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A REVIEW ON DRY EYE AND ITS TREATMENT OPTIONS

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ABSTRACT
Eye is a complicated and visceral organ which is connected with fine muscles, receptor and neurons that collects, analyze and transfer information to the brain where image are recognized. The eye is one of the multiplex organs of the human body which composed of three layers i.e. outer, middle and inner. The common disease in eye is dry eye, meibomian gland dysfunction, cataract, macular degeneration, hypertensive and diabetic retinopathy and glaucoma. Dry eye disease nowadays becomes a most common ocular disease. The main causes for dry eye disease are decreased tear production, excessive tear evaporation and abnormality in production of mucus or lipid of tear layers. This review discusses the classification, grading, sign and symptom, prevalence, diagnosis and treatment of dry eye.

KEYWORDS: Cornea, dry eye, grading, treatment of dry eye.

1. INTRODUCTION

The eye is one of the multiplex organs of the human body which composed of three layers i.e. outer, middle and inner. The outer layer consists of cornea and sclera which connected at the limbus. The middle layer of eye is composed of iris, ciliary body and choroid. The inner layer of an eye is retina.[1]

The superficial layer of the eye consists of a number of structures, each of which has a specific function. The ocular surface, tear film, lacrimal glands, and eyelids act as a functional unit to protect the quality of the refractive surface of the eye; to resist injury and to protect the eye against changing bodily and environmental conditions.[2] The tear film plays a vital role in nourishing, lubricating and protecting the ocular surface.[3] The common disease in eye is dry eye, meibomian gland dysfunction, cataract, macular degeneration, hypertensive and diabetic retinopathy and glaucoma.[4] Among all of these dry eye is most common cause of an eye problem. Dry eye syndrome (DES) is a disorder of preocular tear film which results in discomfort, visual impairment and tears film alteration caused by tear deficiency or excessive tear evaporation.[5]

DES is also called Keratoconjuntivitis Sicca (KCS), Keratitis sicca, Sicca syndrome, Xerophthalmia, Dry eye disease (DED), Ocular surface disease (OSD), Dysfunctional tear syndrome (DTS) or simply dry eye. Keratoconjuntivitis Sicca is Latin word where keratoconjuntivitis means dryness of cornea and conjunctiva and sicca means desiccate. The condition in which eye do not produce sufficient tear is known as sjogren's syndrome.[4]

Dry eye is disorder of the tear film due to tear deficiency or excessive tear evaporation which causes damage to ocular surface with symptoms of discomfort.[6]

2. Classification of dry eye

The major classes and subclasses of dry eye are described below.

a. Aqueous tear-deficient dry eye (Tear deficient dry eye; lacrimal tear deficiency)

Aqueous tear-deficient dry eye implies that dry eye is due to a failure of lacrimal tear secretion. In any form of dry eye due to lacrimal acinar destruction or dysfunction, dryness results from reduced lacrimal tear secretion and volume.

b. Evaporative dry eye

Evaporative dry eye is due to extreme water loss from the exposed ocular surface in the presence of normal lacrimal secretory function. Its causes have been described as intrinsic, where they are due to intrinsic disease affecting lid structures or dynamics, or extrinsic, where ocular surface disease occurs due to some extrinsic exposure.[7]

3. Tear structure

The tear film consist of three distinct sandwiched layers i.e. mucous layer which is closest to the corneal surface, middle layer is aqueous layer and a lipid layer is an

outermost boarder between eye and air. The mucous layer is secreted by goblet cells of conjunctiva epithelium whereas aqueous layer is secreted from lacrimal glands located in upper temporal sides of eyes and lipid layer is secreted from meibomian glands.[8,9]

4. Tear composition

Tears are complex solution composed of water, enzymes, proteins, immunoglobulins, lysozymes, cytokines, lactoferrin, lipids, various metabolites, exfoliated epithelial and polymorphonuclear cells.[10] Lysozymes may act synergistically with IgA in lysis of bacteria where lactoferrin also has antibacterial effect. The average tear glucose concentration is 2.5mg/dl and average tear urea level is 0.04mg/dl. Electrolytes such as K, Na and Cl in tear are in higher concentration than in blood. Tear osmolarity, average tear pH and refractive index of tear film are 309mosm/liter, 7.25 and 1.36 respectively.[4] The lacrimal glands secrete lacrimal fluid, which flows through main excretory ducts into the space between the eyeball and lids. When the eyes blink the fluid is spread across the surface of the eye. Lacrimal fluid gathers in the lacrimal lake, and is drawn into the puncta by capillary action, then flows through the lacrimal canaliculi at the inner corner of the eyelids entering the lacrimal sac, then on to the nasolacrimal duct, and finally into the nasal cavity.[10]

5. Grading of dry eye

On the basis of severity of signs and tear film tests, Dry Eye Workshop (DEWS) report 2007 graded the severity of dry eye into four levels:[7]

- Level 1 (mild and/or episodic)
- Level 2 (moderate episodic or chronic, stress or no stress)
- Level 3 (severe frequent or constant without stress)
- Level 4 (severe and/or disabling and constrant)

6. Causes of dry eye

DED is caused by a cycle of tear film instability, hyperosmolarity and inflammation that can ultimately result in increased friction and damage to the surface of the eye.[11] The deficiency of lipid layer in the tear film is main cause in about 80% of the patients suffering from dry eye, which results in maximum evaporation.[12] The disturbance of lacrimal function unit (LFU) cause dry eye. LFU is an integrated system which interconnects lacrimal glands, ocular surface and lids, as well as sensory and motor nerves. It controls the major components of tear film in a regulated fashion and responds to environmental, endocrinological and cortical influences. The overall function of LFU is to preserve the integrity of tear film, the transparency of the cornea and the quality of image projected onto the retina. Any damage or defect to any component of LFU can result in dry eye.[13] Tear film is exposed to different relative humidity in different environmental conditions and it evaporated when it is exposed to air of less than hundred per cent humidity.[14] Loss due to evaporation of tear fluid and dry eye are usually associated with inadequate lipid layer. Lipid layer stabilizes and slowdown the evaporation of tear fluid.[15] Rosacea, blepharitis and meibomain gland dysfunction are main causes of evaporative dry eyes.[16]

7. Sign and symptoms of dry eye

DES is characterized by many symptoms including feelings of dryness, grittiness or soreness in both eyes, which worsen through the day, watering of eyes, particularly when exposed to wind, no abnormalities on examination, burning, foreign body sensation and sensitivity.[17]

8. Prevalence of dry eye

Dry eye is one of the most prevalent eye disease causing increased risk of ocular infections by use of contact lens, diet, smoking, history of allergies or diabetes, ocular discomfort, fatigue and visual disturbances that interfere with crucial activities such as reading, working on a computer, using mobile phones and driving a car. Studies over the past decades have identified older age, female, reduced androgen level, exogenous estrogen use.[18,19] By using Ocular Surface Disease Index to determine the prevalence of dry eye in a population of South Africa. The result of the study yielded a prevalence of 64%.[20] Other studies reported less value, where prevalence ranged between 0.39% and 33.7%.[21,22] Increase in age also increases the prevalence of dry eye. It is a common disorder of eyes affecting a considerable percentage of population, especially older than 50 years of age.[19,23] The expected number of people affected by DES is in between 25 to 30 million all over the world. Research also shows that DES can affect any race and is more common in women.[24,25] Patients with *Helicobacter pylori*, computer users and long time contact lens wearers are also likely to be affected with DES.[26,27]

9. Factors influencing dry eye syndrome

There are many factors which influence dry eye symptoms, some of them are: diurnal variation in tear volume, contact lens wear, age, systemic disease, gender, diet, water intake and environmental factors. These are discussed below.

9.1. Gender and dry eye

In a large clinical study they found that gender has a large influence on the symptomatology of DED, with significantly higher symptom score and lower correlation between symptoms and signs in women compared to men.[28] Evidence also suggests that gender is an important risk factor for dry eye disease and studies have found that women have a 16% to 300% greater prevalence of dry eye disease compared to men.[29,30] A higher prevalence was reported in females high school students (24.4%) compared to 21% in males.[31] But other study reported that the prevalence of dry eye was 1.4 times higher in males than females.[32] In another study they found that no significant difference in dry eye symptoms between sexes.[33] Other study also reported

no significant differences in tear film stability between males and females.[34]

9.2 Age and dry eye

DED is a disease of adulthood and the risk of developing DED increase with age. The incidence was greater significantly greater in males in 3rd, 4th, 9th and 10th decade, it was greater in females in 5th, and 6th decade of life.[35] This finding is also supported by one study who also reported increasing incidence and prevalence of DED in both men and women with age.[36] The prevalence of dry eye increases with age, increased sunlight and ambient temperature.[37,32]

9.3 Dry eye in urban and rural areas

In one Indian study of the 21,290 patients with DED, 59% were from an urban area and 41% from a rural area. The overall incidence of DED was significantly higher in the urban community as compared to rural community.[35] Where as in another Indian study they found that dry eye was more prevalent in rural areas compared to urban areas. This may be due to that the rural residents in India are mostly laboures/farm workers who work outsides and in direct sunlight for most of the time.[38] DES was more commonly reported in urban areas than in the rural areas, possibly due to higher levels of air pollution in the city.[39]

9.4 Dry eye and tear volume

Evaporation of the tear is low on waking and within two hours and it rises to a constant level for the rest of the day. It may be due to low tear production during sleep and the presence of tick lipid layer of tear on waking.[40] A diurnal decrease in tear volume may be one of the reasons responsible for the common increase in 'end of day' ocular dryness symptoms by many patients.[41]

9.5 Occupations and dry eye

In a large population-based study showed that people with indoor and sedentary occupations have a higher prevalence of dry eye disease, although this was largely mediated via dry eye associated comorbidities and traits that were more common in these occupations. Of all occupations, the most prevalence of dry eye was found in the clerical support workers and professionals. These occupations are associated with a relatively high use of visual display terminals (VDTs) and are mostly desk-bound, sedentary occupations. After correction for dry eye associated aomorbidities and traits, the craft workers and more specially the building workers and metal and machinery workers showed the highest risk of symptomatic dry eye.[42] A longitudinal study conducted among pregnant women in Nigeria, found that civil servant are 32.8%, housewife 29.8%, trader 20.9%, artisan 5.2% and student 11.2%.[43] In an Indian study of the 21,290 patients with DED, 28.24% were homemakers; 26.49% were professionals; 14.33% were manual laborers; 10.16% were retired or unemployed; 8.53% were students and remaining 12.25% the occupational category was not applicable.[35]

9.6 Contact lens and dry eye

In a Japanese study, they found that 2.1% male and 5.7% female with DED used contact lens[44], where as in a other study they found that only 1% patient with DED used contact lens.[45] Dry eye symptoms during contact lens wear leads to a decrease in wearing duration or discontinuation of use.[22] Contact lens wear was also associated with ahigher prevalence of severe dry eye.[31]

9.7 Menstruation and dry eye

In one cross-sectional analysis of the Korean population, they found that women with irregular menstruation were more likely to have a DED diagnosis or DED symptoms, compared with women with regular menstruation. These associations remained significant after adjusting for age, BMI, lifestyle factors and parity.[46]

9.8. Refractive error and dry eye

In an Indian study they found that there was a higher prevalence of dry eye in people with uncorrected refractive errors (25.3%) as compared to those with corrected refractive errors (15.6%) in their study.[38] A population based study in China, they found that undercorrection of a refractive error was a significant factor associated with dry eye symptoms.[39] In another study they reported that the prevalence of dry eye was higher in those with refractive error as compared to emmetropes. Dry eye was reported mostly by contact lens wearers (52.3%) and spectale wearers (23.9%) as compared to emmetropes.[47]

9.9. Migraine headache and dry eye

Association between headache/migraines and dry eye has been found by researchers. In that research the prevalence of headache in Sjogrens syndrome was also discussed.[48] In another research an increased frequency of dry eye disease was found to occur in patients with migraine. Which suggests that migraine headache are related to dry eye disease.[49]

9.10. Dry eye and systemic disease

In a study researcher found a greater prevalence of dry eye signs and symptoms in non-insulin dependent diabetes mellitus (NIDDM) subjects. It was assumed that parasympathetic innervations alteration in NIDDM could lead to reduced nervous supply in the lacrimal glands and thus less aqueous tear production.[50] Other researchers also found that dry eye has been associated with diabetes. Dry eye and the use of artificial tears in diabetics over the age of 50 were significantly higher compared with non-diabetics.[51]

9.11. Dry eye and psychiatric disorders

Researchers have been found that there is a close relationship between depression or anxiety disorder and dry eye. Patients with psychiatric disorders may have dry eye symptoms including dryness, burning and itching. Patients with dry eye disease may have greater chances of having depression and psychosis than those without dry eye disease.[52] The use of medications such

as anti-depressant, anti-anxiety and medication for prostatic hyperplasia all were associated with an increased risk of dry eye syndrome. In this study author also found that several medical conditions were found to increase the risk of dry eye disease such as post-traumatic stress disorder, depression, thyroid disease and sleep apnea.[53] In a Korean study, they found that depression was associated with dry eye disease symptoms in patients with normal or mildly reduced tear production. They also have opinion that symptoms and signs of dry eye disease in certain patients may be due to depression.[54] A study conducted in Shanghai, they observe dry eye disease in patients with depressive illness and anxiety disorder. Of the 472 patients included in the study, 37% were diagnosed with depression, 36% had generalized anxiety disorder, 13% had both depression and generalized anxiety disorder, 12% had obsessive compulsive disorder and 2% had a panic disorder. They found that dry eye disease was present in 60% of the patients.[55]

10. Diagnosis of dry eye

Diagnostic tests are used for different purposes such as assessing eligibility in a clinical trial and monitoring changes quantitatively. Ophthalmologist diagnoses and characterize dry eye as part of clinical syndrome such as sjogren's syndrome There are different diagnostic procedures to test the dry eye; they are Schirmer test, Tear Film Break up Time Fluorescein dye test, Lissamine green test, etc.[4] The most common objective of diagnostic test for dry eye is schirmer test which has been in use for more than 100 years.[56]

10.1. Schirmer test

Schirmer test is frequently performed to evaluate aqueous tear production, but it gives variable results and should not be used as the only criterion for diagnosing dry eye. This test was used to determine schirmer value by measuring the length of the wetted part of the standardized filter paper strip i.e. whatmann filter paper no: 41 in the lower fornix. Aqueous tear production is measured by the length in mm that the strip wets during the test period, generally 5 minutes. Though there are several versions of the test, the most common are schirmer I without topical anaesthesia and a variation with anaesthesia.[57,58]

10.2. Tear film breakup time (TBUT)

The time required for the tear film to break up following a blink is called tear film breakup time. It is a quantitative test for measurement of tear film stability.[59] The normal time for tear film breakup is 15-20 sec. A fluorescein strip impregnated with normal saline is applied to inferior cul-de-sac. After several blinks, the tear film is examined using a broad-beam of slit lamp with a blue filter for the appearance of the first dry spots on the cornea. The TBUT values less than 5-10 seconds indicate tear instability and are observed in patients with mild to moderate dry eye disease.[60]

10.3. Fluorophotometry

Tear turnover can be measured by the measurement of fluorescein disappearance via fluorophotometry or other fluorescein clearance tests. Tear turnover is the percentage decrease of fluorescein concentration in tears per unit of time.[61]

10.4. Epithelial Staining

In this technique, dyes such as Rose Bengal, lissamine green, fluorescein are used to determine abnormalities of surface of the eye, quality of tear film and severity of dryness.[62] Staining pattern can be snaped and graded by using number of scoring systems.[59]

10.5. Tear function index

This test evaluates the tear dynamics of production and drainage and helps subjects suffering from dry eye. The higher the numerical value the better the ocular surface. Value less than 96 suggest dry eye.[63]

10.6. Phenol red thread test

This is a modified form of Schirmer test, it this test cotton thread moistened with phenol red dye is used instead of strip. Phenol red is sensitive to pH and changes colour from yellow to red when wetted by tears. Compared to Scirmer's test this test takes less time interval (15 seconds). After 15 seconds, the length of the colour change of thread wetted by tears is measured in millimeters. Wetting length should be between 9mm to 20mm. Wetting length less than 9mm indicated patients with dry eyes.[64] Some researcher suggest that this test can assist in differentiating aqueous deficient and non-aqueous deficient dry eye.[65]

10.7. Tear Ferning Test (TFT)

In this test a drop of tear fluid is collected from the lower eyelid and then placed on a microscope slide and allowed to dry by evaporation. After evaporation different forms of branching crystallization patterns are observed and classified. This test diagnose dry eye on the basis of the ferning patterns.[66]

10.8. Tear Film Osmolarity

Increase in tear film osmolarity is a sign of dry eye disease. The benefit of measuring tear osmolarity in the diagnosis of dry eye disease has been undetermined by the difficulties of its measurement. The first methods for measurement of tear osmolarity was through observation of the change in the freezing point of tear samples. Some of the researcher also utilizes electrical conductivity of tear samples to determine osmolarity.[67] Tearlab osmolarirty system enables the clinician to collect and measure the osmolarity in 50nL sample. In this technique sampling is performed in five or six seconds and the calculation of tear osmolarity is performed in less than twenty seconds.[68]

10.9. Thermography

It is a non-invasive method of measuring the surface temperature of an object. Cornea is warmest over the

limbus and coolest at the center. In dry eyes, the mean ocular surface temperature is higher than the normal eyes. Conjunctivial hyperaemia associated with dry eyes colud be a reason for the higher temperature. Researcher also states that ocular temperature is higher in dry eye patients because they blink at a higher frequency.[69]

10.10. Other tests

Tear evaporation is measured by evaporimetry. Meniscomery is used to help diagnose aqueous tear deficient dry eyes. Lcarimal gland or salivary gland biopsy may be used for diagnosis of Sjogren's syndrome. Histopathological findings also help to characterize DES. Meibomain gland dysfunction is diagnosed by techniques such as meibometry, meibography or meiboscopy.[70] The results of diagnostic tests discussed above poorly correlates with symptoms.[71] Though the literature emphasizes hyperosmolarity as a mechanism of DED, indicating tear osmolarity measurement as a gold standard for diagnosis[72,73] unfortunately no single qualitative/quantitive test is capable of assessing integrity of tear film and severity of disease. Therefore the results of multiple abnormal tests can be used to diagnose DES accurately.

11. Treatment of dry eye

Only a limited number of therapies are available for DE patients and are used according to the disease severity.[74] The aim of treatments are to alleviate the symptoms of dry eye, recover the patient's comfort, come back the ocular surface and tear film to the normal state and whenever possible, avoid corneal damage.[59] A number of treatments are available to manage dry eye, of which these may range from life style change, environmental or dietary modifications, artificial tear substitutes, punctual plugs and topical and systemic anti-inflammatory drugs to surgical procedures.

11.1. Life style change

The simplest and most valuable way to relieve symptoms of dry eye is a life style change. In this, patients should be informed to avoid long exposure to computers, television, mobile phone and reading which is associated with a reduced blink rate and thus increased evaporation. The avoidance of hot, windy, low-humidity and high altitude environment as well as smog and smoke is also desirable. The humidification of air in workplace or inside home could also reduce unwanted effects of dry eye symptoms.[75]

11.2. Tear substitutes

Use of artificial tear to the deficient tear production remains the basis of treatment for tear deficiency state. Soothing effect to dry eyes was found with the use of normal saline drop. However soothing effects to the dry eyes was transitory. The duration of action can be enhanced by the addition of thickening agent. Thus several attempts have been tried to prolong the action which mostly includes addition of high molecular weight polymers to normal saline solution.[76] Most of the early polymers used were cellulose ether, carbomers, plyvinyl alcohol, lipid based formulations, methylcellulose, hydroxyethyl cellulose, and hydroxypropylmethyl cellulose.[77] Carboxymethylcellulose as lubricating can also be used in the treatment of dry eye.[76]

11.3. Preservation of existing tears

When there is severe case of dry eye i.e. 1 mm or less wetting on the Schirmer strips at 5 minutes on repeated testing and when the frequent use of artificial tear has not controlled the symptoms, at that time it possible to close the opening of punctual to prevent the drainage of existing tears. This is generally done with electrocautery and it is very useful.[76] Occlusion of the lacrimal canaliculi improves the sign and symptoms of aqueous tear deficiency.[78]

11.4. Stimulation of tears

A cholinergic agent tends to stimulate tear production, provided that there is enough normal acinar tissue remaining in the tear glands. However the use of cholinergic agents have several side effects and this mode of treatment is not generally useful. However, at present there is no generally useful tear stimulant.[76]

11.5. Decrease in tear viscosity

Tear viscosity increases in KCS and can be the source of considerable discomfort. In addition of artificial tear, it is possible to use 10% or 20% solution of acetylcystein 3 to 4 times a day which has certain mucolytic action and tends to break up the viscous mucin in the tear film.[76]

11.6. Anti-inflammatory treatments

11.6.1. Topical cyclosporine

Topical cyclosporine has been reported to have an anti-inflammatory effects and suppressing effects which improve tear production, increases conjunctival goblet cell density and have therapeutic effect on various ocular disorders.[79]

11.6.2. Corticosteroids

Corticosteroids possess potential anti-inflammatory properties, thereby used in controlling inflammation in many organs. The FDA has approved the prescription of topical corticosteroids for inflammatory conditions such as DED.[80]

11.6.3. Tetracyclines

They have anti-inflammatory, antibacterial, antiprotease, antilipase and immunomodulatory actions.[81] They are mainly used in meibomian gland dysfunction.[82]

11.6.4. Essential Fatty acids

Omega-3 fatty acids play an important role in the synthesis of meibum which forms the lipid layer of tear film.[83] Omega 3 is the precursor of Eicosanoids which mediate inflammatory response.[84] They help in clearing and thinning of meibomian gland secretions which in turn improves symptoms of dry eye.[83]

11.7. Punctual plugs

Another treatment option is the application of tear retention devices. Implants are used to permanently occlude the lacrimal puncta. These types of implants are also known as punctual plugs.[85] Punctual plugs relieve DED in patients with Sjogrens syndrome, filamentary keratitis, chronic Stevens-Jhonson syndrome, trachoma, neuropathic and diabeteic keratopathy, keratitis sicca and in patients with dry eye after refractive surgery. The obstruction or inflammation of lacrimal canaliculi or duct as well as active blepharitis is a condition in which punctual plugs are not used.[75]

11.8. Vitamin A

Vitamin A protect the eye from free radicals, toxins, allergens and inflammation. Topical retinoic acid therapy in combination with use of vitamin A has been investigated to treat xerophthalmia.[86]

11.9. Surgical procedure

Surgical procedure is suitable for treatment of dry eye include lid procedures which include (permanent punctual closure usually with cautery and tarsorrhaphy) and conjunctival procedures which includes conjuntival transplantation, amniotic membrane transplant, free conjunctival graft and stem cell replacement.[75]

CONCLUSION

In conclusion, the overarching complexity of the dry eye disease makes it challenging to classify, diagnose and treatment accordingly. With the development of specific tests with precise diagnostic value and minimal disruption of normal physiological function, accurate diagnosis of disease is possible. Up to date knowledge regarding classification, causes, symptoms, and diagnostic test of dry eye to clinicians provides better opportunities for improving treatment. Development of additional targeted drug delivery systems such as epithelial barrier, corneal nerves, conjunctival goblet cells and cytokines involved in the ocular inflammatory reactions would provide hope for the patients who experience dry eye.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this review article.

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