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Dry Eye Disease- Current Perspective

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Introduction

The preocular tear film is three layered consisting of mucous layer (posterior most), aqueous layer and lipid layer (anterior most). Any abnormality or dysfunction in tear film results in dry eyes, more appropriately called as dry eye disease or dysfunctional tear syndrome (DTS).[1] Prevalence of DTS in general population is highly variable across the world ranging from 10.8% to 57.1% [2-8] and is among the most prevalent ocular disorders responsible for visits to ophthalmologists.

Historical perspective and landmark studies

Prior to 1995, there was no consensus on definition, diagnosis or management of dry eye disease. A consensus on definition was developed at a workshop at National eye institute (NEI) in 1995, where Dry eye disease (DED) was defined as a "disorder of the tear film due to reduced tear production or excessive tear evaporation, which causes damage to the inter-palpebral ocular surface and is associated with symptoms of ocular discomfort and/ or visual symptoms."

In 2006, a panel of dry eye experts from across the globe, used the Delphi approach to establish diagnosis and treatment guidelines for dry eye.[1] Four levels of disease severity were outlined as well as recommendations were given for managing patients with lid margin disease and abnormal tear distribution. These guidelines primarily focused on patient signs and symptoms and were accompanied by the suggestion that the terminology 'dysfunctional tear syndrome' could replace the term 'dry eye disease'.

In 2007, the Dry Eye Workshop (DEWS) added to the criteria and made additional treatment recommendations.[9] They redefined 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, accompanied by increased osmolarity of the tear film and inflammation of the ocular surface." The key additions to previous definition were the inclusion of symptoms of visual disturbance, osmolarity and inflammation.

In 2011, an international subcommittee elaborated in detail about various aspects of meibomian gland dysfunction.[10]

Risk factors

Various risk factors identified for development of dry eye disease include old age, female gender, smoking, environmental factors such as air conditioning, heaters, low humidity, systemic medications like antihistamines, beta blockers, anticholinergics, antidepressants, systemic retinoids, diuretics and hormone replacement therapy, systemic diseases like Sjogren syndrome, ocular cicatricial pemphigoid (OCP), Stevens-Johnson syndrome (SJS), sarcoidosis, lymphomas, rheumatoid arthritis, graft vs host disease (GVHD), recipients of allogenic bone marrow or stem cell transplants (BMT).[11-18] Ocular conditions like eyelid malposition, lagophthalmos, Bell's palsy, chemical injuries and blepharitis etc can also lead to development of dry eye disease.

Air pollution, especially in Indian metropolitan cities, is also associated with increase in the incidence of dry eye disease in the exposed population. Gupta et al, studied the effect of exposure to high level of air pollution on ocular surface health and found that people travelling in highly polluted areas and exposed to high level of air pollutants are likely to suffer from significantly high incidence of subclinical ocular surface disorders.[19]

Uchino et al, studied the association of dry eye disease among visual display terminal (VDT) users like computers, laptops, tablets and large screen mobile phones among Japanese population and reported high incidence of dry eye disease. They emphasized the need to improve the awareness among VDT users to decrease adverse effect on ocular surface.[20]

Clinical presentation and Types

The suggested clinical categories for DTS are shown in (Fig 1) and include

- DTS with lid margin disease
- DTS without lid margin disease
- DTS with altered tear distribution and clearance

The patients who do not have coexistent lid margin disease, is the most common form of presentation of DTS. Within each of these 3 categories, the panel listed the main subsets or specific disease entities or, in the case of DTS without lid margin disease, the patients were divided by severity level as shown in (Table 1).

Assessment of DTS severity is important in guiding appropriate therapy, especially in the subset of DTS patients without lid margin disease. The level of severity should be based primarily on symptoms and clinical signs and the diagnostic tests are secondary considerations in determining disease severity. Depending on the frequency and impact on the quality of life of these elements, symptoms could be categorized as either mild to moderate or severe. Dry eye severity grading is shown in table-2.

Diagnosis

Diagnostic scheme adapted from DEWS (2007) is shown in fig 2. Common tests for dry eye disease include:

Tear film break up time

This test determines the stability of the precorneal tear film and is performed by instilling fluorescein dye in the inferior

cul-de-sac and then determining the stability of the precorneal tear film. Any value less than 10 sec is abnormal. It is beneficial in both aqueous deficient and evaporative dry eye disease.

Schirmer's test
It is used to assess aqueous tear production. Although the results may be variable and should not be used as a sole criterion for diagnosing dry eye disease. Values less than 10 mm over a period of five minutes is considered as abnormal.

Tear osmolarity test
Sensitivity and specificity of this test is low and has poor correlation with symptoms of dry eye disease. Tear osmolarity of > 305mOsms/L is taken as a cut off value for diagnosing dry eye although at a cut off value of > 312mOsms/L, sensitivity and specificity of the test increases significantly. Further studies are required to validate this test to make it more relevant in diagnosis of dry eye disease.

Vital dye staining
Fluorescein, rose bengal or lissamine green vital dyes can be used to stain and assess the ocular surface. Fluorescein dye stains corneal and conjunctival areas with disrupted intercellular junctions which allow the dye to permeate in to tissues. Exposure zone punctate or blotchy stain pattern is observed in dry eye disease which is more apparent over cornea.

Newer biomarkers
Individuals with dry eye disease have been found to have lower protein contents and higher levels of inflammatory biomarkers such as matrix metalloproteinase-9 (MMP-9) in their tears. Tests such as InflammaDry Detector (Rapid Pathogen Screening Inc, Sarasota, FL, USA) can detect MMP-9 levels in the tears and may help in early diagnosis of dry eye disease. It has been found to be 85%sensitive and 94% specific in diagnosing dry eye disease.[21] TearScan MicroAssay System (Advanced Tear Diagnostics, Birmingham, AL, USA) assesses allergy biomarkers like lactoferrin and immunoglobulin E in the tear film and is helpful in evaluating dry eye disease associated with ocular allergy.[22] A new laboratory test known as Sjö (Nicox, Sophia Antipolis, France) evaluates salivary gland protein 1, parotid secretory protein, and carbonic anhydrase- 6 in tears in patients with Sjogren syndrome and has been found to be helpful in early diagnosis as these autoantibodies are seen earlier in the course of the disease than antibodies to Ro or La.[23]

Various tests suggested for diagnosis of systemic diseases associated with dry eye disease are shown in Table 3.

Management
The aims for treating dry eye disease include:

- Reducing or alleviating signs and symptoms of dry eye
- Maintaining and improving visual function
- Reducing or preventing structural damage

Treatment recommendations according to severity of dry eye disease are shown in table-4 and various tear substitutes available are shown in table-5.

Secretagogues are also being increasingly used in management of dry eye. Mucin secretagogue such as rebamipide 2% suspension, which is a derivative of quinolone-class antibiotics, has been found to be superior to placebo at improving objective measures of dry eye, including fluorescein corneal staining score (FCS) and lissamine green conjunctival staining (LGCS). Subjectively, patients reported significantly more relief from photophobia, dryness, foreign body sensations, pain, and blurred vision.

Cosmetics may contain various ingredients like nickel, colophane, cobalt, paraben and animal products which may lead to severe intolerance in patients with dry eye disease. Use of hypoallergenic products, which are free of these ingredients, may enhance tolerance of cosmetics, mascara and eyeliners etc in patients with dry eye disease.

Conclusion
The most important aspects of caring for patients with dry eye are to educate them about the chronic nature of the disease process and to provide specific instructions for therapeutic regimens. Environmental and dietary modifications can be very helpful for symptomatic improvement. Patients with dry eyes should be advised to avoid low humidity, high temperature environment, windy conditions, excessive use of heaters and air-conditioning. Frequent breaks should be taken while watching television or working on computer screens for long duration. Dietary modifications like proper hydration and increased intake of food containing vitamin A, omega-3 fatty acids and essential fatty acids like linoleic and linolenic acids may be helpful. Any systemic disease associated with dry eye diseased should be appropriately managed by concerned physician. It is helpful to reassess periodically the patient's compliance and understanding of the disease, the risks for associated structural changes and to re-inform the patient as necessary. The patient and ophthalmologist together can establish realistic expectations for effective management.

Legends
Figures
Figure-1 Clinical categories of dysfunctional tear syndrome (DTS)

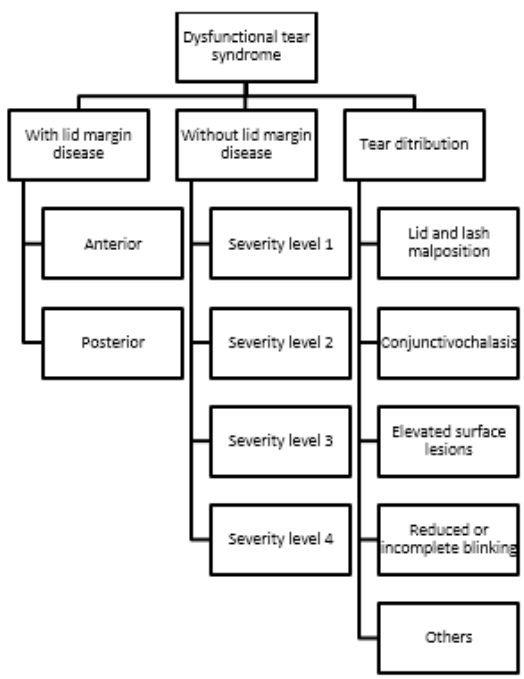
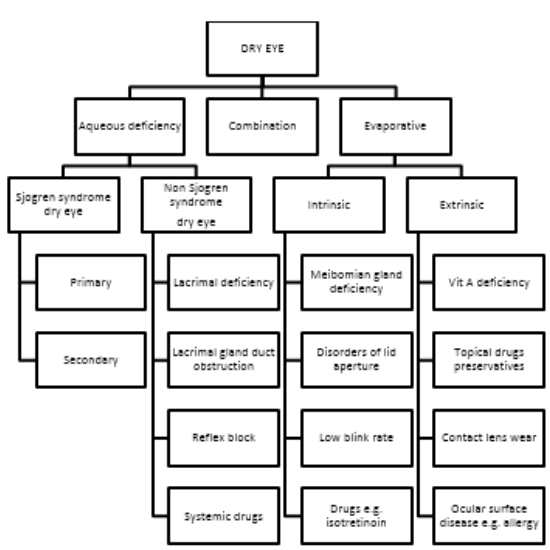


Figure-2: Diagnostic scheme adapted from DEWS (2007)



Tables

Table-1 Levels of severity of DTS without lid margin disease

Level 1	Mild to moderate symptoms and no signs Mild to moderate conjunctival signs
Level 2	Moderate to severe symptoms Tear film signs Mild corneal punctate staining Conjunctival staining Visual signs
Level 3	Severe symptoms Marked corneal punctate staining Central corneal staining Filamentary keratitis
Level 4	Severe symptoms Severe corneal staining, erosions Conjunctival scarring

Table-2 Dry eye severity grading system (DEWS)

Dry Eye Severity Level	1	2	3	4*
Discomfort, severity and frequency	Mild and/or episodic; occurs under environmental stress	Moderate episodic or chronic 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 (Severity/ Location)	None to mild	Variable	Marked Central	Severe punctate erosions
Corneal/ tear signs	None to mild	Mild debris, reduced meniscus height	Filamentary keratitis, mucus, clumping, increased tear debris, ulceration	
Lid/meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinization, symblepharon
TFBUT	Variable	< 10 seconds	< 5 seconds	immediate
Schirmer's score (per five min.)	Variable	< 10mm	< 5mm	< 2 mm

TFBUT = Fluorescein Tear break-up time; MGD = Meibomian gland disease

* Must have Signs and Symptoms

Reproduced from the article "The definition and classification of dry eye disease: report of the Definition and classification Subcommittee of the International Dry Eye Workshop (2007). ***Ocul Surf*** 2007;5:88."

Table-3 Various tests suggested for diagnosis of systemic diseases associated with dry eye disease

Disease	Tests
Sjogren syndrome	SSA, SSB, ANA, RF
Thyroid eye disease	Anti-thyroid peroxidise antibody, Anti-thyroglobulin antibody, B scan to assess extraocular muscle thickness
Sarcoidosis	Serum lysozyme, ACE, Conjunctival biopsy, CT chest
OCP	Conjunctival biopsy with light microscopic and immunofluorescent or immunohistochemical studies

SSA- Sjogren syndrome A, SSB- Sjogren syndrome B, ANA- Anti nuclear antibody, RF- Rheumatoid factor, ACE- Angiotensin converting enzyme, OCP- ocular cicatricial pemphigoid

Table-4 Treatment recommendations according to severity of dry eye disease

Severity	Treatment recommendation
Level 1	Environmental management Preserved tears Use of hypoallergenic products Avoidance of drugs contributing to dry eye Water intake Psychological support Anti allergic drops
Level 2	Unpreserved tears Secretagogues Gels Topical steroids Ointments Topical cyclosporine A Nutritional support (flaxseed/fatty acids)
Level 3	Any of the above modality plus tetracycline
Level 4	Punctal plugs Surgery Punctal cautery Systemic anti-inflammatory Acetylcysteine therapy Contact lenses Oral cyclosporine Moisture goggles

Table-5 Commonly used tear substitutes

Composition	Properties	Advantages	Disadvantages
Cellulose esters (eg HPMC 1%, 2%, methylcellulose, CMC 0.5%, 1%,) -Refresh liquigel (Allergan) CMC 1% -Optive (Allergan) CMC 0.5% -Refresh tears (Allergan) CMC 0.5% -Genteal (Novartis) HPMC 0.3% -Extra lube (Microlabs) CMC 0.5% -Soft drops (Ajanta) CMC 0.5% with glycerine -Flogel (Cipla) CMC 1% -Lacrigel (Sunways) HPMC 2% -Eyemist (Sun) HPMC 0.3% -Veldrop (Alembic) CMC 0.5%	Viscoelastic polysaccharides Increase viscosity of tears	Useful in aqueous tear deficiency Good retention time Mix well with other ophthalmic products Viscosity not influenced by blinking	HPMC can cause crusting of lids mimicking blepharitis

Sodium hyaluronate 0.1%, 0.15%, 0.2%, 0.4% etc. -Hyla (Entod) Sod hyaluronate 0.1% -Hyvet (Sunways) Sod hyaluronate 0.18% -Optive fusion (Allergan) CMC 0.5% with sod hyaluronate -Eubri (Pfizer) Sod hyaluronate 0.1%	Mucopolysaccharides Viscous formulations	Good retention time Beneficial in corneal wound healing	
Acetylcysteine 5%	Mucolytic agent, Breaks down mucin molecules Can be coformulated with other lubricant such as Hypermellose	Useful in severe dry eyes with dense mucin and plaques	
Polyvinylpyrrolidone (Povidone) 0.6% -Aqua tears (Cipla) Povidone 0.6%, polyvinyl alcohol 1.4% - I Lube (FDC) Polyvinyl alcohol 1.4%, Povidone 0.6% - Tears plus (Allergan) Povidone 0.6%, polyvinyl alcohol 1.4%	Synthetic polymer Coformulated with electrolytes Superior wetting ability when coformulated with polyvinyl alcohol	Beneficial in mucus layer deficiency	
Polyvinyl alcohol -Tears plus (Allergan) Polyvinyl alcohol 1.4% -Dudrop (Sun) Polyvinyl alcohol 1.4% -I Lube (FDC) Polyvinyl alcohol 1.4% -Moss (Syntho pharma) Polyvinyl alcohol 1.4%	Synthetic polymer Low viscosity but optimal wetting characteristics in conc of 1.4%	Beneficial in aqueous, lipid and mucus layer deficiencies Water soluble, doesn't cause blurring of vision	Short retention time Doesn't mix well with other ophthalmic products
Polyethylene glycol 400 -Systane (Alcon) - Polyethylene Glycol 400 (0.4%); Propylene glycol -Foug (Pharmatak) polyethylene glycol 400 0.4% + propylene glycol -Normotears (Sun) polyethylene glycol 400 0.4% + propylene glycol	PEG 400 is low molecular weight grade of polyethylene glycol	Strongly hydrophilic, low toxicity	
Lipids (e g Petrolatum (Vaseline, paraffin, mineral oil), lanolin, lecithin) -Adlube (Cipla) liquid paraffin 42.5 % w/v -Lubrilac (Sunways) Paraffin 80% w/v	Organic substances Formulated as drops and ointment	High viscosity High retention Re build lipid layer Useful adjunct to other artificial tears when used at night	Cause blurring of vision
Carbomers (Polyacrylic acid) Viscotears (Novartis) 0.2% Carbomer ophthalmic solution Clinitas gel 0.2% Carbomer ophthalmic gel	Synthetic polymers High viscosity while eye is static but thins due to shearing during blinking or eye movement	Good retention time	Blurring of vision
Preservatives			
Benzalkonium chloride		Chemically stable, doesn't degrade even at high temperatures Increase corneal penetration of some drugs	Can accumulate in ocular tissues causing cell death with frequent dosing Frequency shouldn't be more than 4-6 times per day
Sorbate		Useful for sensitive eyes and contact lens wearers	May cause punctate keratitis
Sodium perborate	Changes to oxygen and water on contact with tear film		Even low conc. Can cause ocular stinging
Stabilized oxychloro complex (Purite)	Oxidative preservative that is converted into tear components	Safe Well tolerated	Least cytotoxic effects

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