Dry eye and systemic diseases

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Abstract:

Tear film instability and reduced tear production initiate a vicious circle where hyperosmolarity, ocular inflammation, and apoptosis may induce a damage of the ocular surface including keratitis which is all included in a common condition called dry eye disease (DED). DED can be apparently an isolated ocular surface condition; however, multiple ocular and systemic risk factors have been identified. The association with systemic diseases such as autoimmune diseases, hormonal imbalance, dietary imbalance, metabolic diseases, infections, psychological conditions, and aging together with external causative factors may act independently or interacting each other to initiate and/or perpetuate signs and symptoms typical of this very common ocular surface disease. Rheumatological disorders are most typically associated with dry eye; therefore, strict interaction with rheumatologists is important for the diagnosis and management of DED patients. In the present narrative review, we highlight associations between DED and some of the systemic disorders that may be implicated in the development of the disease.

Keywords:

Autoimmunity, dry eye disease, Sjögren's syndrome hormonal dysfunction, systemic diseases

Introduction

The composition, integrity, and stability of the tear film can be adversely affected by multiple internal and environmental factors, resulting in the development of dry eye disease (DED) whose incidence and prevalence are continuously growing making DED one the most common ocular disorders worldwide. Aging is one of the main contributors to tear film changes; in fact, DED prevalence goes from 8% in subjects under 60% to 20% in those over 80.[1] However, the high prevalence of autoimmune diseases in young adults, the huge spread of digital devices, surgical refractive treatments, and contact lens use is causing an increasing prevalence of DED among young people and adults.

According to the revised definition in the Tear Film Ocular Society – Dre Eye Workshop II (TFOS DEWS II) report, DED is a multifactorial disease of the ocular surface characterized by the loss of tear film homeostasis, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles. DED can heavily impact patients' quality of life limiting daily activities such as reading, using digital devices, watching television, and driving,[2] which can have a negative impact on visual performance and ability to perform daily tasks.[3-5] This definition introduced the key pathologic mechanisms involved in the development of the disease: tear film imbalance and instability, hyperosmolarity of the exposed surface, inflammation, and tissue damage. Therefore, DED is not simply a lack of tears, but a complex ocular surface disease, in which the tear film is unstable and no longer provides sufficient nourishment or protection to the ocular surface which becomes inflamed and damaged.[6] This may lead to the unbalance in electrolytes, proteins, and mucins and permanent damage to the corneal and conjunctival epithelial cells and the corneal nerve fibers that trigger secretion. Two primary categories of DED are identified: aqueous deficient and evaporative DED. However, mixed forms are quite common and account for about one-third of cases.

However, in this definition, the influence of internal and external exposome on the potential development of a DED is not well defined. The

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exposome can be defined as the measure of all the exposures of an individual in a lifetime and how those exposures relate to health. An individual's exposure begins before birth and includes insults from environmental and occupational sources.[7] Three main domains overlap in the definition of exposome: a general external environment (urban environment, climate factors, social capital, stress, etc.); a specific external environment (diet, physical activity, tobacco, infections, etc.); an internal environment (metabolic factors, gut microflora, inflammation, oxidative stress, etc.). Indeed, a vast amount of risk factors for the development of DED have been identified,[5,8] including eye disorders (ocular surface abnormalities, decreased corneal sensation, thyroid ophthalmopathy, and meibomian gland dysfunction), refractive surgery,[9] and a variety of systemic diseases such as hormonal imbalance, especially menopause and reduced androgen levels, dietary imbalance in omega-3 and omega-6 intake,[10] autoimmune diseases, diabetes mellitus, and Parkinson's disease. Many of these factors independently or interacting with each other, may lead to entry into what has been called the *vicious circle* of DED.[11] Therefore, DED is not only associated with the prototype autoimmune condition, Sjögren's syndrome (SjS) but to a variety of different diseases suggesting the multifaced aspects of DED explaining its high prevalence in the population.

Signs and Symptoms

DED is considered in the definition as a *symptomatic* disease with a wide variety of symptoms reported by the patients, such as discomfort, gritty eyes, stinging, burning photophobia, pain but also blurred vision, itching, and tearing sensation. DED symptoms and varying degrees of patient's activity limitations may generate anxiety, depression, and frustration.[12] Clinical signs include conjunctival injection, conjunctival and corneal staining, mucous discharge, corneal/tear signs (i.e., filamentary keratitis), lid/meibomian glands dysfunction, reduced tear break-up time (TBUT; fluorescein based), and low Schirmer score. Many terms have been employed to describe punctate staining of the ocular surface, such as superficial punctate keratitis, punctate epithelial erosion, or simply, punctate corneal staining. Punctate staining is a common diagnostic feature of ocular disease, encountered in a wide range of external eye disorders, and considered and indirect sign of inflammation.

Most patients have mild-to-moderate complaints and can be treated symptomatically with lubricants for long periods of time.[13] Patients with more severe conditions such as those with severe keratitis represent a group of patients with worse prognosis and in need of more effective treatments. Severe DED patients are trapped in a vicious cycle of ocular surface inflammation with the risk of complications such as keratinization, corneal scarring, thinning, neovascularization, sterile or microbial ulcerations with a risk of corneal perforation, and vision loss.

For the majority of DED patients, there is a partial relation between signs and symptoms. While symptoms are thought to be characteristic, several studies have shown that <60% of subjects with objective evidence of DED are symptomatic.[14] No association between the Schirmer test/staining and symptom frequency was found.[15] Similarly, meibomian gland disease (MGD) is more commonly asymptomatic than symptomatic, and symptom presentation did not correlate with the severity of ocular surface damage.[16] However, in a significant proportion of patients who had conflicting signs and symptoms, corneal staining is considered one of the most reliable criteria to evaluate the damage to the corneal surface.[17] Therefore, an apparent paradoxical disconnect between signs, symptoms, and severity is frequently found in DED patients making symptomatology alone a relatively poor indicator of severity in some patients, and also a confounding variable in daily practice and in the relations, for example, between ophthalmologist and rheumatologists.

Dry Eye Disease and Inflammation

Inflammation is the body's defense to microbial invasion or a *critical* response to tissue injury under sterile conditions. Whatever the cause of the inflammatory response, its *purpose* is to remove the source of the disturbance, to allow the host to adapt to the abnormal conditions, and to restore functionality and homeostasis. Para-inflammation is defined as the innate and self-limiting physiological mechanism, with the role to maintain tissue homeostasis and restore its function.[18] This *low-grade,* subclinical chronic inflammation contributes critically to many human diseases not previously not considered inflammatory disorders including DED.[19] Well-controlled para-inflammation may be beneficial, whereas dysregulated para-inflammation is detrimental and probably at the origin of DED. In fact, stressing factors that are not controlled or *re-set* by the para-inflammation may adversely affect tear film stability and osmolarity that can induce ocular surface damage and initiate a clinical inflammatory cascade that generates innate and adaptive immune responses.[20,21] A self-perpetuating cycle develops that includes antigen-presenting cells (APCs), CD4+ helper T-cells (Th), particularly Th1 and Th17, multiple cytokines such as interferon-γ, tumor necrosis factor-α, and several interleukins (IL), corneal nerve abnormalities, and corneal epithelium apoptosis.[21-23]

One of the main pathogenic factors in DED is the hyperosmolarity of tears resulting from dysfunction of the tear secretory glands and stimulating the production of inflammatory mediators on the ocular surface.[6,24-26] Inflammatory mediators promote the activation and migration of immature APCs to draining lymphoid tissues,[20] where are responsible for priming naive Th, leading to the expansion of autoreactive CD4+ Th1 and Th17 cell subsets.[23,27] T-cells subsequently infiltrate the ocular surface, where they secrete additional proinflammatory cytokines initiating a sort of local autoimmune reaction.[20,24,27] Interestingly, the conjunctiva of patients with DED, with and without SjS, exhibited similar infiltrating lymphocytes and evidence of immune activation/inflammation markers.[28] In particular, IL-17 has a role in promoting autoimmunity in part

through directly enhancing B-cell proliferation, differentiation, and plasma cell generation.[29] How these mechanisms are dependent or independent of systemic and autoimmune disorders is still unknown.

The ocular surface system is not only a morpho-functional unit which manage the interaction of the eye with the environment, but a real "solid organ" which includes a complex interaction between different mucosal tissues, immune cells, nervous fibers, vascular and lymphatic vessels, and local microbiome. All these embryologically and anatomically different tissues and cells accurately interplay to guarantee the ocular surface ultimate function, hence the preservation of sight.[19,30-32]

Ocular surface, as well as all body tissues, is continuously challenged by daily repetitive stimuli, injuries, and insults from the environment. Homeostatic physiologic balance is preserved by a strictly regulated inflammatory mechanism. This innate immune inflammatory response, also termed "para-inflammation," is self-limiting and directly proportioned to the insult intensity. Para-inflammation is an adaptive response of the immune system to maintain homeostasis (or reset the homeostatic threshold of the tissue) and restore tissue functionality.[19,33] A persistent or disproportionate para-inflammatory response may cause a shift toward an inflammatory disease. Therefore, the innate immune system has critical regulatory roles in preserving ocular surface homeostasis, in amplifying and instructing the adaptive immune response that follows[34,35] and in the defensive function reducing the risk of pathogenic insults.[36]

Dry Eye Disease and Rheumatological Diseases

In systemic rheumatological and autoimmune disorders, the cause of dryness is mostly secondary to inflammatory lacrimal damage and tissue destruction. In addition, circulating antibodies to the muscarinic M3 receptor can also cause a neurosecretory block. Chronic lymphocytic infiltration of the principal and accessory lacrimal glands and salivary glands, and the conjunctival was found in biopsy specimens of SjS patients.[28] Among the rheumatological disorders, primary SjS is most typically associated with DED. Rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and graft-versus-host disease are frequently associated with DED of various degrees of symptoms and inflammation [Figure 1]; in some patients, the aforementioned rheumatic autoimmune systemic conditions can co-exist with SjS. These conditions are also characterized by the positivity for specific autoantibodies, anti-citrullinated peptides for rheumatoid arthritis, anti-Sm

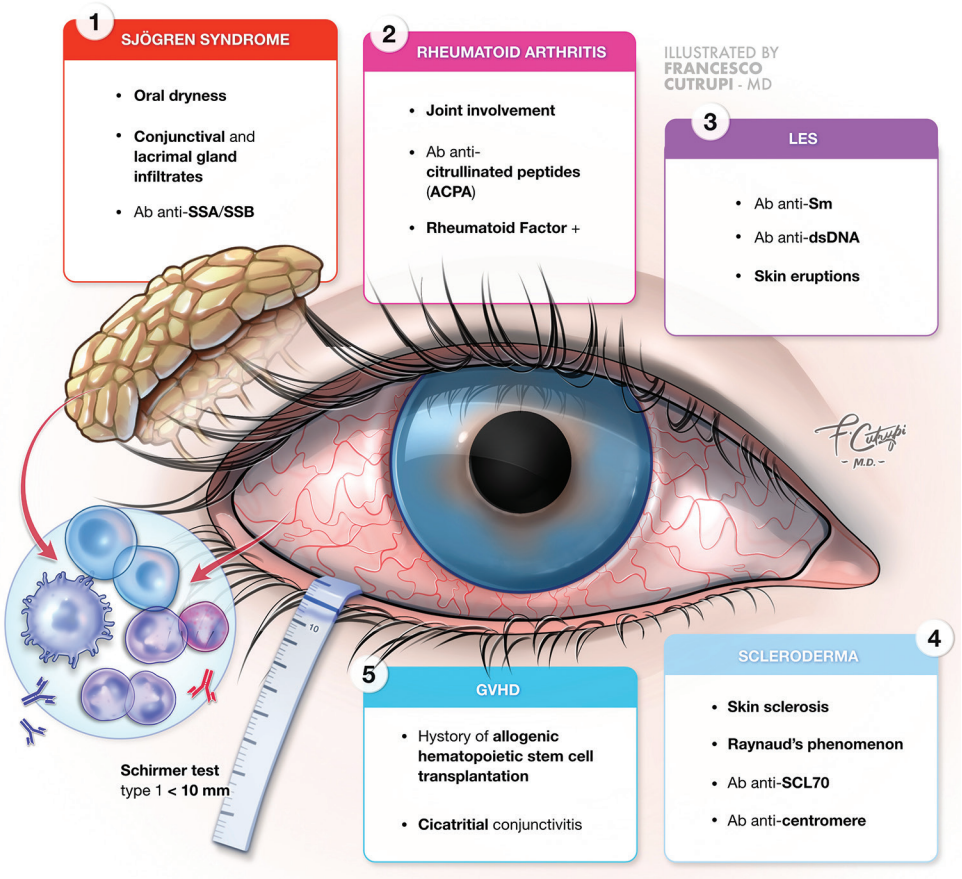

Figure 1: Low aqueous production (Schirmer test <10 mm) and mucosal infiltration of monocytes are typical of dry eye disease associated with rheumatic and autoimmune diseases. The main clinical features of Sjögren's syndrome (1), rheumatoid arthritis (2), systemic lupus erythematosus (3), scleroderma (4) and graft-versus-host disease are shown in the boxes (5)

or anti-dsDNA for systemic lupus erythematosus, anti-Scl70 or anti-centromere for systemic sclerosis, and anti-SSA and/or anti-SSB for SjS. In many cases, other organs and systems are involved, including joints, skin, lung, kidney, and central and peripheral nervous system.

Ophthalmologists, at the time of diagnosing a patient with a DED based on signs and symptoms and local tests, should always consider a potential systemic comorbidity or a systemic cause of DED [Table 1]. While the definition of specific statements for the standardization of "red flags" for rheumatologist and ophthalmologist referrals for the management of patients with rheumatic diseases and uveitis has been suggested,[37] a definite rheumatologist/ophthalmologist joint approach for DED patients has not been established. However, similarly to what stated in the paper by Olivieri *et al*.,[37] the co-operation between rheumatologists and ophthalmologists is essential for a better understanding and evaluation of patients with rheumatic disease and/or related DED. On the other hand, the "multidisciplinary ophthalmologist-rheumatologist approach may improve early differential diagnosis and the prognosis of patients with rheumatic disease and DED through shared management and, when possible, earlier etiological treatment, to design the optimal management and to prevent potential complications.

Unfortunately, there is no standardized systemic treatment for patients with DED in non-Sjogren and even in SjS patients. The treatment decisions remain challenging in clinical practice, without a specific therapeutic strategy beyond the relief of symptoms. The European League Against Rheumatism (EULAR) promoted an international collaborative study aimed at developing consensus-based recommendations for the management of patients with SjS. Treatment was subdivided in "topical" and "systemic" medications to be useful for all healthcare professionals.[38] Ocular involvement is considered only one of the multiple aspects of SjS highlighting the need for a multidisciplinary approach to the disease. The first therapeutic approach for dryness should be the symptomatic relief using topical artificial tears and ointments, local glucocorticoids, cyclosporine A (CsA), and muscarinic agonists (orsl pilocarpine) for refractory cases. On the other hand, there is no evidence that systemic therapies including oral glucocorticoids, hydroxychloroquine, immunosuppressants, and B-cell target therapies give a symptomatic relief in patients with DED; therefore, these therapies are suggested only for patients with systemic manifestations of the disease (polyarthritis, parotid enlargement, polyneuropathy, and interstitial lung diseases), in which the evidence of efficacy is robust.[38] The EULAR algorithm suggested to assess and treat patients with primary SjS with DED considered the results of the Schirmer test < or > than 5 mm, of ocular surface disease index score (OSDI) < or > than 33, and additional severity criteria such as presence of neuropathic pain, impaired visual function, blepharospasm, severe MGD or eyelid inflammation, impaired corneal sensitivity, and severe keratitis following recommendations from relatively old literature papers.[13,39] In fact, the value of the Schirmer test and the use of OSDI instead of other questionnaires are still debated. Anyway, a detailed assessment as suggested by EULAR, needs definitely an expert cornea specialist which is not always possible for the management of these patients. New semiautomatic systems have been developed to objectively measure several ocular surface parameters. More recently, clinically applicable fully automated deep learning-based systems for the severity assessment accordingly to a corneal fluorescein staining scale have been shown to be highly correlated with the score determined by ophthalmologists, predicting 88% of disease improvement or deterioration.[40,41] The clinical application of these systems is still limited but opens up a different perspective to achieve reliable and reproducible methods for DED severity assessment, potentially useful both in clinical trials and in real life.

Table 1: Ophthalmologist/rheumatologist referral in dry eye patients

When an ophthalmologist should refer a dry eye patient to the rheumatologist (at least one of them)	When a rheumatologist should refer to the ophthalmologist
Patients with hypo-secretive dry eye and Schirmer test <10 mm	All patients with red eye, photophobia, blurred vision and/or reduction in visual acuity, ocular dryness, burning sensation and pain
Patients suffering from recurrent episodes of conjunctivitis	
Patients with concomitant oral dryness	
Patents with personal history of joint inflammation, skin eruptions, Raynaud's phenomenon, erythema nodosum	All patients with a history of ocular inflammation
Laboratory abnormalities: Hyper-gammaglobulinemia, rheumatoid factor positivity, ANA and anti-ENA positivity (especially anti-SSA and/or anti-SSB), low C3, and C4, cryoglobulinemia	Patients with lid or lid margin hyperemia
	Patients with a documented diagnosis of dry eye (i.e. Schirmer test <10)
	Patients with persistent use of topical corticosteroids

In a recent study, 3 distinct subgroups of SjS were identified using cluster analysis based on subjective symptoms and clinical and biological manifestations: (1) patients with B-cell active disease and low symptom burden; (2) patients with high systemic disease activity; (3) patients with low systemic disease activity and high symptom burden.[42] This clustering classification did not specifically mention DED and did not correlate with a previous classification based on symptoms only but stratified patients with different prognosis, suggesting that different subgroups represent different heterogeneous pathophysiological disease mechanisms, stages of disease, or both. It is possible that lymphocytic infiltration of the epithelia of different organs, including the ocular surface, may be critical in the development of a localized (ocular) involvement. Since systemic manifestations occur in approximately 30%–60% of SjS patients,[43] it is not clear which one of these clusters is the one that the ophthalmologists frequently have to deal with, patients with low systemic disease activity but high ocular symptom burden; therefore, patients without the potential support of systemic treatment.

Unfortunately, there are no guidelines or recommendations aimed at evaluating and managing eye dryness in patients with

other systemic rheumatic autoimmune diseases; therefore, for these patients, clinicians should refer to the EULAR recommendations for SjS.

Dry Eye Disease, Gender, Aging, and Hormonal Factors

In the era of gender and precision medicine, the ocular surface system perfectly adapts its function and dysfunction to such a novel point of view. Each of us differently reacts and interacts with environmental stimuli, injuries, and traumas depending on its personal and unique proteomic and genomic expression, immune endotype growth,[44] gender, age, and lifestyle. Even sleeping hours or drug use may impact ourselves. Sex hormones and their physiological or pathological impairment critically impact on highly regulated innate immune cellular barrier, causing a dysregulation of homeostatic mechanisms and leading to a subclinical persistent chronic inflammation inducing an ocular surface system failure, particularly in DED.

Epidemiological sexual disparity of DED prevalence suggests that sex hormone changes may influence the composition of the tear film and the function of different ocular surface structures.[45-49] Estrogen, progesterone, and testosterone are known to play important and different roles in the ocular surface homeostasis acting through their receptors on glands, conjunctiva, and corneal epithelium[50] and modulating the production of the main tear film components. The absolute hormone levels, their fluctuations, and changes in receptor's responsiveness are all important factors in determining ocular surface stability [Figure 2].

Systemic sex hormones and their local receptor expression levels may be up or downregulate themselves during the physiological fluctuation of menstrual cycles or menopause.[50-58] Moreover, in mucosal tissues, the mucin protection barrier appears to be largely influenced by local and circulating sex hormones' levels, by modulating key mucin components.[59] The apical epithelial barrier is constituted by transmembrane mucins and carbohydrate-binding proteins named galectins, which are highly expressed by the ocular surface.[60,61] In women after breast cancer surgery, the drastic and unexpected estrogenic block subverts the hormonal asset, leading to psychological and physical not well-known systemic effects, and ocular and vaginal dryness. Brest Cancer Iatrogenic Dryness causes a two-fold increase in symptoms compared to untreated women and critically impacts on daily life activities of such patients.[62] Ocular surface immunology and its relationship with steroid sex hormones represent an interesting evolving field with potential implications for eye health. The decrease in E2 levels during menopause is associated with a concomitant reduction in B and T lymphocyte levels, which can, in part, be counteracted by hormone replacement therapies.

Aging is the dysregulation of para-inflammation which evolves into a chronic, persistent, and mostly subclinical inflammatory response. This "chronic abnormal inflammatory process" leads to chronic detrimental inflammatory reactions and immunologic events, to various immune-related diseases, such as infection and autoimmune disorders.[63,64] Low-grade chronic inflammation contributes to many human diseases that were previously not considered inflammatory disorders, including obesity, atherosclerosis, and neurodegenerative

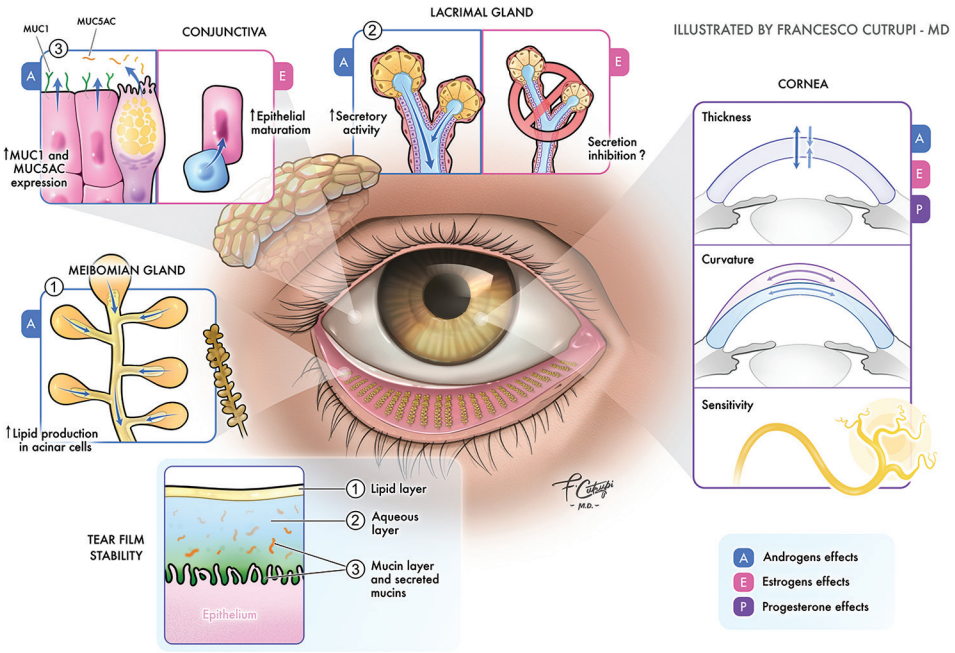

Figure 2: Effects of androgens, estrogens, and progesterone on the ocular surface: Androgens enhance lipid production in the meibomian glands (1) and stimulate secretion in the lacrimal glands, whereas estrogens may inhibit this process (2), Androgens also promote the production of both soluble and transmembrane mucins, while estrogens facilitate the maturation of the conjunctival epithelium (3), Additionally, androgens, estrogens, and progesterone influence the cornea by altering its thickness, curvature, and sensitivity

disorders.[65] It is now clear that chronic inflammation is involved in almost all age-related degenerative diseases, including those that occur in "immune privileged" tissues such as the brain (Alzheimer's and Parkinson's diseases)[65] and the eye (age-related macular degeneration and DED).[66] If the inflammatory response does not shut down in a timely way, the inflammatory cascade becomes chronic and smoldering.[67] Therefore, aging is associated with a persistent low-grade activation of the systemic immune system, frequently defined "inflammaging."[33] Dysregulated age-related systemic para-inflammation plays a major role in the development of frailty and age-related pathologies not only for an excessive inflammatory stimulation but also for an insufficient anti-inflammatory response.

Several clinical and biochemical markers and parameters express the different constitutive ocular surface tissues' function,[68] unveiling all together the aging state of such a complex system even in asymptomatic volunteers. This suggests a lack of awareness from older subjects relative to their age-related ocular surface failure [Figure 3]. An Ocular Surface Frailty Index has been recently proposed as a predictor of ocular surface symptom onset in this unaware population.[69] Therefore, aging and sex hormones physiological, pathological, or iatrogenic impairments are not only risk factors for ocular surface disease but may represent preclinical and/or subclinical conditions.

Dry Eye Disease and Infections

Viral infections have been related to the onset of autoimmune diseases including DED and in particular SjS. Viral infections may have the potential to initiate a local pro-inflammatory response in the lacrimal gland stimulating the production of autoantibodies from lymphoid structures in genetically disposed subjects. Different viral infections have been suggested to play this role, in particular hepatitis B and hepatitis C (HCV) viruses, Epstein–Barr, acquired immunodeficiency syndrome virus (HIV), and lately coronavirus 2019 (COVID-19). For example, DED has been reported from 10% to 50% of HCV-infected patients.[70] DED is also a common finding in HIV patients with a prevalence of around 40% of them.[71] Differently from SjS, in HIV-related DED, the lymphocytic infiltration of the lacrimal grand is characterized by CD8+ cells rather than CD4+ helper cells.[72]

During the recent COVID-19 pandemic, the term "quarantine dry eye" was introduced to highlight the frequent ocular surface symptoms not only related to the disease itself but also associated with the new environmental conditions and the increased use of screens for work or free time.[73] The use of masks also increased symptoms related to MGD worsening ocular surface staining scores. In the early phase of the infection, patients experienced dry eye symptoms in 5%–15% of cases,[74] whereas chronic dacryoadenitis and possible nerve fiber damage into the lacrimal gland, have been described as a post-COVID-19 complication.[75] Several clinical observations reported increased symptoms of DED between 2 and 10 months after infection probably related to a corneal small fiber neuropathy and other morphological changes in corneal microstructure similar to those found in diabetic cornea and DED.[76]

Dry Eye Disease and Depression

Discomfort of DED and interference with daily activities contribute to lower quality of life and may put patients at greater risk for depression. Conversely, patients with depression were found to spend more time watching TV and using computer contributing to evaporative DED.[77] A recent meta-analysis confirmed that DED patients are associated with an increased prevalence of depression, whereas depressed patients have a concurrent higher risk of DED.[78] Interestingly, a genome-wide association study, supported by a transcriptome

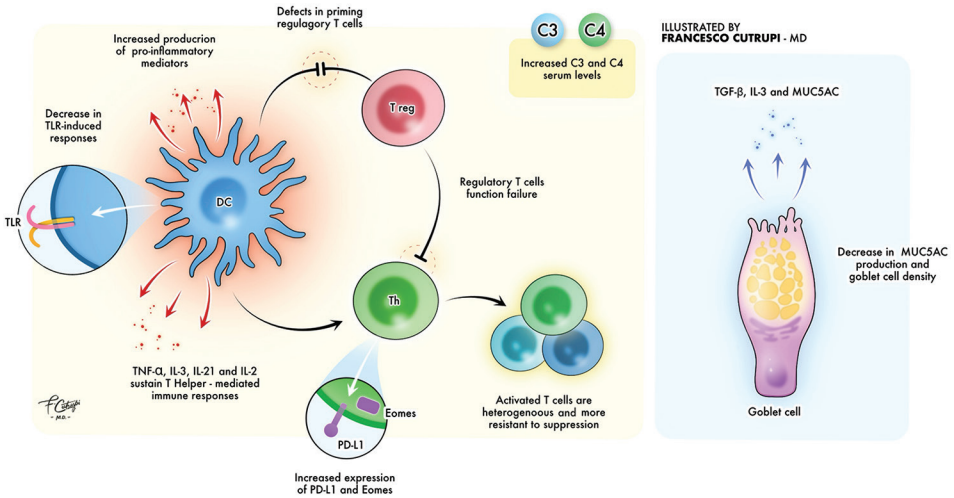

Figure 3: Inflammaging: Immunological alterations underlie the heightened inflammatory state of the ocular surface associated with aging. These include dysregulation in dendritic cell responses, regulatory T cells, and T helper cells, along with modified cytokine secretion and complement system activation. Additionally, there are significant changes in goblet cells and their secretory functions

systemic review, showed a similar gene expression in both diseases and the bidirectional exposure-outcome causation for DED-to-depression and depression-to-DED.[78] Another recent study showed that depression was associated with more severe dry eye symptoms and overall signs, suggesting that among patients with moderate-to-severe DED, those with depression may be likely to have more severe DED.[79]

Principles of Treatment

Independently from systemic comorbidities, different profiles of signs and symptoms have been associated with different severity levels of DED to suggest the appropriate range of therapeutic options.[80,81] For the treatment of mild DED, education, and environmental modifications, elimination of offending topical or systemic medications, lubrication using artificial tear substitutes, gels/ointments, and eyelid therapies are the first approach.[81] For the treatment of moderate DED, in addition to the treatments for mild DED, the use of anti-inflammatory agents, such as topical CsA and corticosteroids, and systemic omega-3 fatty acids supplements are suggested and proven to be effective. Since the long-term use of topical corticosteroids is limited by potential sight-threatening side effects, such as glaucoma, cataracts, and infection, CsA has been widely used in the management of DED with long-term data and clinical experience of improvement in signs and lowering of DED symptom severity. The first formulation of CsA 0.05% was approved by the Food and Drug Administration (FDA) in 2002. In 2016, EMA approved the CsA 0.1% formulation in cationic emulsion based on the result of the SANSIKA study with the indication for the treatment of severe keratitis in DED patients not responsive to tear substitute treatment.[82] Several other CsA formulations have been proposed with potential new options for the treatment of severe DED. A nanomicellar topical CsA formulation of 0.09% has been recently approved by the FDA, showing significant improvement in signs and symptoms.[83] Lifitegrast 5% reduces T-cell activation and migration blocking the interaction between lymphocyte function-associated antigen-1 and intercellular adhesion molecule-1. It was the second FDA-approved topical ocular anti-inflammatory drug for the treatment of DED based on the results of the OPUS studies.[84,85] Diquafosol is approved only in Japan for the treatment of DED: binding to the P2Y2 receptor and diquafasol increases the tear volume stimulating conjunctival epithelial cells and goblet cells.[86] Several other drugs with anti-inflammatory effects have been proposed for the treatment of DED including IL-1 receptor antagonists, janus-kinase inhibitors, lubricin, lacritin, thymosin beta-4, serine protease inhibitors, resolvin analogs, integrin antagonists and many others; however, the solution for DED patients remains far to be resolved.[74]

In addition, polyunsaturated fatty acids, such as omega-6 (linolenic acid) and omega-3 (a-linolenic acid), diets based on calorie restriction and supplementation with vitamins and antioxidants have gained popularity as potential strategies to prevent age-related diseases.[87,88] Fascinating, actions pointed toward rejuvenating the immune system may have a beneficial impact on the progression and severity of certain diseases in the elderly.[89,90] Aging is a heterogeneous process among people and species and it varies between different organs and tissues of the same individual. Our genes, our lifestyles, and our response to stress are at the same time unique and variable but mostly a critical target of our prophylactic management. The immunobiography of every single life tells a different story of how each person will respond to the internal and external stressors.[90]

Conclusion

DED should be considered a localized inflammatory/autoimmune disease which can be frequently associated with a multitude of systemic disorders. In the management of all DED patients is important to understand if an underlying systemic disease may be involved in the development of typical ocular signs and symptoms and therefore, multidisciplinary care in particular (but not only) with a rheumatologist, may be required to initiate an appropriate local and systemic treatment to improve lifespan and quality of life of affected patients.

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Conflicts of interest

There are no conflicts of interest.

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