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Dry Eye Syndrome: Mechanism, Diagnosis and Treatment Strategies

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ABSTRACT

Introduction and Purpose: Dry eye syndrome is a set of ophthalmic complaints frequently reported by ophthalmology patients. It is a chronic, multifactorial disorder of the ocular surface that significantly impacts visual function and the quality of life of patients across all age groups. The condition is more prevalent in women and becomes more common with advancing age. Dry eye syndrome presents a wide range of symptoms with varying degrees of severity, contributing to the complexity of its diagnosis and treatment. This review examines the diagnostic approaches and management strategies for dry eye syndrome, with a particular focus on the most common underlying factors.

Materials and Methods: A comprehensive survey of articles published in scientific journals was conducted via the online research platforms PubMed and Google Scholar. Articles were searched by entering keywords in the appropriate configuration: "dry eye syndrome," "management" and "diagnosis."

Description of current knowledge: Studies have indicated that the approach to diagnosing and managing dry eye syndrome is largely contingent on the underlying cause and the intensity of the patient's symptoms.

Keywords: "dry eye syndrome", "management" and "diagnosis".

Introduction: Dry eye syndrome is a common eye condition in modern society. Computer monitors, electronic devices and an increasingly polluted environment have a huge impact on our body and its functioning. A patient with dry eye syndrome complains of a foreign body sensation, burning, photophobia, blurred vision and sometimes tearing [1][2][3]. Millions of people worldwide, with varying degrees of severity. At a minimum, dry eye causes discomfort, but it can also cause disabling pain and fluctuating vision, significantly affecting vision-related quality of life by limiting activities such as driving and reading, as well as recreation[4]. The correct structure of the tear film provides an adequate degree of lubrication of the surface of the eye, prevents infections and allows proper nutrition of the corneal epithelial layer. Abnormalities in the structure of any of the three layers that make up the tear film can contribute to the "dry eye" syndrome. Both endogenous and environmental factors contribute to the syndrome. These include genetic conditions, disease, mood, work performed and indoor conditions, among others.This multifactorial disorder often progresses to more severe stages, in which inflammatory processes on the surface of the eye, combined with tear film instability, hyperosmolarity and mechanical factors play a key role. These pathological mechanisms culminate in chronic inflammation of corneal and conjunctival epithelial cells.

Eye structure: The eyeball and its associated accessory organs, including the lacrimal apparatus, conjunctiva, eyelids, and ocular muscles, comprise the visual system. The eyeball itself is composed of three primary layers: the sclera, choroid, and retina. The retina, which contains photoreceptors, is the light-sensitive component of the eye. The choroidal membrane encompasses the iris, ciliary body, and choroid, with the pupil situated in the middle of the iris, allowing for the regulation of light entering the retina. The fibrous layer consists of the cornea at the front and the sclera at the back of the eye. The cornea refracts light more significantly than the lens and lacks blood vessels or lymphatic vessels. The corneal epithelium is a multilayered, flat, non-keratinized structure. The conjunctiva, a thin membrane made up of the dermis and a multilayered cylindrical epithelium, covers the front of the eyeball and the inner eyelid, constantly moistened by the secretion of the lacrimal glands [5].

Functions of the tear film: The tear film is a thin, heterogeneous layer that covers the cornea and conjunctiva of the eye. A healthy, stable tear film is essential for the proper functioning of the visual system. As the cornea lacks blood vessels, the tear film is crucial for its nutrition and metabolism. The tear film provides the cornea with essential nutrients, oxygen, and maintains a neutral pH. To fulfill its role, the tear film must have a consistent qualitative and

quantitative composition. This ensures the proper functioning of the visual system. The tear film's primary functions include: shaping and preserving the smooth refractive surface of the cornea, creating an environment conducive to the proper development of corneal and conjunctival epithelial cells, wetting the eyelids, transporting metabolic waste, cleansing the cornea and conjunctiva of harmful substances, exhibiting bacteriostatic and bactericidal properties, and facilitating the migration of leukocytes in case of ocular trauma. Additionally, the tear film prevents damage to the epithelium of the cornea and conjunctiva caused by dryness and facilitates eyelid movement during blinking. Optically, the tear film plays a vital role in smoothing the corneal surface and creating a sharp retinal image by filling the spaces between epithelial cells, providing a regular, uniform optical surface.

Structure and function of the tear film

The traditional depiction of the tear film structure as consisting of three primary layers - mucin, aqueous, and lipid - oversimplifies its complexity. Recent research has revealed that the tear film is far more intricate, comprising more than 18 types of mucins, 491 proteins, and at least 153 lipid species. These diverse components interact dynamically to maintain the structural integrity of the tear film while fulfilling their individual roles. The three main layers of the tear film each possess a complex structure and serve a variety of functions [6][7][8]. The tear film is constantly in motion, gliding across the surface of the eye and covering the cornea and conjunctiva. After moistening the eyelid portion of the conjunctiva, the tear film flows from the conjunctival sac through the lacrimal puncta on the eyelid margins, then proceeds through the lacrimal duct into the lacrimal sac. Subsequently, the tear film enters the nasolacrimal duct, which connects the eye to the nasal cavity [9][10][11]. The mucin layer is produced by cup cells, Henle's crypts and Manz's glands. Bonding tightly to the glycocalyx of corneal epithelial microvilli, it determines the permanent adhesion of the tear film. Mucin, by binding through lipophilic groups to lipids of the cell membrane and through hydrophilic groups to water molecules, changes its character to hydrophilic, which facilitates even distribution of the aqueous phase across the surface of the eye and ensures full wetting of the corneal epithelium. The mucin layer is the innermost layer of the tear film produced. Directly on the corneal epithelium, mucins form a mucin layer, whose most important function is to fill the spaces between the cells and folds of the corneal epithelium. In this way, they enable its lubrication. In addition, by filling the spaces between cells and folds, it makes the surface of the cornea very smooth. This smooth, slippery coating minimizes friction during blinking and

eye movements. The continuous distribution of mucin gel on the surface of the eye ensures eyelid movement. Another important function of the mucin layer is to protect the epithelial surface from mechanical damage. Mucins are responsible for coating foreign bodies with a slippery mucus layer to protect the cornea and conjunctiva from abrasion, and for draining foreign bodies from the surface of the eye.

The aqueous component constitutes the bulk of the tear film, accounting for over 98% of its thickness. This aqueous phase is primarily derived from the lacrimal gland, situated in the upper temporal region, as well as the Krause and Wolfring glands. Secretion of the aqueous layer is regulated by the sympathetic adrenergic system, resulting in the production of a thickened fluid rich in minerals, proteins, and enzymes. Floating mucins in the aqueous layer serve as a medium for diffusion, allowing oxygen to penetrate, cleanse, protect and transport nutrients to corneal structures [12]. The primary functions of the aqueous layer are to hydrate, nourish, and provide immunological protection for the cornea. As the cornea lacks blood vessels, this layer is crucial in supplying oxygen and essential nutrients. The presence of proteins and mucins in the aqueous phase lowers the surface tension, facilitating more efficient distribution across the corneal surface and enhancing wetting and lubrication of the conjunctiva. Electrolytes within this layer help maintain the integrity of the epithelium. Additionally, the aqueous layer transports and removes various particles, such as damaged cells, foreign bodies, and exfoliated epithelium. Its composition, which includes lysozyme, immunoglobulins, complement, and lactoferrin, also confers antimicrobial properties, effectively safeguarding against microbial colonization. The outermost layer of the tear film is a thin, oily, lipid layer approximately 100 nanometers thick. This layer is primarily produced by the Meibomian glands [13], with additional contributions from the Zeis and Moll glands located in the upper and lower eyelids. The lipid layer consists of various components, including esters, triglycerides, and free fatty acids. The primary functions of this lipid layer are to prevent tear evaporation and ensure the stability of the tear film surface. In the absence or discontinuity of the lipid layer, a significant increase in tear evaporation has been observed, particularly in cases of reduced humidity and wind exposure. Furthermore, the lipid layer plays a crucial role in creating an optically smooth surface, facilitating the formation of a sharp retinal image. Additionally, this layer protects and stabilizes the tear film by preventing the aqueous layer from binding to the polar lipid groups, which would lead to premature tear film breakup. Analysis of the chemical composition of secreted lipids in healthy individuals

revealed a clear separation of two layers containing polar lipids (at the junction of the aqueous and lipid layers; phosphorus-containing lipids, among others) and a thicker layer of non-polar lipids (such as waxes, triglycerides and cholesterol esters), located above the polar lipid layer and in contact with the air [14]. Carbohydrates and fatty acids are also present. The concentration of the lipid layer components varies significantly among individuals, highlighting the highly personalized nature of this layer. Importantly, the lipid layer can still perform its corneal coating function even in the absence of the aqueous layer, as it is anchored to the Meibomian gland orifices and does not participate in tear outflow.

The epidemiology of dry eye syndrome: Dry eye syndrome is a multifactorial disease characterized by a persistent disruption of the tear film, leading to ocular surface damage and various symptoms, such as eye discomfort, visual disturbances, tear film instability [15], photophobia, redness, foreign body sensation under the eyelid. The prevalence of dry eye syndrome has been reported to range from 5% to 50% in different populations, with a higher prevalence in older individuals, women, and individuals with certain underlying medical conditions [16] such as connective tissue diseases, androgen deficiency, Sjoegren's syndrome, rheumatoid arthritis, use of medications (antihistamines, β-blockers, diuretics, serotonin reuptake inhibitors, anti-anxiety medications, tricyclic antidepressants, antipsychotics, oral hormonal contraception, Parkinson's disease medications and isotretinoin are also at risk for ocular surface disorders), diabetes, thyroid disease or rosacea. Symptoms of “dry eye” syndrome also occur in neurological disorders, leukemia, infectious mononucleosis, and AIDS [17]. Vitamin A deficiency, commonly observed in malnourished individuals and those with alcohol use disorders, has been associated with an increased prevalence of dry eye syndrome symptoms. Studies have reported that administering topical vitamin A formulations, such as eye drops or ointments, can enhance mucin production and positively impact the aqueous and lipid components of the tear film in this population. Studies have shown that chronic use of eye drops containing the preservative benzalkonium chloride can have detrimental effects on the goblet cells responsible for producing the normal mucin layer of the tear film.. Factors that contribute to the development of dry eye syndrome include environmental conditions, such as low humidity and increased digital screen time, as well as various systemic and ocular conditions, including autoimmune disorders, medications, and meibomian gland dysfunction [18]. A contact lens dramatically changes conditions on the surface of the eye. The presence of a contact lens on the eye can alter the production of

mucins, the flow rate of the aqueous layer of the tear film, and the concentration of specific proteins in the tear film [19]. When a contact lens is worn, the tear film becomes divided, with the mucin layer, which serves a crucial function, becoming trapped beneath the lens. This significantly reduces the volume of the aqueous layer and disrupts the lipid layer. Theresulting thinner pre-lens tear film layer evaporates more rapidly, leading to a shorter tear film breakup time and potentially compromising visual quality [20]. Dry eye syndrome can arise from either an aqueous-deficient state, characterized by inadequate tear production, or an evaporative state, characterized by excessive tear film evaporation [21]. Additionally, a history of eye trauma, intraocular surgery, or conditions following laser refractive error correction can also predispose individuals to ocular surface disorders. Additionally, various lifestyle and environmental factors can also contribute to the development and exacerbation of dry eye syndrome. Smoking, improper spectacle correction, and poor eyelid hygiene have been shown to play a role in the symptoms experienced by individuals with this condition. Furthermore, it is not uncommon for patients to encounter periodic disruptions in tear film stability and integrity, often due to environmental influences, such as changes in humidity or exposure to certain environmental conditions. Dry eye symptoms may also manifest in specific circumstances, including during prolonged air or car travel, periods of sleep deprivation, extended reading sessions, and when working in suboptimal lighting environments.

There are two main forms of dry eye syndrome. One form of dry eye syndrome is called “aqueous deficient dry eye”(ADDE), associated with aqueous film deficiency. Another form is called “evaporative dry eye”(EDE) caused by excessive tear evaporation [22]. The form of dry eye syndrome associated with aqueous layer deficiency is less common, affecting approximately 20% of cases. There are two primary subtypes within this category. The first is linked to the presence of primary or secondary Sjögren's syndrome, while the second is related to diseases that damage the lacrimal glands through mechanisms such as scarring, degeneration, or denervation. Conversely, the more prevalent form is characterized by a deficiency in the fatty layer, resulting in excessive tear evaporation. The primary contributing factors to this condition are impaired lipid secretion from the Meibomian glands and abnormal blinking patterns.

Symptoms and management: Patients with dry eye syndrome frequently present with ocular symptoms, including redness, irritation, and visual disturbances. Specifically, they may

experience burning, itching, and blurred vision upon blinking. Additionally, these individuals may exhibit heightened sensitivity to light, a sensation of pressure within the eyeballs, and the accumulation of a characteristic mucous discharge at the outer corners of the eyes. Furthermore, their symptoms tend to worsen in dry, air-conditioned, or well-ventilated environments, and can be further exacerbated by exposure to irritants such as dust, cigarette smoke, and volatile chemicals [23]. Individuals with aqueous-deficient dry eye typically experience sensations of dryness and difficulty in blinking. Conversely, those with lipid layer dysfunction more frequently report excessive tearing. Additionally, patients often describe the presence of discharge along the eyelid margins and inner corners, especially upon waking. If left untreated, dry eye syndrome can lead to a variety of complications, including recurrent conjunctivitis, abnormal eyelash growth, recurring chalazia and eyelid sclerosis, corneal epithelial erosions, and even keratitis. In moderate to severe forms of dry eye syndrome, the symptoms become exacerbated, significantly impairing the patient's quality of life across multiple domains. The management of dry eye syndrome requires a multifaceted approach due to its complex etiology. Interventions may include modifying environmental conditions, supplementing the tear film with appropriate components, addressing coexisting Meibomian gland dysfunction, and in more severe cases, employing anti-inflammatory therapies or even surgical treatments.

The diagnosis of dry eye syndrome requires a comprehensive assessment, including obtaining a detailed patient history, conducting a thorough physical examination with a biomicroscopic evaluation of the ocular condition, and performing appropriate diagnostic tests [24].

Examples of diagnostic tests:

-the Schirmer I test indirectly assesses the volume of tears produced by measuring the wetting of a paper strip. The Schirmer II test evaluates the maximum reflex tear secretion after nasal mucosa stimulation, but it has low sensitivity and repeatability

-the Fluorescein Breakup Time test measures the time from the last blink to the appearance of dark spots on the cornea, indicating tear film instability. It is recommended to calculate the average of at least three measurements, and a FBUT of less than 10 seconds is considered abnormal

-rose bengal dye is commonly used to assess the ocular surface, as it has an affinity for epithelial cells that have an altered or lost mucosal layer. This dye can effectively visualize corneal filaments and mucosal plaques when applied using infrared-free light. Typically, a 1%

rose bengal solution or a rose bengal-saturated strip is administered to facilitate this diagnostic evaluation

-impression cytology involves applying a cellulose acetate filter to the conjunctiva, which then collects the outermost epithelial cells. This method allows for the analysis of changes on the ocular surface, such as epithelial metaplasia, keratosis, and atrophy, without being affected by temporary variations in tear production.

Changing environmental and lifestyle factors

Management of dry eye syndrome requires addressing various environmental factors as an initial step. This includes using air humidifiers, avoiding excessive air conditioning, maintaining proper hygiene when working with digital screens, practicing good sleep hygiene, correcting any distance or near vision defects, wearing sunglasses, consuming an adequate amount of fluids, and adhering to a balanced diet(rich in omega-3 fatty acids and vitamin A)[25].

Artificial tears

Any form of dry eye syndrome requires tear supplementation. Artificial tear solutions are the first-line and mainstay treatment for dry eye disease, providing significant symptomatic relief [26][27].The use of artificial tears and gels, containing polymeric moisturizers or viscosity enhancers, is recommended at a frequency of at least twice daily to provide symptomatic relief. Additionally, eye ointments with higher density should be utilized to manage symptoms at night. Furthermore, preservative-free products are preferred, as research has shown that preservatives can disrupt the stability of the tear film. Specifically, preservatives act as detergents on the lipid layer, leading to the degradation of conjunctival goblet cells and compromising the integrity of the tear film. Lipid-containing tear supplements are particularly beneficial for individuals with evaporative dry eye caused by Meibomian gland dysfunction [28].

Corticosteroids and non-steroidal anti-inflammatory drugs

Patients with moderate dry eye syndrome may benefit from incorporating anti-inflammatory therapy alongside the use of artificial tears and lifestyle adjustments. Clinical studies have demonstrated that the application of corticosteroids or nonsteroidal anti-inflammatory drugs can lead to a reduction in subjective symptoms associated with ocular irritation, a decrease in fluorescein corneal staining, and the alleviation of thread-like keratitis. However, topical corticosteroid treatment should be limited to low doses and short durations, typically no longer than a few weeks, with patients under regular monitoring for potential side effects. Comparative research on topical corticosteroid and nonsteroidal anti-inflammatory drug treatments suggests that patients with dry eye syndrome may experience more favorable outcomes with the use of corticosteroids.

Drugs with immunomodulatory effects

Topical cyclosporine may be a suitable option for patients with severe or treatment-resistant dry eye syndrome who have required repeated corticosteroid eye drop therapy. In contrast, topical corticosteroids should be limited to low-dose and short-duration use, while cyclosporine can provide longer-term management of ocular inflammation.

Tear point plugs

For patients with insufficient aqueous tear production, tear duct occlusion may be a viable option if other interventions have proven inadequate or impractical. Temporary or permanent tear plugs can be an effective treatment once the tear film has achieved a more balanced state. However, this approach should be implemented cautiously in individuals with concurrent inflammatory ocular surface disorders, such as ocular rosacea and/or allergic conjunctivitis, as it may exacerbate their symptoms. Importantly, any existing inflammatory conditions affecting the ocular surface, including eyelid margin inflammation, must be completely resolved before considering the use of tear plugs.

Muscarinic receptor agonists

In severe cases of dry eye disease, oral pharmacological interventions may be a suitable option, particularly for individuals with co-occurring dry eye and dry mouth, such as those affected by Sjögren's syndrome. Relevant studies have demonstrated that the administration of

pilocarpine preparations can lead to improvements in subjective symptoms, corneal fluorescein staining, rose bengal staining, and conjunctival goblet cell density; however, no significant enhancement in tear production has been observed in Schirmer tests. The most prevalent adverse effect associated with pilocarpine use is excessive sweating. The utilization of oral muscarinic receptor agonists may be considered as a salvage therapy for patients suffering from debilitating dry eye syndrome, given the documented efficacy of these agents in alleviating subjective symptoms, as evidenced by clinical trial findings.

Serum eye drops

Studies have demonstrated that the application of autologous serum eye drops effectively mitigates ocular irritation and reduces corneal and conjunctival staining in individuals with dry eye syndrome. It is recommended to consider the use of autologous serum eye drops for patients with treatment-resistant or severe dry eye syndrome associated with their primary condition, who have not responded to or tolerated topical cyclosporine therapy. Following several months of use, the majority of patients exhibited improvements in their symptoms. Moreover, enhancements were observed in tear film break-up time testing, fluorescein staining of the corneal surface, and conjunctival impression cytology results, while Schirmer test findings remained unchanged.

Mucolytic drugs

It has been confirmed in studies that the use of acetylcysteine was more effective in relieving the subjective symptoms of dry eye syndrome than the use of artificial tears; however, it had no effect on the subjective symptoms. Dry eye syndrome symptoms were also shown to improve after oral ambroxol.

In severe cases of dry eye syndrome, permanent procedures such as thermal electrocoagulation or laser coagulation of tear ducts, or tarsoraphy, which involves partial surgical closure of the eyelid, may be employed to reduce the surface area for tear film evaporation [29].

Summary: Dry eye disease can have significant adverse effects on physical and mental well-being, with consequential social costs related to direct healthcare expenditures and reduced productivity. Dry eye syndrome is a chronic condition stemming from tear film instability, resulting in discomfort, visual disturbances, and ocular surface damage. Management approaches encompass, but are not limited to, comprehensive diagnosis and clinical assessment, lifestyle interventions, pharmacological therapies, and advanced treatments such as tear duct occlusion or autologous serum eye drops. Regular ophthalmologic monitoring is essential to evaluate the efficacy of therapy and guide necessary treatment adjustments.

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Grzegorz Szcześniak: Conceptualization, Writing-rough preparation

Aleksandra Kiełczewska: Methodology, Investigation Resources

Anna Kiełczewska: Formal analysis, Visualisation, Writing-review and editing

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