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DRY EYE DISEASE: A REVIEW ARTICLE

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ABSTRACT

Dry eye disease (DED) is a tear film disorder due to tear deficiency or excessive tear evaporation, which cause damage to the interpalpebral ocular surface associated with symptoms of discomfort, visual disturbances and tear film instability with potential damage to ocular surface. Globally its prevalence is ranging from 20 to 50%, which is growing day by day worldwide. It's pathogenetic mechanisms include hyperosmolarity of tear film, inflammation of the ocular surface and lachrymal gland. Dry eye is clinically divides into two subtypes: one with increased tear evaporation (evaporative DED) & one with decreased tear secretion (aqueous deficient DED). The diagnostic evaluation of dry eye should include patient detailed history, slit lamp examination and some diagnostic test. According DEWS treatment option of DED is depend on its severity level graded from 1 to 4. Beside that a new concept of treatment strategy was developed by Japanese & Asian Dry-Eye Societies called 'Tear film oriented therapy' (TFOT), have primary target to produce healthy stable tear film rather than controlling ocular inflammation.

KEYWORDS: Dry eye disease, aqueous deficient DED, evaporative DED etc.

INTRODUCTION

The dry eye per se is not a disease entity, but a symptom complex occurring as sequelae to deficiency or abnormalities of tear film. It is very common condition with a high prevalence among the elderly. In 2007, International Dry Eye Workshop revised the original definition and classification scheme of dry eye disease (DED) and developed a new definition based on

aetiology, mechanism and severity of the disease. The term dry eye syndrome (DES) according to DWES has been defined as a "a multifactorial and chronic disease of the tears and ocular surface that result in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface.[1]" It is accompanied by increased osmolarity of the tear film and subacute inflammation of the ocular surface.

In addition to being dry eye syndrome (DES), there are some alternative medical terms used to describe dry eye include dry eye disease (DED), ocular surface disease, dysfunctional tear syndrome keratoconjuctivitis sicca, keratitis sicca, sicca syndrome and xerophtalmia.[2]

- Keratitis sicca: generally used to described dryness and inflammation of cornea.
- Keratoconjuctivitis sicca: used to described dry eyes that affecting both cornea & conjunctiva.
- Dysfunctional tear syndrome: used to show that inadequate quality and quantity of tears.

Recent studies shown that DED is an inflammatory disease that has many features which common with autoimmune diseases. Stress to ocular surface (antigens, genetic factor, endogenous stress, environmental factor, infection) is postulated as the pathogenic triggering mechanism. When there is inadequate tear volume or function resulting in an unstable tear film affecting more in women (in postmenopausal women) than men.

The four core interrelated mechanism thought to be responsible for the manifestation of dry eye are tear instability, tear hyperosmolarity, inflammation and ocular surface damage. Patient with dry eye often complain of pain, redness, photophobia, gritting sensation, excess tearing, ocular fatigue and dryness. DED is classified into two types such as: "dry eye with reduced tear production (Aqueous deficient DED) & dry eye with increased evaporation of tear (Hyperevaporative DED).[3]"

The diagnosis of DED is based in part on the patient's history & symptoms and in part on the application of specific tests such as: Schirmer test, tear film break up time (TBUT), tear osmolarity etc. DWES have produced guideline based on earlier international taskforce guideline for dry eye, in which suggested treatment option depends on the level of severity of disease graded from 1 to 4.[4]

Epidemology of dry eye disease

The prevalence of dry eye syndrome increases with age. DES is a common disorder of eyes affecting mostly elder people more than 50 years age.[5] Because of the autoimmunae disease, systemic drug effects, refractive surgeries, more use of contact lenses, computers & TV the middle age and older adults are commonly affected with dry eye.[6] The prevalence of DED is greatly affected by geographic location, climatic condition, lifestyle of the people and ranges from 5% to 35%.[7]

The reported prevalence of DED in the literature is diverse, ranging between 7.8% in one study in western world and 93.2% in one study in Asia.[8] This is probably because of two factors: first, the geographical location of the study population and secondly, there is no standardization of the selected population, dry eye questionnaires, objective test and dry eye diagnostic criteria.[9]

There was 25-30 million people estimated to be affected by DES all over world.[10] There is no population based study in relation to dry eye disease in India. There was only 3 studies occur in India and two of them from the North and one from Eastern India. With different diagnostic criteria the prevalence of dry eye in these studies was between 18.4% and 40.8%.[11.12] One small study from Leha showed that the higher prevalence of dry eye was 54% in high altitude.[13]

Risk factors for DED

Risk factor of dry eye disease included advanced age, female sex, systemic disease, smoking, medications, environmental factor, contact lens wear, excessive use of computer, TV, mobiles etc.

Older age and female gender have been identified as risk factors for dry eye.[14] Arthritis, Smoking and multivitamin use were found to be associated with risk of developing DED, While caffeine use was associated with a decreased risk.[15,16] Hormonal replacement therapy, especially when estrogen is used alone, was associated with an increase risk of clinically diagnosed dry eye syndrome.[17]

Associated Factors and Conditions

- Preservative eye drops instilled frequently for more than 6 weeks.

- Use of systemic medications- such as anti depressant, antihistamine, anticholinergics, beta-blocker and diuretics etc.
- Exogenous irritants and allergens, although not a causative factor for dry eye, but it may exacerbate the symptoms.
- Environmental factors, such as increased wind, drafts, heating, air conditioning and decreased humidity may accelerate the symptoms of dry eye.
- Patient with history of blepharitis, as well as rosacea and skin disorder, can cause meibomian gland to block making dry eye very quickly.[18]
- Associated systemic disease: such as Sjograins syndrome, in which an inflammatory cellular infiltration of the lacrimal gland leads to aqeous tear-production deficiency, and rosacea, which is associated with posterior blepharitis or meibomitis with increased tear evaporation.
- Patient have history of viral infection may develop the dry eye. It has been reported that patients infected by the human T-cell lymphocyte virus (HTLV) type1, Epstein-Barr virus, HIV and Hepatitis C virus may tend to develop DED.[19]
- As a result of infiltration of lacrimal gland and replacement of the secretory acini such as sarcoidosis, lymphoma, amyloidosis and hemochromatosis aqueous tear deficiency dry eye may develop.
- Local condition associated with dry eye: such as eyelid malposition, lagophthalmos, blepharitis, neuromuscular disorder that affects blinking e.g. Bell's palsy, Parkinson disease.
- Local ocular surface trauma: such as orbital surgery, radiation and injury chemical or thermal, may also cause dry eye.
- Disease such as ocular cicatricial mucus membrane pemphigoid (OCP) and stevens-Johnson syndrome produce tear deficiency due to inflammation, scarring and destruction of the conjunctival globet cells. Atopy and chronic allergic conjunctivitis may produce dry eye due to blephritis, scarring and long term use of histamine.
- Oxidative stress damages the ocular surface and plays important role in the mechanism of DED.[20]

Tear fluid and composition: Dry eye is recognized as a consequence of disruption of lachrymal functional unit consist of lachrymal gland, ocular surface including cornea, conjunctiva, eyelids, meibomian gland, ocular nerves and globet cells.

Tear film is composed of mainly three layers.[21]

The outermost, thinnest layer of tear film contains lipids, which secreted by meibomian, molls and zeis gland. This layer helps to prevent evaporation of tears and maintain tear film thickness. Its deficiency results in evaporative dry eye. The middle or aqueous layer is thickest, largest layer secreted by lachrymal and its accessory gland, contain sodium chloride, sugar, urea, mucin, protein, cytokines & antibacterial substances. This layer provides oxygen to cornea, keep eye moist, wash away debris, shows antibacterial activity. Defect of this layer causes DES in most cases. The innermost layer of tear film, which get produced by conjunctival goblet cells. It converts the hydrophobic corneal surface to a hydrophilic surface. Deficiency of this layer may be a feature of both aqueous and evaporative states. The mucus layer also reduces the surface tension between water layer and lipid layer of tear film, thus contributing to maintain stability of tear film.

Tear fluid also consist of mixture of mucins, electrolytes, water, proteins, cytokines, laysozymes, immunoglobulins, lactoferin and growth factors.

Etiology & Classification: DED is differentiated from other ocular diseases and subcategorized into 2 types i.e. aqueous deficient and evaporative DED. Aqueous-deficient DED results from reduced lacrimal secretion in the presence of normal rate of tear evaporation, while evaporative DED results from excessive water loss through tear film in the presence of normal lachrymal function.[22]

According to international dry eye workshop report (DEWS report 2007), the causes of dry eye can be classified as follows.[23]

1} Aqueous deficient DED: also known as keratoconjuctivitis sicca (KCS). Its causes include:

a) Sjogren's syndrome (primary or secondary)

b) Non-sjogren' keratoconjuctivitis sicca: causes can be grouped as follow.

- Primary age related hyposecretion is the most common cause.
- Lachrymal gland deficiencies as seen in congenital alacrima, infiltration of lacrimal gland, e.g. in sarcoidosis, tumor, post radiation fibrosis of lacrimal gland.
- Lachrymal gland duct obstruction e.g. old trachoma, chemical burn, cicatrical pemphigoid and stevens-johnson syndrome.

- Reflex hyposecretion as seen in Riley-Day syndrome, Parkinson disease, reflex sensory block (contact lens wear, diabetes, refractive surgery, neurotrophic keratitis) or reflex motor block (e.g. 7th cranial nerve damage, systemic drugs).

2) Evaporative DED: It is caused by decreased tear film stability and thus increases evaporation.

Intrinsic

- Meiobomian gland dysfunction as seen in chronic posterior blephritis, rosacea and congenital absence of meibomian gland.
- Disorder of lid aperature, e.g. excessive sclera show, lid retraction, proptosis, lagophthalmus as seen in facial palsy, symblephron and eyelid scarring.
- Low blink rate, e.g. Parkinson disease, prolonged computer users, watching television, reading.
- Drug action, e.g. antihistamines, beta-blocker, antispasmodics, diuretics.

Extrinsic

- Vitamin A deficiency
- Topical drugs including the effect of preservatives.
- Contact lens wear.
- Ocular surface disease such as allergic conjunctivitis**.**

3) Effect of environmental factors

These can be both internal, such as age, hormonal status and behaviour patterns, and external, such as the exacerbation of evaporative factors in an atmosphere with low relative humidity.

Symptoms: The main symptom of dry eyes is feeling of dryness, gritting sensation, Itching, excessive tearing, pain and redness of both eyes. Sometime burning and photophobia occur in some cases.[24] Sometimes it is also associated with blurry vision &stringy discharge that specifically worsen in dry, hot weather and low humidity.[25] On the basis of clinical features and severity of symptoms, DED can be classified into grades as follows.[26]

Dry eye severity grading scale

Dry eye severity level	grade 1/ mild DED	grade 2/ moderate DED	grade 3/ severe DED	grade 4/
Discomfort, severity and frequency	mild & or episodic, occurs under environmental stress	moderate episodic or chronic, stress or no stress.	severe frequent or constant without stress	severe & or disabling and constant
Visual symptoms	none or episodic mild fatigue	Annoying & or activity- limiting episode	Annoying, chronic & or constant limiting activity.	constant & or possibly disabling
Conjunctival injection	none to mild	none to mild	+/-	+/++
Corneal staining	none to mild	variable	marked central	N/A
corneal/ tear sign	none to mild	mild debris, ↓ meniscus	filamentary keratitis, mucus clumping, tear debris	filamentary keratitis, mucus clumping, tear debris ulceration
Lid/ meibomian glands	MGD variably present	MGD variably present	MGD frequent	Trichiasis, keratinizaation, symblepharon
Tear film breakup time	Variable	≥ 10	≥ 5	Immediate
Schirmer score (mm/5minutes)	Variable	≥ 10	≥ 5	≥ 2

MGD= meibomian gland dysfunction; - not present, + mild, ++ moderate, N/A not applicable.

Signs[27]

- Tear film: In the dry eye, lipid contaminated mucin accumulates in the tear film as particles. Marginal tear strip is reduced or absent (normal height is 1mm). Froth in tears along the lid margin.
- Conjunctiva: It becomes lustureless, shows redness, keratinisation and conjuctivochalasis may occur.
- Cornea: It may show punctuate epithelial erosion that stain well with fluorescein. Mucous plaque, filaments may occur. Cornea may loose lusture.
- Sign of causative disease such as posterior blephritis with meibomian gland dysfunction, lagophthalmos, conjunctival scarring diseases (trachoma, steven's Johnson syndrome, chemical burn, ocular pemphigoid).

Pathophysiology of DED: DED is result as a disturbance of the lacrimal functional unit (LFU), which is in integrated system include the: Lacrimal gland, Ocular surface (cornea, conjunctiva & meibomian gland), lids, sensory & motor nerves that control the blink reflex.

Dysfunction of LFU results in an unstable tear film that causes damage to corneal epithelium and ocular irritation symptoms. The dysfunction of this LFU may develop from systemic inflammatory disease, increased stress, ageing, decrease in supportive factors (lack of androgen hormones), viral disease (HLTV, HIV, EBV)and surgeries that disrupts trigeminal afferent sensory nerves. Systemic medication & diseases that disrupts the efferent cholinergic nerves that stimulate tear secretions.[28] Decrease tear secretion and clearance initiates an inflammatory response on the ocular surface that involves both soluble and cellular mediators. The clinical research suggests that this inflammation plays a role in the pathogenesis of dry eye.[29]

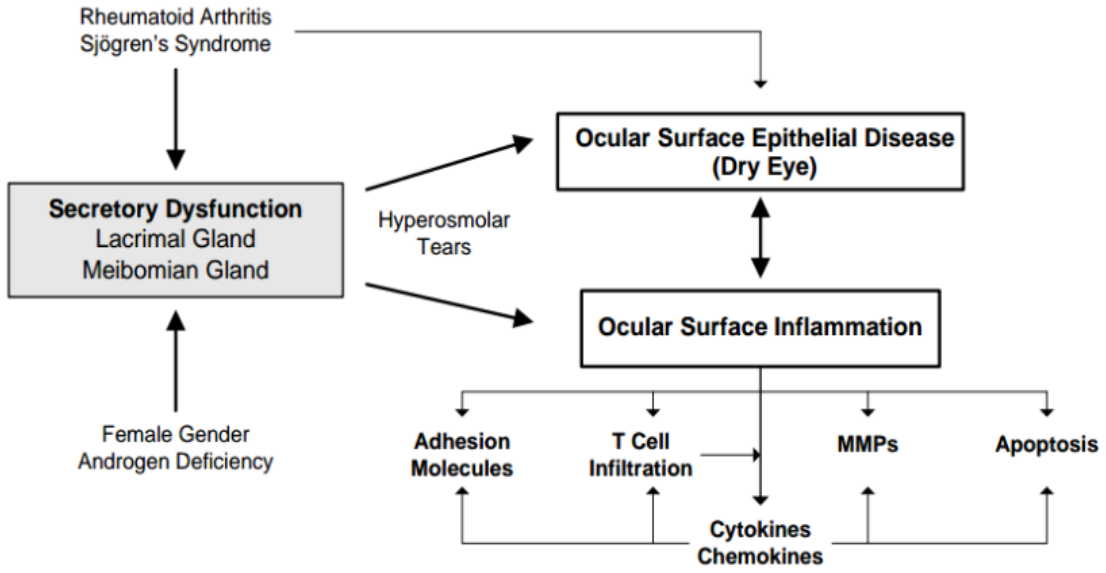

Fig 1: Inflammatory mediators in dry eye. (MMPs= matrix mellaloprotenaise) Modified from SC Pflugfelder; anti-inflammatory therapy for dry eye. Am Ophthalmol 2004; 137: 338.

Diagnosis of DED: The diagnosis of DED is based in part on the patient's history & symptoms and in part on the application of specific tests. Several non-invasive tests are slitlamp examination, meniscometry, interferometry. Mildly invasive tests are the fluorescein tests, staining with lisamine green, meibometry and meibography. Markedly invasive tests include Shirmer's test & staining with rose Bengal. Additional histological procedures are the ocular ferning test & impression cytology.[30] Out of these TBUT, Schirmer-1 test and rose Bengal staining is most important and when any two of these are positive, diagnosis of dry eye syndrome is confirmed. Lid margin assessment with the help of slit lamp examination is also necessary because of evaporative DED is occurred with meibomian gland dysfunction.

Symptoms Questionaries: It is developed in order to quickly assess the dry eye symptoms, helps for early diagnosis and treatment. There are many questionnaires are available which helps for completing patients history, including Ocular surface disease index(OSDI), dry eye questionnaires and the impact of dry eye on everyday life questionnaires. These questionnaires has 3 subscale i.e: ocular symptoms, vision related activities and environmental triggers.

1) Tear film break up (TBUT): The time required for the breakup of tear film following a blink is called TBUT. It is quantitative test for measurement of tear film stability.[31] It is abnormal in aqueous tear deficiency and meibomian gland disorder. It is interval between a complete blink and appearance of first dry spot on the cornea. It is noted after instilling a drop of fluorescein and examining in cobalt blue light of a slit lamp. BUT is an indicator of adequacy of mucin component of tears. Its normal values ranges from 15-35 seconds. Values less than 10 sec imply an unstable tear film and observed in mild to moderate.[32]

2) Schirmer test: It is quantitative test measuring the total tear production by the lachrymal gland during fixed time period.[33] It is performed with the help of a 5 × 35mm strip of Whatman-41 filter paper which is folded 5mm from one end and kept in lower fornix at the junction of lateral one-third and medial two-third. The patients ask to look up and not to blink or close the eyes. After 5 minutes wetting of the filter paper strip from the bent end is measured. Normal values of Schirmer-1 test are more than 15mm. Values of 5-10mm are suggestive of moderate to mild KCS and less than 5mm of severe KCS.[34]

3) Rose Bengal staining: Rose Bengal dye has an affinity for dead or devitalized epithelial cells. It is very useful test for detecting even mild cases of KCS. Depending upon the severity of KCS three staining pattern A,B, and C have been described: ‘C’ pattern represents mild or early cases with fine punctate stains in the interpalpebral area; ‘B’ the moderate cases with extensive staining; ‘A’ the severe cases with confluent staining of conjunctiva and cornea.

The patter of staining may aid diagnosis.

- Interpalpebral staining of the cornea and conjunctiva is common in aqueous tear deficiency.
- Superior conjuctival stain may indicate superior limbic keratoconjunctivitis.

4) Tear Function Index (TFI): It is quantitative test for measurement of the tears. It evaluates the quantity of tear production, its drainage and helps to detect subjects suffering from dry eye. It is performed by instilling fluorescein into the conjunctival fornix, followed by a Shirmer's test. The colour of fluorescein on strip is then compared with known standards to give the tear clearance rate (TCR). TFI is then calculated by by dividing the Shirmer value by the TCR.[35] The higher value of TFI, indicate the better ocular surface. Values below the 96 suggest dry eyes. It is also called Liverpool modification.[36]

5) Tear Osmolarity: 309-312 mOsm/L is a normal osmolarity of eyes and its value increases in DED. It gives qualitative information of tear production. I-PEN , the world first, hand held point of care, solid state electronic diagnostic device used to detect the tear film osmolarity levels associated with mild, moderate and severe DED.[37]

6) Tear Ferning test (TFT): Tear ferning is a simple lab test for tear film quality at a gross biochemical level. The pattern of the tear fern depends upon the composition of the tear sample. Drying a small sample of tear fluid onto a clean, glass microscope slide produces a characteristic crystalline pattern described as a 'tear fern'. Currently this test not widely used because of some limitations.[38]

7**) Impression Cytology:** It is a very useful tool for assessing ocular surface in various dry eye disorder, such as KCS, cicatricial ocular pemphigoid and vitamin A deficiency. The basic principle of impression cytology is application of cellulose acetate filter paper to the ocular surface for the collection of conjunctival specimans, following which histological, immunohistological or molecular analysis of the cells can be done.[39]

8) Flurophotometry: Flurophotometry is a valuable objective method to detect changes in the corneal epithelium by qualitatively measuring its barrier function or permeability. All flurophotometry of the corneal epithelium was done utilizing Fluorotron Master. Each eye had a baseline fluorescein scan performed, after which 50-1% sodium fluorescein dye was instilled. Three minutes later, fluorscein was washed with NS. Scans were recorded at 10, 20, 40 and 60 minutes thereafter. The corneal peak values of fluorescein were recorded. Higher concentration of corneal tissue fluorescein suggests presenting dry eye.[40]

9) Tear Film Protein Immunoassay: The protein component of tears may be quantified by measuring tear lysozymes, tear lactoferrin, epidermal growth factor (EGF), lipocalin,

aquaporin and immunoglobulin A (IgA) concentrations with enzymes-linked immunosorbent assay techniques, as well as tear osmolarity.[41]

10) Other test

To diagnose aqueous tear deficient dry eyes Meniscometry is used. Lacrimal gland or minor gland biopsy may be used for diagnosis of Sjogrens's syndrome. Evaporimetry used to test tear evaporation. Histopathological findings also help to characterize DES and MGD. Meibomian gland dysfunction (MGD) is diagnosed by techniques such as meibometry, meibography or meiboscopy.

Other investigations

- Fluorescein clearance test and tear function index may be assessed by placing 5ul of fluorescein on the ocular surface and measuring residual dye in a shirmer strip placed on the lower lateral lid at se intervals. Delayed clearance is observed in all dry eye states.
- Tear constituents measurement: Tear sample can be assayed for the presence of markers known to be elevated (e.g. atrix metalloproteinase-9) or decreased (e.g. lactoferrin) in dry eye.
- Phenol red thread test: It uses a thread impregnated with a pH –sensitive dye. The end of the thread is placed over the lower lid and the length wetted is number after 15 seconds. A value of 6mm is abnormal. It is comparable to the schirmer test but takes less time to perform.

Differentiating between aqueous deficient & hyperevaporative dry eye: A reduced tear meniscus, low Scirmer 1 test indicate tear deficiency DED. Patient with hyperevaporative dry eye usually shows blocked meibomian gland, lid marginal changes & thickened meibomian gland secretion. TBUT is reduced. Tear film osmolarity is elevated.

Treatment = DWES have produced guideline based on earlier international taskforce guideline for dry eye, in which suggested treatment option depends on the level of severity of disease graded from 1 to 4.[42]

Level 1

1} Education and environmental / dietary modification

- Lifestyle review including the importance of blinking while reading, watching tv, computers etc & management of contact lens wear.

- Environmental review: Reducing room temperature and increases humidity.
- Instillation aids for eye drops.
- Caution the patients who have refractive surgeries**.**

2} Systemic medication review

3} Artificial tear substitutes including gels and ointments

4} Eyelid therapy

Level 2

- Non-preserved tear subsitutes
- Anti-inflammatory agents
- Tetracyclins
- Punctual plugs
- Secretagogus
- Moistures chamber spectacles and spectacles side shields

Level 3

- serum eye drop
- Contact lenses
- Permant punctual plugs

Level 4

- systemic anti-inflammatory agents
- Surgery: Eyelid surgery such as tarsorrhaphy, salivary gland auto-transplantation, mucus membrane and amniotic membrane transplantation for corneal complications.

Medical Managment

1) Autologous Serum Eye Drops: It is better tear substitute, contained a hepatocytes growth factor, epidermal growth factor, vitamin A, and fibronectin are effective in severe dry eye disease. Since, they are help for maintaining healthy ocular surface.[43] Artificial tear eye drops increases tear film stability, reduce ocular stress. A large number of preparations based on polyvinyl alcohol, hydroxypropyl guar, cellulose derivative are available. Depending upon severity of disease, drops, gel & ointment can be used.

2) Non-steroidal anti-inflammatory drugs and antibiotics: NSAID drops reduce the inflammation associated with dry eye disease.

3) Corticosteroids: Topical corticosteroid is an effective anti-inflammatory drug such as loteprednol etabonate, dexamethasone are found to be effective in inflammatory conditions associated with KCS. They are generally used for short time period to quickly manage symptoms.[44]

4) Cyclosporin: Immunomodulatory drugs with anti-inflammatory effects such as cyclosporine eye drops have been shown to reduce symptoms and corneal surface damage.[45] Tacrolimus eye drops are a viable alternative for patients who are unable to use cyclosporine. Topical application of it leads to increased production of tears, possibly via local release of parasympathetic neurotransmitter.[46] It reduces T-cells mediated inflammation of lachrymal tissue, result in increasing numbers of globet cells and reversal of squamous metaplasia of conjunctiva.

5) Tetracyclines: It used to treat meibomian gland dysfunction and rosacea, which is one of cause for DED.

6) Punctal plug: It is tiny, biocompatible device that can be inserted into tear ducts of an eye to prevent the nasolachrymal drainage of tears. It's usually used in patient with moderate to severe aqueous deficient dry eye disease. This increase the eyes tear film and surface moisture to help relive certain forms of dry eye, Also known as lachrymal plugs or occulders.[47]

7) Vitamin A: Vitamin A is an important in production of mucin layer, that essential for healthy tear film. Deficiency of vitamin A leads to loss of mucin layer and goblet cell atropy. Vitamin A eye drops protect eyes from allergens, inflammation, free radicals, toxins etc. Topical retinoic acid therapy in conjunction with systemic administration of vitamin A has been investigated to treat xerophthalmia.

8) Omega-3 fatty acids: These acids especially work by blocking pro-inflammatory eicosanoids and reducing cytokines through anti-inflammatory actions. The fatty acids enhanced tear film stability & reducing tear evaporation, DES symptoms. Dietary intake of n-3 fatty acid help to relieve DED.[48]

9) Eyelid hygiene: As evaporative DED can occur in patients with meibomian gland dysfunction. Since, It is basis of successful treatment of meibomian gland dysfunction.

10) Surgical management: Surgical technique using graft of minor salivary gland to provide a substitute for tears. In this technique minor salivary gland are autotransplanted into the conjunctival fornix, leads to drainage of saliva goes to conjunctival fornix and causes corneal lubrication.[49]

CONCLUSION

Diagnosis & Management of DED is very complicated because of its multifactorial etiology. Since, for early diagnosis and treatment we should clearly know about its etiological factors, signs, symptoms diagnostic test etc. Recent knowledge about causes, signs, symptoms, diagnostic test and treatment of DED help us for its diagnosis & treatment. Questionnaires can help to detect cause of DED from patient's daily activities. This knowledge is essential to know the depth of the problem in terms of healthcare cost, create awareness in public era.

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