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DRY EYE - A REVIEW

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ABSTRACT

Of the myriad reasons for visits to an ophthalmologist, one of the most common maladies afflicting patients is Dry Eye Disease (DED), which can cause mild discomfort in the early stages and end-stage ocular surface damage in its more severe forms. Dry eye is a problem of utmost importance, more in the developed rather than developing nations. Various aspects of the manifestation, including the tear osmolarity, ocular surface homeostasis and the role of ocular surface epithelial stem cells in maintaining the ocular surface homeostasis have been discussed. The objective tests to assess and grade dry eye have been noted. A systematic approach to the affected eye and the patient has also been outlined. The major categories of medications used along with the methods of delivery are specified in this review. A systematic approach in understanding the type and grade of Dry Eye Disease is mandatory for good clinical response. Along with clinical management the doctor should also stress on environmental changes that exaggerates dryness.

Key words: Dry Eye Disease, tear osmolarity, ocular surface homeostasis, lacrimal functional unit, and objective tests for dry eye, dry eye management.

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INTRODUCTION

Of the myriad reasons for visits to an ophthalmologist, one of the most common maladies afflicting patients is dry eye disease (DED), which can cause mild discomfort in the early stages and end-stage ocular surface damage in its more severe forms. Dry eye was defined by the 2007 International Dry Eye Workshop (DEWS) "as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tears lm instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear lm and in ammation of the ocular surface."[1] However, the current terminology "Dysfunctional Tear Syndrome (DTS)" implies that symptoms related to the tear lm can occur even in the presence of normal tear production.[2] Dry eye is usually classi ed into two major categories (Figure 1) : aqueous-de cient dry eye, in which tear production is reduced, and evaporative dry eye, in which evaporation of the tear lm is high.[1] Both conditions often occur simultaneously.

Scope of the problem

The prevalence of dry eye in the general population is still not precisely known. Past studies suggest that dry eye prevalence ranges from 10.8% to 57.1%. [4-8] Based on data from the largest studies of dry eye to date, the Women's Health Study (WHS), the Physicians Health Study

(PHS), and other studies,[9,10-12,13] it has been estimated that about 3.23 million women and 1.68 million men, aged 50 years and older have dry eye in the US. [10,13] In recent literature, it has been estimated that dry eye affects 6–34% of the global adult population.It has been estimated that about 3.23 million women and 1.68 million men, aged 50 years and older have dry eye in the US.[10,13]

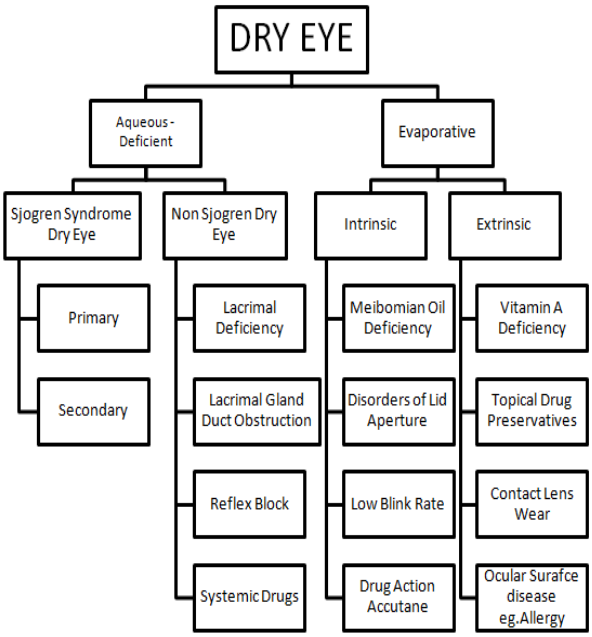

Figure 1

Tear osmolarity

In healthy participants tested in open-eye laboratory conditions, tear osmolarity were maintained within narrow limits. Tomlinson reported a value of 302 ± 9.7 mOsm/L based on data from several studies and importantly, between-eye differences were also limited (normal value, 6.9 ± 5.9 mOsm/L).[14] Evaporation during the blink interval causes a measurable thinning of the tear film, and a consequent rise in tear film osmolarity.[15] With each blink, the tear film mixes partially with tarsalfornical fluid of lower osmolarity, and the osmolarity of the preocular film is assumed to be lower just after the blink than just before.[15] However, tear osmolarity in the menisci is remarkably stable in healthy eyes.[14]

Tear film stability and tear film breakup

The stability of the precorneal tear film is vital for proper image fromation by the eye. Clinically, stability is assessed by the tear film breakup test (TBUT), which can be conducted either after fluorescein instillation (the fluorescein breakup test, FBUT) or noninvasively (the noninvasive breakup test, NIBUT).[16-21] The test assesses the time required for a random break to appear in the tear film after a spontaneous blink. The relationship between the blink interval and the breakup time can be captured in an individual by measuring the **ocular protection index (OPI),** which is the breakup time divided by the blink interval.[22] OPI of < 1 indicates that breakup is occurring within the blink interval.

Ocular surface epithelial stem cells and their role in ocular surface homeostasis

Stem cells are essential for replenishment of self-renewing tissues such as stratified epithelia. In their dormant state, stem cells have a long life span and replicate infrequently. When proliferation is induced, they give rise to transient amplifying cells, which replicate rapidly. These eventually become postmitotic, and finally, terminally differentiated cells. Conjunctival epithelial stem cells are thought to originate in the fornices, although they may also be present in the bulbar and forniceal conjunctiva. They are believd to be bipotent, able to differentiate into epithelial or goblet cells.[58] Limbal stem cell deficiency results in abnormal healing and epithelization of the cornea and is characterized by recurrent epithelial defects, ulceration, corneal vascularization, stromal inflammation and scarring, and conjunctivalization, with resultant loss of the clear demarcation between corneal and conjunctival epithelium at the limbal region [23,24]

Dysfunction of the lacrimal functional unit

THE LACRIMAL FUNCTIONAL UNIT (LFU) comprises the ocular surface, (including the cornea,conjunctiva & the meibomian glands),the main and accessory lacrimal glands,and the neural network that connects them. This functional unit controls secretion of the three major components of the tear film in a regulated fashion, incorporating feedback from environmental, endocrinological, and cortical factors and maintains a stable, protective , and supportive tear layer which is critical for optimal functioning of the optics of the eye.[25]

Impact of systemic immune disease on the LFU

Sjogren's syndrome is a systemic autoimmune disease affecting the lacrimal and salivary glands.Pathological findings include infiltration of lymphocytes, a decrease in the rate of lymphocyte apoptosis, destruction of some glandular tissue and reduced function of the remainder, and loss of immunological tolerance to self-antigens SS-A and SS-B.

Objective tests to assess dry eye

Tests of tear function

Evaluation of the clinical signs of dry eye generally considers three features of the tear lm and ocular surface: tear function, tear composition, and ocular surface alterations(Figure 2). The tear function can be assessed by direct observation of the corneal light re ex. A diffuse or shattered light reflex indicates either instability of the tear lm or irregularities of the ocular surface. Observation of the tear meniscus with the slit lamp provides an indication of the volume of the tear lm. The marginal tear strip can be measured with the slit-lamp and the height of the tear lm meniscus is normally 1 mm. Special instruments are also available to quantify the contour and height of the meniscus. The biomicroscopic examination can reveal debris and presence of in ammatory cells in the tear lm, and interference fringes indicating an excess of lipid in the tear film.[26]The presence of foamy debris, especially at the lateral canthus, is a sign of meibomian gland disease, which is the major cause of evaporative dry eye.[27] Tear lm instability is a valuable sign in dry eye disease and can be produced by either aqueous-de cient dry eye or evaporative dry eye or a combination of both mechanisms. The most common method for determining tear lm stability is the uorescein Tear Film Break Up Time (FTBUT). A small amount of uorescein dye is instilled in the tear film and the patient is asked to blink to allow dispersion of the dye. The ocular surface is observed using the cobalt blue filter and diffuse illumination of the slit lamp. The time taken for the appearance of the first non-random black spot is measured, and is normally greater than 10 seconds. Rapid tear lm breakup is an indicator of tear instability that can be due to dry eye or ocular surface irregularities. There are instruments that allow non-invasive evaluation of tear breakup.[28] Assessment of tear secretion rate is done using the Schirmer's Test or the Phenol Red Thread test.[28] The Schirmer's test is performed by placing a small strip of No 41 Whatman lter paper of known dimension (5 x 35 mm), with the bent 5 mm portion in the lower fornix at the junction of the lateral and middle third of the lower lid. It is left in place for 5 minutes, and the length of the wet strip is measured. If thetest is done without prior instillation of topical anaesthetic, it is a measure of re exand basal secretion of tears (Schirmer 1 test); if the test is done following instillation of topical anaesthetic, it is a measure of baseline tear secretion (Basal Tear secretion test). The normal values of the test are greater than 10 mm of wetting for the Schirmer 1 test, and 5 mm for the test with anaesthetic. The phenol red thread test is performed by placing a small thread impregnated with phenol red dye on the lower eyelid margin and measuring the amount of wetting of the thread after 15 seconds. When the phenol red comes in contact with alkaline tears, it changes color from white to red and the red portion is measured. The normal value of the phenol red thread test is greater than 10 mm of wetting.[28]

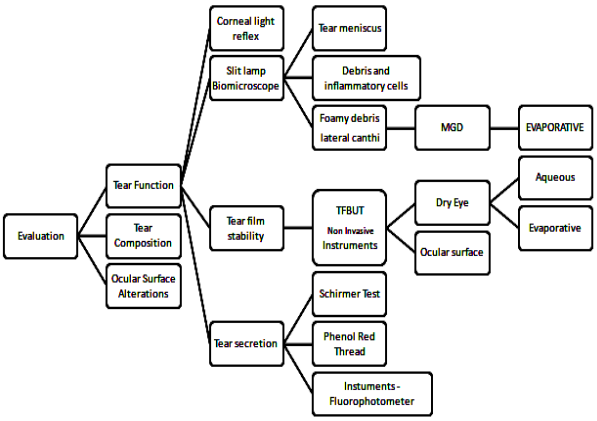

Figure 2

Composition of Tear Film

Measurement of the levels of in ammatory mediators in the tear lm serves to identify the contribution of in ammation to the severity of dry eye disease. In ammatory cytokines produced by ocular surface epithelial cells and leukocytes that invade the conjunctiva cause ocular surface epithelial disease. Interferon gamma (IFN-g) and interleukin (IL)-1 promote conjunctival

squamous metaplasia with accompanying decrease in the number of mucus producing goblet cells.[29,30] IL-17 stimulates production of proteases that cause loss of the super cial corneal epithelium, leading to an irregular and poorly lubricated corneal surface.[31,32] Increased production and activity of matrix metalloproteinase (MMP)-9 has been measured in dry eye and other ocular surface disorders, as a surrogate measure of inflammation.[33]

Assessment of Ocular Surface

The health of the ocular surface is evaluatedusing vital dyes to assess the integrity of the epithelial layers of the cornea and conjunctiva (Figure 3) .[28] Fluorescein is the most commonly used dye and is conveniently observed after measurement of the uorescein TFBUT. Rose bengal and lissamine green are the two dyes most often used for evaluating the integrity of the conjunctiva.[28] Both dyes stain the same features of the ocular surface, including mucus strands, laments, and areas of epithelium unprotected by normal mucin components of the glycocalyx. A classic pattern of interpalpebral staining across the medial conjunctiva, cornea, and temporal conjunctiva occurs in advanced dry eye disease. Early staining is more often on the medial conjunctiva followed by inferonasal cornea. Instruments using computer-analyzed re ections from the ocular surface have also been used to noninvasively evaluate tear stability and corneal surface smoothness.

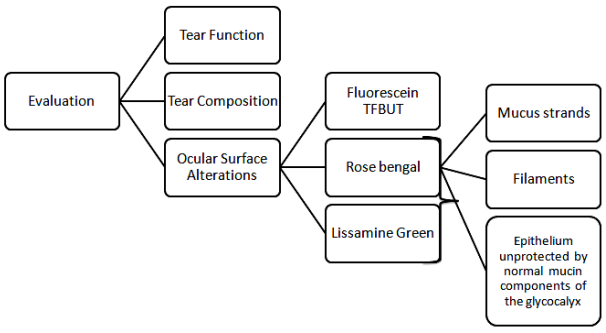

Figure 3

The most commonly used scheme for grading the severity of DED, using patient symptoms and signs, is the one proposed by the DEWS study (Table 1), given below.

Table 1

Dry eye severity level	1	2	3	4
Discomfort, severity, frequency	Mild; occurs under environmental stress	Moderate, stress or no stress	Severe frequent or constant without stress	Severe and or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and or activity limiting episodic	Annoying, chronic and or constant limiting activity	Constant and or possibly disabling
Conjunctival injection	None to mild	None to mild	+/-	+/++
Conjunctival staining	None to mild	variable	Moderate to marked	marked
Corneal staining	None to mild	variable	Marked central	Severe punctuate erosions
Corneal tear signs	None to mild	Mild debris, decreased meniscus	Filamentary keratitis, mucous clumping increased tear debris	Filamentary keratitis, mucous clumping increased tear debris, ulceration
Lid/meiboman glands	MGD variably present	MGD variably present	frequent	Trichiasis, keranitization, symblepharon
TBUT (sec)	Variable	<=10	<=5	Immediate
SCHIRMER	Variable	<=10	<=5	<=2

III. Management of dry eye

Communication between the practitioner and the patient is critical to assure that the patient understands the disease, the aggravating factors, and the management strategy. This also helps to establish the trust and rapport essential when managing a chronic ocular problem, with significant psychological elements. Therapy is based upon the severity of the dry eye disease and the patient response to each added therapy.

A. Topical Tear Substitutes and Lubrication

The rst line of therapy for dry eye is volume replacement and lubrication (Figure 4) with "arti cial tears." Their main ingredients are lubricants with a polymeric base or viscosity agent. The commonest base polymers are carboxymethylcellulose, hydroxymethylcellulose and Hydroxypropyl-guar (HP-guar), a gelling agent that has been combined with glycol 400 and propylene glycol to prevent corneal desiccation. The ingredients add volume to the tear film, as well as increase the residence time of the tear

supplement on the ocular surface. The lubricants may also cushion the ocular surface, reducing friction between lid and globe, and provide additional comfort in the dry eye condition. Tear supplements have varied formulations.[34] Some tear substitutes contain electrolytes, which are present in normal tears, to help prevent ocular surface damage. Potassium and bicarbonate ions are important for ocular surface health. Hyaluronic acid is a highly hygroscopic viscous agent that has surface coating properties. It has a prolonged residence time in the ocular surface, aids in maintaining the health of the surface epithelium, and lowers tear osmolarity with extended use.[35] Certain tear supplements attempt to mimic the lipid component of tears using castor oil to retard evaporation. Since hyperosmolarity of the tear lm is a feature of dry eye states, and such tears are pro-in ammatory, [36] with resultant epithelial cell desiccation and death due to the osmotic imbalance, tear substitutes try and address this problem. This is done by the addition of compatible organic solutes (e.g., glycerine, erythritol, and levo- carnitine) that distribute between the tear lm and intracellular uid in a way that protects the ocular surface against the effects of hyperosmolarity of the tear lm. Preservatives in the tear supplements can affect the ocular surface, especially with prolonged use of these medications. Benzalkonium chloride and EDTA are potentially toxic to the ocular surface. Newer preservatives like Sodium Perborate and Purite (stabilised oxychlorocomplex), are called "transient" or "disappearing", as they disassociate to harmless substances when instilled in the eye. However, when supplemental tears are used more than 6 times a day, preservative-free unit dose vials are recommended (Figure 4).

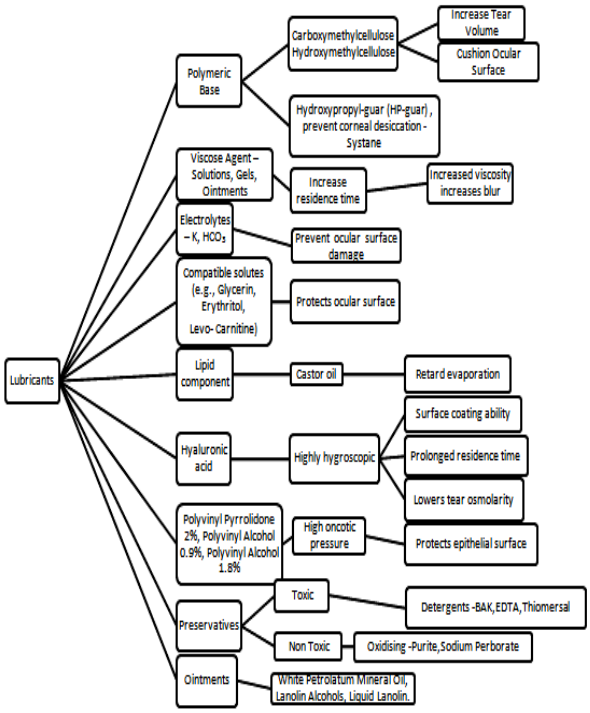

Figure 4

B. Anti-in ammatory Therapy

1. Topical Corticosteroids

Topical 0.1% uorometholone has been reported to decrease inflammation, improve uorescein staining, aid in resolution of lamentary keratitis, increase mucin secretion and increase Schirmer's scores.[37, 38] Unpreserved methylprednisolone can be considered in eyes with significant ocular surface damage. Complications like cataracts, glaucoma, and infection are usually associated with long term usage (more than 3 months). For long-term control of inflammation, therefore, topical 0.05% cyclosporine (CSA) eye drops can be helpful. Topical steroids, given in the initial 2 weeks of CSA therapy may decrease the burning and stinging associated with the drug.[39]

2. Topical Cyclosporine

Topical cyclosporine (Restasis - 0.05% emulsion) acts primarily by decreasing activation of T-lymphocytes, and inhibiting calcineurin and apoptosis in other cell types.[40] Topical cyclosporine is formulated as a lipid emulsion of castor oil that also includes glycerine, polysorbate , and sodium hydroxide (to adjust the pH). It has no preservative and is dispensed in unit dose ampoules. It is used twice daily in evaporative and aqueous deficient dry eye.[41]

3. Omega 3 Essential Fatty Acids

Essential fatty acids are polyunsaturated fats that cannot be synthesized by humans and therefore must be included in the diet or as nutritional supplements. Essential fatty acids are divided into two groups: omega 6 and omega 3, named by the location of the rst double bond in the carbon chain. Both forms are digested by the same enzymes but omega 6 breakdown components are associated with increased in ammation, and omega 3 components decrease in ammation.

C. Secretogogue Therapy

Oral pilocarpine and cevimeline are lacrimal and salivary gland secretagogues that stimulate secretion of lacrimal gland uid (tears) and saliva. They act on the lacrimal and salivary gland M3 muscarinic receptors. The recommended dose for oral pilocarpine is 5 mg, two to four times a day. The predominant side effect of both medications is sweating. Topical secretagogues Diquafosol and Rebamipide can help due to their mucin-inducing and secretion-promoting effects.

D. Punctal Occlusion

Blockage of the tear drainage system at the level of the puncta or canaliculus helps preserve natural tears and instilled arti cial tears. Punctal occlusion can be performed by using collagen as a temporary measure to access if the improvement in symptoms and signs justifies the use of a permanent device (as these are more expensive). It also helps determine if troublesome epiphora occurs as a complication of occlusion.

E. Autologous Serum

This is reserved for the most severe cases that have not responded to other treatments. It has also been used for ocular surface disease, including Sjögren disease,[42] graft-versus-host disease, Stevens-Johnson syndrome, neurotrophic keratopathy, and cicatricial pemphigoid.[43] The disadvantages of using autologous serum include the complex preparation process, the need to refrigerate the drops, and the potential risk of infection if contamination of the solution occurs.[44] The serum is used as a 20% solution 4 times a day, and once prepared, is stable for up to 3 months.[45]

F. Mucolytic Therapy

Acetyl cysteine is used as 10-20% solution three times daily for 2 weeks, in patients with excessive filament formation. The drops may sting on instillation and have an unpleasant odour.

G. Therapeutic Contact Lenses

Contact lenses are recommended in severe dry eyes as they can promote corneal healing, protect the ocular surface from the lids and environment, reduce desiccation, and relieve discomfort. Silicone-Hydrogel soft contact lenses have lower water content and are preferred. However, the use of a contact lens in an eye with deficient tears can have problems, and the decision to use this option must be made on a case-by-case basis.

H. Management of Eyelids

For patients with meibomian gland dysfunction (Figure 5), manual expression of the meibomian glands using two cotton-tipped applicators pressed together to compress the eyelid is commonly performed. A device recently approved by the FDA, continuous controlled thermal compression (Lipi ow System), lique es the meibomian gland secretion and then expresses the material.[45, 46]

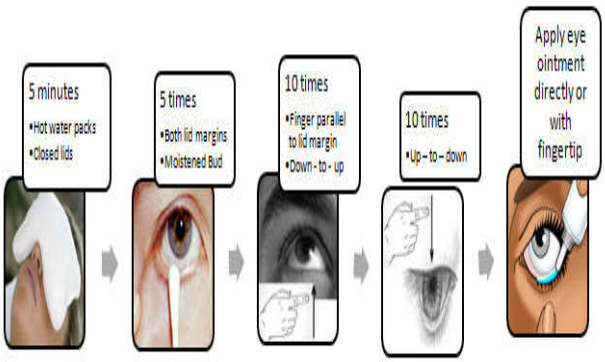

Figure 5

Systemic doxycycline has anti-inflammatory, as well as antibacterial activity, when used in DED. It decreases the activity of collagenase, phospholipase A_2, and several matrix metalloproteinases. This is often combined with topical therapy and lid massage in eyes with significant lid margin changes.

CONCLUSION

In conclusion, DED is now a common condition, with an aging population, changes in the environment and work practices, increasing use of medications and corneal surgeries. A rationale approach to the evaluation of such patients, appropriate tests, and knowledge of the various

exacerbating conditions, can help manage most of these patients in a satisfactory manner.

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