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LITERATURE REVIEW

Обзор
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Лечение синдрома сухого глаза, комплексный подход

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РЕФЕРАТ

Синдром сухого глаза (ССГ) представляет собой хроническое состояние глазной поверхности, характеризующееся неспособностью вырабатывать достаточное количество или оптимальное качество слезы для увлажнения глаз. Во всем мире при начальном лечении ССГ применяются искусственные заменители слезы, однако они не устраняют основные причины заболевания. В целом, современные методы лечения либо уменьшают воспаление поверхности глаза, либо стабилизируют слезную пленку, тем не менее все еще не ясно, какая терапия лучше для тех, у кого ССГ связан с дефицитом слезы или является следствием аномально быстрого испарения. ССГ относится к спектру хронических воспалительных заболеваний, следовательно, изменение образа жизни, оценка и коррекция питания, наряду с приемом лекарств, направленных на уменьшение воспаления, могут быть эффективной стратегией. «Целостный», персонализированный подход может дать начало новому поколению клинических исследований, которые позволят получить более эффективные решения для лечения ССГ.

Ключевые слова: *сухой глаз, роговица, глазная поверхность, питание*

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Review

Management of Dry Eye Disease, Integrative approach

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ABSTRACT

Dry eye disease (DED) is a chronic condition of the ocular surface characterized by failure to produce sufficient amounts or optimal quality of tears to moisturize the eyes. Worldwide, ocular lubricants are used in the initial management of DED, but they do not address the underlying causes of the disease. Overall, current therapies either reduce ocular surface inflammation or stabilize the tear film, but currently, it is still not clear which medication is best for those who has aqueous deficient DED or evaporative DED. DED is on the spectrum of chronic inflammatory disorders, thus lifestyle changes, nutritional status assessment and correction along with medications aimed to reduce inflammation could be an effective strategy. «Holistic», personalized approach, might give the way for a new generation of clinical studies to provide more effective solutions for management of DED.

Keywords: *Dry eye, cornea, ocular surface, nutrition*

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INTRODUCTION

Dry eye disease (DED) is a chronic condition of the ocular surface characterized by failure to produce sufficient amounts or optimal quality of tears to moisturize the eyes [1, 2]. Messmer (2015) indicated that DED can be categorized as «dry eye with reduced tear production (aqueous deficient) and dry eye with increased evaporation of the tear film known as the hyperevaporative type» [3]. Although 10 % of individuals have aqueous deficient DED, more than 80 % have either the hyperevaporative type related to meibomian gland dysfunction (MGD), or a combination of both types.

DED can affect vision and quality of life, as symptoms often interfere with daily activities (reading, writing, or

working on display monitors). Prevalence rates range from 5 % to 50 %, but can be as high as 75 % among adults over age 40, and women are affected most often [4].

Several risk factors are linked to DED development:

• personal (advanced age, sex, Asian ethnicity, and contact lens use [4–5];

• environmental (low-humidity environments, windy settings, air-conditioned rooms, extended periods of reading or driving or exposure to screens (e.g., computer, tablets, smart phones), and second-hand smoke exposure);

• clinical illnesses (autoimmune diseases (rheumatoid arthritis, sarcoidosis, Sjögren syndrome) and chronic conditions, such as thyroid abnormalities, Bell palsy, diabetes, rosacea, hepatitis C infection, seasonal and perennial allergies, and Demodex mite allergic conjunctivitis) [6];

• ocular factors such as ocular surgery or injury or contact lens wear [5, 7, 8]. Clinical conditions that increase DED risk include Parkinson disease, as the normal blink reflex of 16 to 18 times per minute is reduced to 1 to 2 blinks per minute [9], can also result in DED [7];

• females are more likely to experience DED, with increased prevalence after menopause. Hormone replacement therapy such as the use of estrogen alone or with progestin may worsen symptoms [10], and androgen treatment can improves dry eye symptoms [11];

• low dietary intake of omega-3 fatty acids is an additional risk factor associated with DED [12, 13];

• medications such as antihistamines, beta-blockers, decongestants, diuretics, selective serotonin reuptake inhibitors, anxiolytics, tricyclic antidepressant medications, antipsychotics, oral contraceptives, antiparkinsonian agents, and oral isotretinoin are also associated with DED [6];

• altered immunity is a significant factor in DED [6].

As for pathogenesis DED is recognized as a localized autoimmune disease driven by dysregulated immunoregulatory and inflammatory pathways on the ocular surface [14].

Mucosal tolerance disruption [14], starts when the immune balance of the ocular surface is altered due to internal or external factors. Stress to the ocular surface initiates a cascade of acute response cytokines and sequestering of auto response T cells that results in a chronic autoimmune response [15].

In addition to the localized autoimmunity, it has been recognized that systemically delivered antibiotics can worsen ocular surface inflammation [16].

Management of DED

Although majority of guidelines categorize DED as either an aqueous or evaporative process [2], symptoms differ from patient to patient they may have either evaporative or aqueous disease, or even combination of both conditions [7]. Although the main treatment goal is to restore tear film homeostasis [2], heterogeneity exists in the presentation of DED and a variety of treatments are used to manage this syndrome.

Recent review presented by the American Academy of Ophthalmology regarding the use of oral antibiotics for meibomean gland disease-related ocular surface disorders [17] reported antibiotic treatment in animal models actually did worsen DED rather than improve it.

Worldwide, ocular lubricants are used in the initial management of DED, but they do not address the underlying causes of the disease [16]. Studies in the past two decades were dedicated to find potentially more effective, ophthalmic pharmacological drugs targeting pathophysiological pathways of DED, but it is resulted in the official approval of very few drugs, one of the is cyclosporine [16]. Overall, current therapies either reduce ocular surface inflammation or stabilize the tear film [18], but currently, it is still not clear which medication is best for those who has aqueous deficient DED or evaporative DED.

Dry eye medication aims to provide relief in both signs and symptoms. However, a recent review presented by Holland and colleagues [16] provides a systematic analysis of topical ophthalmic drugs for treatment of dry eye that have been reported over the last twenty years. Surprisingly, the authors reported a lack of relief of signs and symptoms in more than 100 studies reviewed. The review categorizes the various products into anti-inflammatories, mucin and tear secretagogues, and other products [16].

The role of the tear film

The corneal surface of the eye is a barrier that protects the orbital structures from ultraviolet light exposure, infections and other potential harmful substances [19].

Human tears play an important role in keeping the ocular surface moist, and protect the corneal surface from trauma and infection.

Tear film structure is complex, consists of three layered structure, that includes the mucous, aqueous, and lipid layers. They are recognised as separate entities unrelated to the corneal and conjunctiva! Epithelia, with complex interactions of the tear components within the tear layer and with the epithelial microvilli and glycocalyx structure [20].

The well-being of the tear film is dependent on a healthy cornea and conjunctival epithelium and a biochemically correct secretion from each of the tear glands:

• the normal chemical composition of the tear film;

• the origins of these components;

• the mechanism of secretion of each of the tear glands.

If we look detailed at every layer we can see that each of them is multicomponent, complex structure.

Dysfunction in any layer lead to hyperosmolarity of tear (less water in the tears) from either decreased aqueous tear production, and/or increased tear evaporation due to problems with production of the meibomian gland oils, or reduced production of mucin [20].

The outermost lipid layer is secreted by the Meibomian glands, which is composed mainly of wax monoesters, cholesterol esters, and a variety of diesters that are mostly fluid at body temperature. Most of the lipids secreted by

these glands are manufactured within the gland, but some, such as cholesterol, may be accumulated whole from the blood as suggested by the fact that tear levels reflect serum levels [21, 22].

There is also a very small amount of highly polar lipid composed of triglycerides, free fatty acids, and phospholipids in this outer layer.

The meibomian gland is a large sebaceous gland and, that is why its secretions are susceptible to changes in body chemistry. Androgen receptors are present in meibomian glands [23], and androgen deficiency is associated with the dysfunction of Meibomian glands and development of DED. Androgens enhance sebaceous gland function, while estrogens and progestogens suppress it. There is much evidence that shows increasing androgen levels in mammals causes an increase in the quality and quantity of meibum secreted, and low androgenic activity results in meibomian gland dysfunction and its compromised secretions. In clinical studies, dysfunction of Meibomian glands and lipid tear deficiency have been found in various androgen-depleted states [24].

The aqueous layer consists of water, electrolytes, proteins, peptide growth factors, immunoglobulins, cytokines, vitamins, antimicrobials, and hormones secreted by the lacrimal glands.

Electrolytes include sodium, potassium, magnesium, calcium, chloride, bicarbonate, and phosphate ions [25]. The electrolytes are responsible for the osmolarity of tears, acting as a buffer to maintain a constant pH and contribute to maintaining epithelial integrity of the ocular surface [26, 27]. An increase in osmolarity of the aqueous layer is a global feature of dry eye syndrome and damages the ocular surface directly and indirectly by triggering inflammation [25].

More than 60 proteins have been identified in human tears including albumin, immunoglobulins, metal-carrying proteins, complement, histamine, plasminogen activator, prostaglandins, proteases, and antimicrobials [28]. Presence of lysozyme, lactoferrin, β-lysin, complement, defensins, and group II phospholipase A2 and the specific immunity of antibodies, such as secretory immunoglobulin A (sIgA) are responsible for primary defense system of the ocular surface [25]. It was found that in aqueous-deficient dry eye syndrome, the concentration of lysozyme, lactoferrin, lipocalin, and sIgA are reduced, compromising the integrity of the defense system, which may make the ocular surface more susceptible to infection, in addition to the symptoms of dry eye. Presence of growth factors such as EGF, transforming growth factor-β (TGF-β) and hepatocyte growth factor [HGF]), together with vitamin A participate in regulation of epithelial proliferation, motility, and differentiation, corneal wound healing and immune modulation [29]. It was found that EGF is decreased in DED, similar to other growth factors secreted by the lacrimal glands.

Ocular mucus is composed of mucin, immunoglobulins, urea, salts, glucose, leukocytes, cellular debris, and enzymes [30]. Mucins are high molecular weight glycoproteins that are heavily glycosylated: 50 to 80 % of their mass can be attributed to their carbohydrate side chains [30].

Multiple pathways regulate the secretion of ocular mucin. Cytokines are known to both promote and reduce mucin levels in various mucous membranes. For example, vitamin A and cytokines influence mucin production, absence of vitamin A reduces levels of MUC5AC and MUC4 [31]. Vitamin A act via autocrine and paracrine mechanisms to regulate epithelial proliferation, motility, and differentiation.

There is ample evidence in the literature that malnutrition, especially in the form of insufficient vitamin A and protein, has an adverse effect on tear, conjunctival, and corneal health.

It was reported that vitamin A deficiency is responsible for chalazion formation in Meibomian glands [32].

There is a interesting correlation between DED and iron deposits in the cornea. Excess deposition of iron in the cornea had been observed in a number of corneal diseases as well as after some surgical procedures [33]. Iron lines exist in the basal epithelial cells of the cornea and are visible upon slit lamp examination. Electron microscopy revealed that ferritin is abundant in iron lines. There are four types of known iron lines: Hudson-Stahli Line, Fleischer's Ring, Stocker's Line, and Ferry's Line [34]. Additionally, in the last two decades there have been reports of iron lines following radial keratotomy [35], refractive keratoplasty [36], intrastromal corneal ring insertion [37].

Studies proposed that basal epithelial cell stress leads to an increase in transferrin or lactoferrin receptor expression causing increased iron binding and uptake [38]. Other studies have demonstrated an increase in transferrin-receptor expression in response to cellular stress.

Those lines may be associated with DED. Study that compared tear proteins in patients with DED demonstrated a significant decrease in lactoferrin and a simultaneous increase in ceruloplasmin concentration that could lead to an increase in potentially toxic free iron [38].

These data suggest a relationship between accumulation of oxidative stress and the development of corneal epithelial changes in dry eye [38].

Recent studies discuss the importance of the microbiome changes of ocular surface in DED. In 2007 Graham and colleagues [39] compared the microbiome composition of the ocular surface in a group without dry eye to a group with DED and to identify whether resident bacteria were pathogens or commensals. They reported significant differences between the population and type of bacteria residing on the ocular surface of each group. Using both conventional culture and 16S rDNA they identified specific species including Bacillus spp. and Klebsiella oxytoca, as well as an overall increased bacterial count (CFU/swab) in participants with DED [39]. Staphylococcus epidermidis was present in 100 % of samples, and it suggested that S. epidermidis, as an integral member of epithelial microflora, may exert a probiotic function by preventing colonization of other pathogenic bacteria [40].

Goblet cells are responsible for mucin production and hence reduction in these cells will reduce mucin production and disturb the healthy tear film. Graham et al. [39] showed bacterial growth correlated with decrease of goblet cells. Interestingly, in a mouse model of irritable bowel syndrome in which mucosal inflammation was stimulated using normal colon microflora, a similar reduction in goblet cell depletion and inflammatory cell infiltration was noted [41]. It has been suggested that production of mucin on the ocular surface is analogous to production of glycoproteins in the gastrointestinal tract [42], similarly leading to the release particular glycans and polysaccharides as in the intestinal tract which boosts the growth of certain bacterial species [43].

There is an evidence that the use of probiotic lysates, vitamins and omega-3 fatty acids was effective to treat comorbid ocular, enteral and affective symptoms that comprise a disorder called «irritable eye syndrome» [44].

The authors of the study suggested that, via MALT (mucosal associated lymphoid tissue that is contiguous from the gut to the respiratory system to the naso-lacrimal system), subclinical inflammation arising from dysbiosis can cause or exacerbate signs and symptoms of DED since the eye contains its own local lymphoid tissues; the conjunctiva-associated lymphoid tissue (CALT), which samples antigens and maintains tolerance to commensal microbes [45].

Integrative Management of DED

Clinicians prescribe first-line medication that work for most dry eye symptoms. But what if those treatments are not working?

We need to look at the patient as a whole, not just focusing on their eyes, but rather considering that there may be an underlinig systemic disorder and there is a need to think outside the slit lamp and examine patient with a more systemic approach.

N-acetylcysteine (NAC). NAC is known to be effective in treating filamentary keratitis in patients with DED. NAC reduces oxidative stress on cells, decreasing the inflammatory response, which is important in case of autoimmune disorders.

Schmidl and colleagues found that a single drop of NAC increased tear film thickness for 24 hours in dry eye patients [46].

Testosterone

Sullivan and colleagues hypothesize that topical androgens may be effective for the treatment of DED, targeting both evaporative and aqueous-deficient dry eye [47].

Nutrition and probiotics

In 2016, a group of researchers examined the effect of a combination of probiotics and vitamins in people with DED. Their results suggest that synbiotics, which combine probiotics and prebiotics, can decrease some signs and symptoms of DED while also modulating gut function [48]. This group explored a combination of Lactobacillus acidophilus, Streptococcus thermofhilus, Lactobacillus plantarum, Lactobacillus rhamnosus, Bifidobacteriumlactis, Zn, Vitamins B1, B2, B6 and niacin.

Another study examining the effect of a combination of fish oil, lactoferrin, zinc, vitamin C, lutein, vitamin E, γ-aminobutanoic acid and Enterococcus faecium WB2000 on DED, and reported significant improvement in clinical symptoms at 4 and 8 weeks [49].

A report from Korea [50] explored the use of IRT-5 probiotics (Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus reuteri, Bifidobacterium bifidum and Streptococcus thermophiles) on autoimmune dry eye. IRT-5 was effective in reducing dry eye symptoms through attenuation of autoreactive T cells. Authors suggested that of Sjögren syndrome is correlated with microbial dysbiosis [51], and autoreactive T cells are activated by peptides from oral, skin and gut bacteria which activate autoreactive B cells leading to gut dysbiosis mediated increases in Th17 cells migrating into systemic circulation. IRT-5 probiotics probably suppress cross-reactive T cells against gut peptides resulting in decreased CD8+IFNγhi cells, leading to clinical improvement in DED.

CONCLUSION

Dry Eye Disease is on the spectrum of chronic inflammatory disorders, thus lifestyle changes including nutritional status assessment and correction along with medications aimed to reduce inflammation could be an effective strategy. «Holistic», personalized approach, might give the way for a new generation of clinical studies to provide more effective solutions for management of DED.

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