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DRY EYES: AT THE PEAK OF INCREASE WITH MODERNISATION

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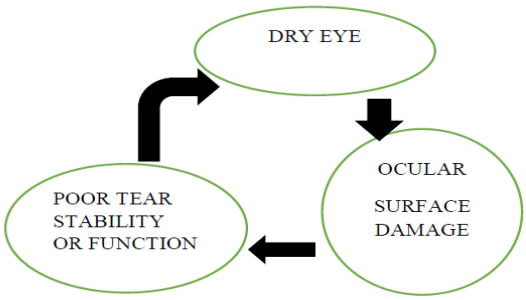
ABSTRACT
Dry eye syndrome (DES) or keratoconjunctivitis sicca (KCS) is a common disorder of the tear film caused by decreased tear production or increased evaporation and manifests with a wide variety of signs and symptoms. The present review gives a detailed information on the prevalence, definition, causes, diagnostic tests, and medical management of dry eye disease. A number of systemic conditions can also contribute to the physiological integrity of the ocular surface and disruption of system that may or may not produce symptoms. Therefore, accurate diagnosis of dry eyes with no or minimal disruption of physiological function is necessary. The paper also discuss current challenges in the development of topical ophthalmic drug delivery systems for treatment of Dry Eyes/KCS. The aim of this review is to provide awareness among the patients, health care professionals, and researchers about diagnosis and treatment of Dry Eyes/KCS and recent developments and future challenges in management of dry eye disease.

KEYWORDS: Therefore, accurate diagnosis of dry eyes with no or minimal disruption of physiological function is necessary.

INTRODUCTION
Dry eye disease (DED) is very common; its prevalence around the world varies from 15% to 43%. Its putative pathogenetic mechanisms include hyperosmolarity of the tear film and inflammation of the ocular surface and lacrimal glands results in damage to the ocular surface and is associated with symptoms of ocular discomfort. DES is also called keratoconjunctivitis sicca (KCS), keratitis sicca, sicca syndrome, xerophthalmia, dry eye disease (DED), ocular surface disease (OSD), or dysfunctional tear syndrome (DTS), or simply dry eyes. Keratoconjunctivitis sicca is a Latin word and its literal translation is "dryness of the cornea and conjunctiva." It may be helpful to know that "sicca" is part of the English word "desiccate." The dry eye syndrome in which the eyes do not produce enough tears is also known as "Sjögren's syndrome"

Dry eye disease is characterized by instability of the tear film that can be due to insufficient amount of tear production or due to poor quality of tear film, which results in increased evaporation of the tears.

Role of the tear film
The tear film is a fluid that covers the cornea (The precorneal tear film) and the conjunctiva (the preocular tear film). The primary role of the tear film is to establish a refractive surface of high quality for the cornea and to ensure the well- being of the corneal and conjunctival epithelium. An adequate volume of tears is also required if the tear film is to provide lubrication and prevent the shear forces of the blinking from damaging the anterior eye.



Dry eye: A cyclic disorder.

Dry eye therefore can mainly be divided into two groups, namely
Aqueous production deficient dry eye disease.
Evaporative dry eye disease.
Insufficient tears cause damage to the interpalpebral ocular surface and are associated with symptoms of discomfort. The International Dry Eye Workshop (2007) defined dry eye as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and

inflammation of the ocular surface. DES is associated with decreased ability to perform certain activities such as reading, driving, and computer related work, which require visual attention. Patients experience dry eyes symptoms constantly and severely, affecting their quality of day to day life.

Clinical features

The subjective symptoms are non-specific. It includes-burning, redness, stinging, foreignbodies sensation, pruritus, photophobia. More or less pronounced conjunctival redness and damage to the ocular surface with punctate epithelial erosions (superficial punctate keratitis) are typical in dry eye; temporal conjunctival folds parallel to the lid margin are indicative. The lower tear meniscus is reduced. In addition, there are often signs of meibomian gland dysfunction with thickened eyelid margins and telangiectasia. The meibomian gland orifices are obstructed with a cloudy, granular or solid secretion that can only be expressed by exerting considerable pressure on the lower lid. If the meibomian gland dysfunction is associated with inflammation, blepharitis (inflammation of the lid margin) or meibomitis (inflammation of the meibomian glands) is present.

Dry eye disease has a significant association with anxiety disorder and depression. In late stages or in severe forms of the disease, conjunctival scarring or corneal complications can occur. Severe complications of dry eye disease are rare and are observed in the context of primary or secondary Sjögren's syndrome, graft-versus-host disease, ichthyosis, Stevens–Johnson syndrome, and xerophthalmia. They can result in loss of vision or even functional blindness.

After the age of 40 years, tear production tends to fall. When it drops to a certain point, the eyes can become dry and easily irritated and inflamed. This is more common in women, and especially after the menopause possibly due to hormonal changes. Reduced tear production is also linked to various other factors such as-Autoimmune diseases, like Sjogren's syndrome, lupus, scleroderma or rheumatoid arthritis. Diseases that can lead to dry eyes include shingles, Bell's palsy, and HIV infection, Radiation treatment, Diabetes, Vitamin A deficiency, Refractive eye surgeries, such as laser-assisted in-situ keratomileusis (LASIK) increase the chance of dry eyes, but the symptoms are usually temporary.

Eyelid problems, Medications, and Environmental factors

Eyelid problems can affect the blinking motion that spreads the tear film evenly across the eyes. Eyelid problems include ectropion, where the eyelid turns outward, or entropion, where it turns inward. Inflammation along the edge of the eyelids, known as blepharitis, may also cause dry eyes, also contact lenses.

Medications that can cause dry eyes include:Diuretics, Angiotensin-converting enzyme (ACE) inhibitors, Antihistamines, Sleeping pills, Birth control pills, Antidepressants. Acne drugs, specifically isotretinoin-type medications. Morphine and other opiate-based painkillers. Other Risk factors includes: Climatic factors include a dry climate, sun, wind, and other types of hot blowing air or dry air, as in an airplane cabin. High altitude, smoke, and the use of contact lenses are also risk factors. Using a computer monitor, reading, or driving a vehicle, as the increased visual concentration may slow down the blinking rate, so that the eyes become dry.

Diagnosis

Diagnostic tests are necessary in order to distinguish between dry eye, infections and allergies, which can present very similar clinical presentation, but require different treatment. If an incorrect clinical diagnosis is made and antiallergic drugs or epitheliotoxic antibiotics are prescribed, dry eye may worsen. The diagnostic tests allow patients to be classified into one of two treatment-based subgroups, "aqueous-deficient" or "hyperevaporative." Diagnostic guidelines were published in 2007 by the Dry Eye Workshop. Practical sequence of dry eyes test:

1. Patient history, perhaps using a symptom-oriented questionnaire
2. Tear film break-up time with fluorescein
3. Ocular surface staining with fluorescein/lissamine green
4. Schirmer test with/without anesthesia
5. Examination of the eyelid margins and meibomian gland orifices with expression of meibomian secretion.

A comprehensive history also play an essential role in diagnosis, includes

1. Time, place, and diurnal variation of symptoms, workplace stress (e.g., VDU work; dry, dusty air; air conditioning)
2. Systemic diseases (especially collagen vascular disease, Graves' disease, diabetes mellitus, infections such as hepatitis C and HIV)
3. Medication history

Therapeutic strategies

Decisions about treatment for dry eye is decided on the basics of underlying conditions, cause and severity of the disease. Since dry eye is a multifactorial disease, therapeutic strategies should address the various disease components. Recent studies shows the administration of artificial tear formulations of varying viscosities and compositions that are intended to enhance tear volume or quality, reduction of inflammation, modification of diet or lifestyle, and treatment of any associated eyelid disease.

In people with Sjögren's syndrome, down-regulation of *PAX6* — the master regulator of corneal lineage

commitment — is inflammation-dependent and linked to ocular surface damage. The studies suggest *PAX6* serve as a biomarker or a potential therapeutic target for Sjögren's syndrome. Few research shows that the multifunctional protein clusterin (CLU) is the most highly expressed transcript in the human cornea, with the protein product localized to the apical layers of the mucosal epithelial of the cornea and conjunctiva. CLU protein is also present in human tears. Many clinical studies suggests, CLU helps seal the ocular surface barrier, thus protecting the eye from desiccating stress. CLU not only may be a promising biomarker but also may be the basis for developing new therapeutics for dry eye disease.

Tear volume and Quality

Three basic strategies can be used in the treatment of aqueous-deficient or evaporative dry eye: increase the amount of liquid on the ocular surface, decrease tear evaporation, and augment the lipid content or lubricity of the tears. All three are aimed at increasing tear volume or improving the quality of the tear film, and treatment should be tailored to the pattern of disease presentation.

Numerous topical lubricants, including drops, gels, and ointments, are available for dry eye. Many formulations of artificial tears are available over the counter. The features of topical lubricants and their clinical usefulness in the treatment of dry eye symptoms played a great role in treatment of Dry Eyes.

Polymer hydroxypropyl guar gellable lubricant eyedrops (Systane Lubricant Eye Drops, Alcon) effectively relieved signs and symptoms of moderate dry eye, with measurable improvements. Topical lubricants are designed to support the quality and quantity of the tear film. The frequency of application of ocular lubricants is based on the needs of the individual patient and can range from once a day to once every hourly. Various studies showed significant impact of diquafosol tetrasodium ophthalmic solution.

Topical therapies also include eye drops prepared with sterile, saline-diluted serum derived from the patient's blood for severe cases of dry eye.

Occasionally, surgery is used to plug puncta, thereby diminishing tear outflow and increasing moisture on the ocular surface. However, lacrimal or punctal plugs are usually temporary solutions, lasting on the order of months to a few years.

Various lines of research are exploring ways to enhance the lipid content of tears, reducing evaporation, or to increase the lubricity of tears.

Some approaches, includes administration of essential fatty acids, cyclooxygenase inhibitors, and resolvin analogues, not only to boost the lipid content of tears but also reduce inflammation to a greater extent.

To reduce the risk of dry eye related to the toxic effects associated with antiglaucoma drops, selected patients with primary angle-closure glaucoma may be treated with laser trabeculoplasty. This treatment, helps to targets the trabecular meshwork so that ocular pressure can be reduced. It also reduce dependence on topical drops, minimizing damage to the ocular surface from preservatives in glaucoma patients.

Reduction of inflammation

A mainstay of dry eye treatment, based on the critical role of inflammation, is 0.05% cyclosporine ophthalmic emulsion (Restasis, Allergan). This prescription-based, non-glucocorticoid immunomodulatory agent, applied topically (one drop twice daily), increases tear production by decreasing ocular surface inflammation and directly affecting lacrimal-gland function. Cyclosporine ophthalmic emulsion has been shown to be effective for dry eye in randomized clinical trials.

In July 2016, the Food and Drug Administration (FDA) approved 0.5% lifitegrast ophthalmic solution (Xiidra, Shire) for treating signs and symptoms of dry eye disease. Applied topically as one drop twice daily, this medication is the first in a new class of drugs, called lymphocyte function–associated antigen 1 (LFA-1) antagonists. The second of two drugs approved by the FDA for dry eye disease, this medication is a welcome addition to the clinical armamentarium and a source of new hope for affected patients.

Unlike topical lubricants, the two FDA-approved therapies for dry eye (Restasis and Xiidra) must be administered for a period of up to several months to achieve therapeutic effects.

Life Style and Dietary approach

Lifestyle approaches to the management of dry eye include ensuring adequate fluid intake, moderating alcohol use, using humidifiers or protective eyewear, and when possible, avoiding air conditioning and forced-air heating. Sleep deprivation can also trigger dry eye symptoms so adequate sleep is also important.

A meta-analysis on diet supports a therapeutic role for polyunsaturated fatty acids. Certain foods, such as fish and flaxseed, contain n–3 and n–6 fatty acids. Women who consume two or more servings of fish weekly are less likely to report dry eye symptoms than women with lower levels of fish consumption. Use of n–3 fatty acid supplements may enhance tear production and quality. Phytoestrogen supplements have been associated with decreased signs and symptoms of dry eye disease and oral flaxseed oil has been reported to reduce inflammation, leading to amelioration of symptoms in patients with Sjögren's syndrome.

Treatment of lid disease

The mainstay of treatment for meibomian-gland disease (posterior blepharitis) is lid hygiene. The use of warm

compresses combined with mechanical cleansing of the eyelid margins decreases the bacterial load and enhances gland function by softening secretions and relieving gland duct obstruction. Topical antibiotics, including azithromycin, topical low-dose glucocorticoids, and combinations of the two agents can also be used for short-term treatment. Oral tetracycline can be used for longer periods. Antibiotics may have therapeutic effects through antiinflammatory mechanisms rather than through, or in addition to, their antibacterial properties.

Hormonal therapies

Despite the greater prevalence of dry eye among women than among men and the intriguing connections between sex hormone levels and the risk of dry eye, reports on the effects of systemic hormone therapy on dry eye symptoms are contradictory.

Several research findings suggest a potential role for androgens as topical therapy for dry eye. More work is needed to assess levels of hormones within ocular tissues and to enhance our understanding of the complex relationships among various hormonal components that are critical for maintaining ocular surface homeostasis. On the basis of current knowledge, hormone therapy cannot be recommended for dry eye.

The diagnostic evaluation of dry eye disease should include a detailed patient history, thorough slit-lamp examination, and additional tests as indicated. Artificial tears of various kinds are recommended if the symptoms are mild. Lid hygiene is helpful in the treatment of hyper evaporative dry eye, while collagen or silicon plugs can be used for partial occlusion of the efferent lacrimal ducts to treat severe hyposecretory dry eye.

The benefit of long-term topical anti-inflammatory treatment of moderate or severe dry eye disease with corticosteroids or cyclosporine A eye drops has been documented in various research studies with clinical trials on a high evidence level. Orally administered tetracycline derivatives and omega-3 or omega-6 fatty acids are also used.

Current challenges

Dry eye syndrome is the most common ophthalmic manifestation and untreated dry eye can cause increased risk of ocular infection, corneal ulcer, and blindness. The clinical diagnosis of dry eye is challenging due to extensive variety of signs and symptoms and the ambiguity in the etiology and pathophysiology of the disease. Unclear symptoms could confuse the clinician with symptoms of other condition, such as conjunctivochalasis (which can easily induce an unstable tear film) or delayed tear clearance (which is a frequent cause of ocular irritation).

Conventional tests for diagnosis include Schirmer test, TBUT, and ocular staining. Some of them have low degree of standardization and some are invasive. The invasive nature of some diagnostic tests can make interpretation challenging. A tear film is a dynamic, open system subject to numerous internal and environmental variations leading to misinterpretations of the obtained result. Thus the use of symptoms alone will result in missing a significant percentage of DED patients.

Clinically, osmolarity has been shown to be the best single metric for diagnosis of dry eyes and is directly related to increasing severity of disease. Clinical examination and other assessments determine the subtype of disease.

An accurate testing and differential diagnosis of dry eye which is crucial for medical management of disease are difficult and results of multiple tests measuring tear volume. The biological components have been used by ophthalmologists to diagnose KCS accurately.

Therefore, the clinicians play challenging role in identification of symptoms of dry eye, selection of appropriate diagnostic tests and products, interpretation, and instructing patients on the proper use of medications.

Future directions

Most exciting drugs in R&D pipeline include diquafosol and rebamipide. Diquafosol (INS 365) acts by stimulating tear components and rebamipide, an amino acid analogue of quinolinone causes mucin secretion. Clinical studies conducted by Santen Pharmaceutical Co., Ltd. demonstrated the effectiveness of diquafosol at an optimal dose of 3% six times a day. Topical administration of diquafosol was shown to be safe and effective in alleviating signs and symptoms of DES as demonstrated with Schirmer test and corneal staining.

Clinical studies also show promise for the use of mucin secretagogues in combination therapy for dry eye. Despite these ongoing advances, development of effective therapies is hampered by extensive evidence gaps related to ocular pain and neural regulation of the ocular surface.

Little is known about ocular pain, and no analgesics are available for ocular use. The field could benefit from the development of tools to evaluate the ocular sensory apparatus. These tools could be used in therapeutics development and to assess patients' reports of pain in the clinic.

CONCLUSION

The overarching complexity of the dry eye disease makes it challenging to diagnose and manage accurately. With development of objective tests with precise diagnostic value and minimal disruption of physiological function, accurate diagnosis of disease is possible. Recent knowledge about causes, symptoms, and diagnostic tests of KCS provides better opportunities for improving medical management. Development of new potential drugs and different colloidal delivery systems

definitely provides a ray of hope for more effective treatment of this widely prevalent and debilitating disease.

Dry eye disease can have serious deleterious effects on physical and psychological health, and the societal costs attributable to this condition are consequential in terms of direct costs of care and lost productivity. Management of dry eye could benefit from a more precise means of assessing the components of ocular surface health, including biomarkers of active disease and identification of the major drivers of symptom-related disease development. Approaches to evaluating more aspects of tear-film function and biochemical properties are needed. The lack of correlation between ocular signs as currently assessed and patient-reported symptoms of discomfort reflects our incomplete understanding of this vexing disease. Novel approaches and technological advances to enhance our knowledge of normal function and how disease perturbs the ocular surface are sorely needed.

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