, **2019**, 8(1): 63–73. <https://doi.org/10.1007/s40123-018-0158-2>.
- [97] Baiula, M., Spampinato, S. Experimental pharmacotherapy for dry eye disease: A review. *Journal of Experimental Pharmacology*, **2021**, 13: 345–358. <https://doi.org/10.2147/jep.s237487>.
- [98] Zernii, E. Y., Gancharova, O. S., Baksheeva, V. E., Golovastova, M. O., Kabanova, E. I., Savchenko, M. S., Tiulina, V. V., Sotnikova, L. F., Zamyatnin, A. A., Philippov, P. P. et al. Mitochondria-targeted antioxidant SkQ1 prevents anesthesia-induced dry eye syndrome. *Oxidative Medicine and Cellular Longevity*, **2017**, 2017: 9281519. <https://doi.org/10.1155/2017/9281519>.
- [99] Papageorgiou, P., Clayton, W., Norwood, S., Chopra, S., Rustin, M. Treatment of rosacea with intense pulsed light: Significant improvement and long-lasting results. *British Journal of Dermatology*, **2008**, 159(3): 628–632. <https://doi.org/10.1111/j.1365-2133.2008.08702.x>.

- [100] Arita, R., Fukuoka, S. Non-pharmaceutical treatment options for meibomian gland dysfunction. *Clinical and Experimental Optometry*, **2020**, 103(6): 742–755. <https://doi.org/10.1111/cxo.13035>.
- [101] Giannaccare, G., Taroni, L., Senni, C., Scoria, V. Intense pulsed light therapy in the treatment of meibomian gland dysfunction: Current perspectives. *Clinical Optometry*, **2019**, 11: 113–126. <https://doi.org/10.2147/opto.s217639>.
- [102] Dartt, D. A. Neural regulation of lacrimal gland secretory processes: Relevance in dry eye diseases. *Progress in Retinal and Eye Research*, **2009**, 28(3): 155–177. <https://doi.org/10.1016/j.preteyeres.2009.04.003>.
- [103] Brinton, M., Chung, J. L., Kossler, A., Kook, K. H., Loudin, J., Franke, M., Palanker, D. Electronic enhancement of tear secretion. *Journal of Neural Engineering*, **2016**, 13(1): 016006. <https://doi.org/10.1088/1741-2560/13/1/016006>.
- [104] Mason, L., Jafri, S., Dortonne, I., Sheppard, J. D. Jr. Emerging therapies for dry eye disease. *Expert Opinion on Emerging Drugs*, **2021**, 26(4): 401–413. <https://doi.org/10.1080/14728214.2021.2011858>.
- [105] Ansari, Z., Singh, R., Alabiad, C., Galor, A. Prevalence, risk factors, and morbidity of eye lid laxity in a veteran population. *Cornea*, **2015**, 34(1): 32–36. <https://doi.org/10.1097/ico.0000000000000286>.
- [106] Mastrotta, K. M. Impact of floppy eyelid syndrome in ocular surface and dry eye disease. *Optometry and Vision Science*, **2008**, 85(9): 814–816. <https://doi.org/10.1097/oxp.0b013e3181852777>.
- [107] Ezra, D. G., Beaconsfield, M., Sira, M., Bunce, C., Shah-Desai, S., Verity, D. H., Uddin, J., Collin, R. Long-term outcomes of surgical approaches to the treatment of floppy eyelid syndrome. *Ophthalmology*, **2010**, 117(4): 839–846. <https://doi.org/10.1016/j.ophttha.2009.09.009>.
- [108] Chhadva, P., Alexander, A., McClellan, A. L., McManus, K. T., Seiden, B., Galor, A. The impact of conjunctivochalasis on dry eye symptoms and signs. *Investigative Ophthalmology & Visual Science*, **2015**, 56(5): 2867. <https://doi.org/10.1167/iovs.14-16337>.
- [109] Singh, V. K., Sharma, P., Vaksh, U. K. S., Chandra, R. Current approaches for the regeneration and reconstruction of ocular surface in dry eye. *Frontiers in Medicine*, **2022**, 9: 885780. <https://doi.org/10.3389/fmed.2022.885780>.
- [110] Pflugfelder Stephen, C., Michael, S., Steven, Z., Amir, S. LFA-1/ICAM-1 interaction as a therapeutic target in dry eye disease. *Journal of Ocular Pharmacology and Therapeutics: the Official Journal of the Association for Ocular Pharmacology and Therapeutics*, **2017**, 33(1): 5–12. <https://doi.org/10.1089/jop.2016.0105>.
- [111] Kawashima, M., Ozawa, Y., Shinmura, K., Inaba, T., Nakamura, S., Kawakita, T., Watanabe, M., Tsubota, K. Calorie restriction (CR) and CR mimetics for the prevention and treatment of age-related eye disorders. *Experimental Gerontology*, **2013**, 48(10): 1096–1100. <https://doi.org/10.1016/j.exger.2013.04.002>.
- [112] Uchino, M., Yokoi, N., Uchino, Y., Dogru, M., Kawashima, M., Komuro, A., Sonomura, Y., Kato, H., Kinoshita, S., Schaumberg, D. A. et al. Prevalence of dry eye disease and its risk factors in visual display terminal users: The Osaka study. *American Journal of Ophthalmology*, **2013**, 156(4): 759–766.e1. <https://doi.org/10.1016/j.ajo.2013.05.040>.
- [113] Kawashima, M., Uchino, M., Yokoi, N., Dogru, M., Uchino, Y., Komuro, A., Sonomura, Y., Kato, H., Kinoshita, S., Tsubota, K. Decreased tear volume in patients with metabolic syndrome: the Osaka study. *The British journal of ophthalmology*, **2014**, 98(3): 418. <https://doi.org/10.1136/bjophthalmol-2013-303953>.
- [114] Mehdi, M. M., Solanki, P., Singh, P. Oxidative stress, antioxidants, hormesis and calorie restriction: The Current perspective in the biology of aging. *Archives of Gerontology and Geriatrics*, **2021**, 95: 104413. <https://doi.org/10.1016/j.archger.2021.104413>.