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**DRY EYE DISEASES – A REVIEW OF CURRENT AND EMERGING TREATMENT
MODALITIES**

DRY EYE DISEASES – A REVIEW OF CURRENT AND EMERGING TREATMENT MODALITIES

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ABSTRACT

Introduction

Dry eye disease (DED), also known as dry eye syndrome (DES), and keratoconjunctivitis sicca (KCS), is a common multifactorial disease of the ocular surface and its associated tear film production. The condition may cause ocular discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. This often results in discomfort to the patient. This article reviews DED with respect to aetiology, presentations and current management as well as new trends in the diagnosis and management of this common disorder.

Methods

This review used extensive literature search of existing body of knowledge and current research findings as presented at conferences and workshops. We have explored the current thinking and trends in this common ocular disorder outlining its causes, presentation and management. What the future portends in the area of research and innovative management strategies is also discussed.

Results

The review showed that early detection of this disorder can be achieved by a high index of suspicion, appropriate history taking and

correct investigations. It is most often managed using benzalkonium chloride (BAK-rich) tear substitutes even though preservative-free eye medications are preferred where available and affordable.

Conclusion

Like other health challenges in our clime, late presentation is not uncommon. Penetrating keratoplasty for non-regressing superficial and deep corneal vascularization may be necessary.

Keywords: Dry eye; Tears; Sicca; Limbal Stem Graft

INTRODUCTION

Dry eye disease (DED), also known as dry eye syndrome (DES), and keratoconjunctivitis sicca (KCS), is a common multifactorial disease of the ocular surface and its associated tear production. The condition may cause ocular discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface.¹

The ocular surface is a complex, integrated system involving the cornea, conjunctiva, tear film, lacrimal gland, nasolacrimal system and the eyelids (incorporating the meibomian glands and lashes). It is also

known as the ecosystem of the outer eye with the normal physiological function of the ocular surface depending on the interaction of these different components.²

Working together, this integrated system maintains a clear optical surface, keeping the eye from drying out, and protecting it from trauma and infection. Any change in the structure and function of any of the ocular surface components can disrupt its delicate balance and lead to pathology (Dry Eye Disease).

The eyelids are an important component of ocular surface ecosystem with both upper and lower eyelids having two lamellae separated by the gray line (Marx's line) with the anterior lamella made up of skin and muscle (orbicularis oculi); and posterior lamella comprising of tarsus and conjunctiva.³ In the posterior lamella are important glands necessary for maintenance of tear production: vertically oriented sebaceous glands (Meibomian glands) about 30 to 40 superiorly and 20 to 30 inferiorly embedded in the tarsal plates with mucus secreting Goblet cells in the conjunctiva. There are also accessory lacrimal glands which comprise of glands of Wolfring located along the antimarginal border of the tarsal plate; and glands of Krause found in the conjunctival fornices.³

Layers of Tear film, Secretion and production

The tear film is a highly specialized and well-organized moist film that covers the conjunctiva (bulbar and palpebral) and the cornea. It is an important part of the first refracting surface of the eye and is the interface between the eye and the atmosphere. It is divided into four main parts namely the marginal tear strips along the moist portions of the eyelid that lie posterior to the lipid strip secreted by the tarsal glands; the tear film that covers the palpebral conjunctiva; the film of tears that overlies the bulbar conjunctiva and the precorneal tear film, with the first three constituting the precorneal tear film.⁴

The tear film is a trilaminar structure with inner layer of mucin secreted by the conjunctival goblet and epithelial cells (20 to 40 μm in thickness); intermediate aqueous layer (6 to 8 μm in thickness) containing mucin in two discrete phases, water, electrolytes and proteins; and surface or outermost layer made up of lipid derived from the marginal tear strips and secreted by the tarsal glands with varying thickness of as thin as a monolayer and at other times being as thick as 9.5 μm .⁴

Tear is produced by the main and accessory lacrimal glands with contributions from conjunctiva goblet cells and tarsal glands.⁵ The total volume of tears present during basal conditions range from 7 to 9 μL or between one and two drops. The maximum quantity that can be retained without overflowing is generally about 30 μL in humans up to about the age of 19 years; thereafter the volume decreases gradually to about 4 to 5 μL by age 70.

The tear then travels across the surface of the globe and eyelids, enters the puncta/ampulla, passes through the canaliculi, and enters the lacrimal sac/nasolacrimal duct/nasal passages while some are evaporated from the ocular surface. The flow rate is 1 $\mu\text{L}/\text{minute}$, and the turnover rate is 0.1- 0.15 $\mu\text{L}/\text{minute}$ in basal condition with all these parameters i.e volume, flow rate, turnover increasing in reflex tear production.⁵

Epidemiology of DED

Dry Eye Disease usually affects the adult population. However, it may start from adolescents with increasing incidence & prevalence occurring with aging. This arises from decreasing tear production and increasing ocular surface exposure. Both sexes are affected but it is usually more in females. There is no known social or geographical preponderance.^{6, 7, 8}

In epidemiological studies performed globally, the prevalence of dry eye disease (DED) ranges from 5 to 50 percent and based on data from the National Health and Wellness Survey in the US, about 6.8 percent of the United States adult population

(approximately 16.4 million people) have been diagnosed with DED; the prevalence increased with age (2.7 percent in those 18 to 34 years old versus 18.6 percent in those ≥ 75 years old); and was higher in women than men (8.8 versus 4.5 percent). Prevalence was not affected by education or location of residence.⁸

Reliable epidemiological studies from the large Women's Health Study and Physician's Health Study indicate that the prevalence of symptomatic dry eye in the United States is about 7% in women and 4% in men over the age of 50 years.^{7, 8} In Nigeria, from studies carried out by Onwubiko in the east; Fasina *et al* in the South-west; Nkiru in the South-east; Onua in the Niger Delta and Olaniyan *et al* in the South-west; the prevalence of dry eye disease was found to be between 19.2% and 32.5% in Nigerian adult population and is significantly associated with increasing age.⁹⁻¹³ In Ghana, the prevalence of symptomatic dry eye among Ghanaian undergraduate students was found to be 44.3%.¹⁴

Classification, Pathophysiology and Diagnosis of dry eye disease

There are two main types of DED, one associated with Sjogren's syndrome (SS) and the other not associated with Sjogren's syndrome.^{5, 6} Dry eye disease can also be divided into aqueous tear deficiency dry eye and evaporative dry eye.⁵ Patients with aqueous tear deficiency (ATD) have SS if they have associated xerostomia or connective tissue disease (CTD) with patients with primary SS having evidence of a systemic autoimmune disease, as manifested by the presence of serum autoantibodies and severe ATD and ocular surface disease. Secondary SS is defined as dry eye disease that is associated with a diagnosable CTD, which is most commonly rheumatoid arthritis (RA) but could also be systemic lupus erythematosus (SLE) or systemic sclerosis. Non-SS dry eye disease is mostly found in postmenopausal women, women who are pregnant, women who are on oral contraceptive pills or women who are

on hormone replacement therapy (especially estrogen-only pills). It is also known that Meibomian gland dysfunction is a key component of dry eye disease.^{5, 6}

The International Dry Eye Work-Shop (DEWS) has developed a 3-part classification of dry eye based on aetiology, mechanisms, and disease stage.⁶

Aetiological classification

1. **Evaporative loss** due to meibomian gland dysfunction, disorders of lid aperture, low blink rate, drug action (eg, isotretinoin), Vitamin A deficiency, topical drugs and preservatives, contact lens wear and ocular surface disease (e.g., allergy).
2. **Limbic stem cell disease (LSCD)** from destruction or dysfunction of the stem cell containing limbal epithelium, leading to failure of corneal epithelial regeneration, with resultant re-epithelialization by the conjunctival epithelial cells, accompanied by chronic inflammation, stromal scarring, neovascularization, and persistent epithelial defects.
3. **Aqueous tear deficiency (ATD)** results from insufficient tear production like Non-Sjogren's syndrome with primary lacrimal gland dysfunction; secondary lacrimal gland disease like lacrimal gland infiltration; systemic vitamin A deficiency (xerophthalmia); lacrimal gland ablation and lacrimal gland denervation; lacrimal obstructive diseases; medications that may impair aqueous production; and conditions that may lead to reflex hyposecretion like neurotrophic keratitis.
4. **Sjogren's syndrome** which could be primary (ATD) with no associated CTD or secondary which may be associated with any of the connective tissue diseases.

Classification by Mechanisms

Classification on the basis of mechanisms is into two classes based on tear hyperosmolarity and tear-film instability.

Classification by Severity

This is usually based on Delphi panel report using a Delphi panel severity table.^{6,7}

Pathophysiology of DED

A lot of factors have been implicated in the pathophysiology of DED. Latest findings however tends to emphasize among others the following mechanisms:

1. SS-associated dry eye (primary or secondary SS). A chronic inflammatory state, with production of autoantibodies, leading to focal lymphocytic infiltration of the lacrimal and salivary gland, with degeneration and induction of apoptosis in the conjunctiva and lacrimal glands. These results in inflammation and dysfunction of the lacrimal gland with reduced tear production.
2. Sex hormone deficiency from decrease in androgens or increased levels of the sex hormone-binding globulin in menopause may affect gland function.
3. Meibomian gland dysfunction resulting in increased evaporative loss and debris formation.
4. Pro-inflammatory activity from inflammatory cytokines is known to be altered in dry eyes & cause cellular damage.
5. Neurotransmitter & nerve growth factor release is also known to activate lymphocyte with tissue damage.
6. Mucin deficiency arising from genetic predisposition, goblet cell damage by cicatricial pemphigoid, Stevens-Johnson syndrome, and vitamin A deficiency often leads to poor wetting and desiccation of cornea.
7. Reduced tear protein production resulting in decreased levels of

lysozyme, lactoferrin, lipocalin, and phospholipase A2 have been implicated in dry eye. Normally this lowers the surface tension of normal tears, and thus provides stability to the tear film.

Diagnosis of dry eye disease

Diagnosis of DED is essentially clinical, by a combination of history, and examination findings together with one or more diagnostic tests. High index of suspicion goes a long way in facilitating early diagnosis.

A detailed history to elucidate the symptomatology of DED is very essential. The symptoms include foreign-body sensation, grittiness, redness, mucoid discharge, ocular irritation, ocular dryness, excessive tearing (secondary to reflex secretion), photophobia, and itching, fluctuating or blurry vision. History of drug use like antihistamines, beta blockers, anti-glaucoma agents and others; is also essential.^{4,5,15}

These symptoms are quantified objectively in the Ocular Surface Disease Index (OSDI) questionnaire with 12 symptoms each graded on a scale of 1-4 and they tend to be worse towards the end of the day, with prolonged use of the eyes, or with exposure to extreme environmental conditions.¹⁵ Other symptom questionnaires in use include SPEED (System for Patient Evaluation of Eye Dryness), VAS (Visual Analog Scale), McMonnies Questionnaire, and SANDE (Symptom Assessment in Dry Eye).^{2,4}

Available diagnostic tests include vital staining of corneal and conjunctival epithelium with fluorescein, Lissamine green, or rose Bengal; Tear film osmolarity; Ocular surface matrix metalloproteinase 9 (MMP-9); Measurement of tear breakup time (TBUT); The Schirmer test; Tear meniscus height; Quantification of tear components through analysis of tear proteins; Tear meniscometry; Impression cytology to monitor progression of ocular surface changes; Meibography; and tear film interferometry.^{2,4}

Additional tests for research purpose include the tear stability analysis system (TSAS), the tear function index (TFI; Liverpool modification), and the tear ferning test (TFT).

The criteria for a diagnosis of dry eye disease associated with Sjögren syndrome (SS) include the following among others: abnormally low Schirmer test result; objective evidence of low salivary flow; biopsy-proven lymphocytic infiltration of the labial salivary glands and dysfunction of the immune system, as manifested by the presence of serum autoantibodies (eg, antinuclear antibody [ANA], rheumatoid factor [RF], and anti-Ro [SS-A] and anti-La [SSB] antibodies).^{2,4,5}

Differential diagnosis of DED

Differentials of Dry Eye Disease include the following: Adult Blepharitis, Allergic Conjunctivitis, Atopic & vernal keratoconjunctivitis, Bell's Palsy, contact lens complications, Floppy Eyelid Syndrome and Neurotrophic Keratitis. Other differential diagnoses are ocular manifestations of HIV Infection, Ocular Rosacea, Superior Limbic Keratoconjunctivitis (SLK), thyroid ophthalmopathy, topical preservative sensitivity and toxic keratopathy among others.

New Trends in Investigation and Management of DED

Newer investigative procedures have been designed to aid the diagnosis and management of DED. These include among others anterior segment imaging techniques including anterior segment FD-OCT; In vivo confocal microscopy; and Scheimpflug corneal imaging for detailed imaging of the anterior segment of the eye and OCT quantification of palisades of Vogts. These are newer techniques that can aid in the diagnosis of not only DED but are also useful in other anterior segment pathologies.^{5,15,16}

Confirmatory test beyond clinical diagnosis may include Impression Cytology, staining for goblet cells (PAS) and monoclonal

antibodies to cytokeratin CK3 & CK19 (conjunctival phenotype) CK7/13 and Mucin MUC1/5AC for detailed analysis of tear film and lipids.¹⁵

LSCD triad of signs are conjunctivalization, neovascularization and decrease in vision; and unstable tear film, surface epithelial changes (defective wound healing, surface instability and destruction) and vision changes (irregular refraction and profound visual loss).^{17,18,19}

New trends in medical therapy

Hitherto, medical therapy for dry eye disease employs the use of topical medications in the form of tear substitutes. Preservative-free topical medications are preferred where available but in most cases due to its scarcity, BAK-rich tear substitutes are used especially in mild to moderate disease. However, newer trends in these aspects include the use of topical NSAIDs, cyclosporine A, mast cell stabilizer, antihistamine agents, and corticosteroids. Topical Vitamin A - formulations, autologous serum, and vascular endothelial growth factor (VEGF) inhibitors have also been tried and portend better prospects and outcomes.⁵

Oral omega-3 fatty acid supplementation has also been found useful. Other clinic procedures which have also been found helpful depending on the aetiology include Meibomian gland probing and intense pulse light therapy as well as devices like LipiFlow®, punctal plugs, bandage contact lens and scleral lenses.^{20,21}

Surgical management

One of the newest approaches to the management of DED that is gaining ground now is surgical intervention which is often employed when there are difficult cases with severe underlying pathology responsible for the DED. Any surgical procedure employed is often dependent on the pathology involved. Examples of what has been tried and found useful in some specific cases include the use of a free conjunctival graft for correction of pterygium, pseudopterygium, and symblepharon; limbal stem cell transplant techniques in ocular

surface chemical burns as describe by Jose Barraquer and use of amniotic membrane for the repair of conjunctival defects and symblepharon.^{20,21,22}

Another novel approach is Amniotic Membrane Transplantation (AMT) using the Innermost layer of placenta with its biological properties such as its transparency, thick basement membrane, avascular stromal matrix, potential to promote epithelialization and epithelial differentiation. Prevention of apoptosis, scarring & inflammation; non-immunogenicity and structural similarity to ocular surface have been attributed to successful amniotic membrane transplantation surgeries.²² These characteristics are also responsible for AMT reducing corneal conjunctivalization in eyes with focal limbal deficiency while promoting adjacent healthy epithelium to repopulate and cover the AM, thereby restoring ocular surface integrity and milieu health.²²

Ocular surface reconstruction procedures require certain prerequisites before such are undertaking. These will include concomitant lid pathology control; dry eye disease severity containment; systemic comorbidity management and excellent lids hygiene.²³ Specific grafts may be in the form of autograft from same patient with focal / limited LSCD usually taken from the contralateral eye or allograft taken from living relatives or cadaveric (within 10 hours) patients.

Limbal Stem Cell Transplantation however requires algorithmic approach as outlined in the following steps:

1. Source - This refers to the source of the limbal stem cells which may be cadaveric or fresh; and oral mucosa or conjunctival epithelial cells.
2. Scaffolds - This is the substrate for cultivation of limbal epithelial cells. It should be transparent with appropriate refractive index; has corneal like dimensions; be tough and malleable for surgical manipulation and be good enough for implantation. It should also be free from toxins; be non-immunogenic and non-

inflammatory; and most importantly, promotes successful corneal tissue regeneration.

Examples include Human amniotic membrane; fibrin gels; anterior lens capsule; corneal or limbal stroma; therapeutic contact lens; tissue engineered substrates; collagen scaffolds; temperature-responsive gels like Myogels; Chitin (Glycosaminoglycans {GAG}) and others like laminin, fibronectin and collagen IV.

3. Media - This includes growth factors, cytokines, salts, amino acid, electrolytes, hormones and carbohydrates maintained at a specific pH and temperature with or without serum supplements.
4. Cultivation technique
5. Characterization like clonal assays, morphology, immune-phenotyping, gene expression profiles and proteomics.
6. Quality control involves screening for any contaminations – bacterial, fungal, viral, mycoplasma, toxoplasma and microbial byproducts like bacterial endotoxins, fungal mycotoxins & aflatoxins (using ELISA, RIA, PCR, direct staining techniques).

The final product of all the above steps results in the ultimate stem cells with the biological attributes of viability; ability to migrate, divide, and differentiate and be infection- and toxin-free. It must also meet the regulatory bodies' cell-therapy standards (USFDA & ICMR). Oral epithelial cells transplanted on to corneal surface tend to adapt to the ocular phenotype better.

CONCLUSION

DED is a form of ocular surface disease, with an overlap existing between DED and other OSDs. It is very common and often under-diagnosed with most patients having mild-to-moderate disease. Early detection can be achieved by a high index of suspicion,

appropriate history taking and correct investigations. Preservative-free medications are preferred in the management of DED but due to non-availability and poor affordability, the condition is most often managed using BAK-rich tear substitutes. Sight, surgical outcomes and, ultimately, patient satisfaction critically depends on the health of the ocular surface. Like other health challenges in our clime, late presentation is not uncommon. Penetrating keratoplasty for non-regressing superficial and deep corneal vascularization may be necessary.

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