



OSI

Ocular Surface Insight

Issue 21

**Dry Eye
and Menopause**

**The Toyos
Dry Eye Diet**

**A Review of Intense Pulsed Light
in the Treatment of Ocular Rosacea**

DAYBREAK
MEDICAL

• ILLUMINATE •

TREAT THE ROOT
CAUSES OF DRY EYE

1

M.G.D
Meibomian Gland Dysfunction



2

INFLAMMATION
Rosacea and blepharitis



3

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Mahatma Gandhi

Welcome to the 21st issue of **OSI** Magazine!

Navigating the Complex Landscape of Dry Eye Disease

As we approach another year filled with groundbreaking research and clinical advancements, we are excited to announce the upcoming OSI Dry Eye Masterclass and Symposium, scheduled for March 27-28, 2025. This event will bring together leading experts to share insights and innovations in managing dry eye disease (DED) and related ocular surface conditions.

In this issue of the OSI magazine, we delve into several critical topics, reflecting the latest in both research and practical management strategies for DED. A review of Intense Pulsed Light (IPL) therapy for ocular rosacea offers a comprehensive look at its effectiveness and emerging role in treating this challenging condition. Dr. Rolando Toyos presents “The Toyota Dry Eye Diet,” a dietary approach that emphasises the importance of nutrition in managing dry eye symptoms.

Our feature articles also explore the intricate relationship between menopause and dry eye disease. With a focus on how hormonal changes impact the ocular surface, we examine the correlation between severe dry eye and menopause, with emerging data suggesting a complex

interplay between estrogen, androgens, and meibomian gland function. In light of these findings, we highlight lifestyle modifications, such as reducing screen time, incorporating Omega-3 fatty acids, and using optocosmetics, that can mitigate the severity of dry eye symptoms in postmenopausal women.

The ongoing debate surrounding hormone replacement therapy (HRT) and its effects on dry eye disease is also addressed. We present the latest research on the clinical effects of estrogen and progesterone, discussing both the potential benefits and risks of HRT. As we consider the divergent perspectives, the need for collaborative care between ophthalmologists and gynecologists becomes increasingly apparent, underscoring the importance of integrated approaches to patient care.

We hope you find this issue insightful and look forward to seeing you at the OSI Dry Eye Masterclass and Symposium next March, where we will continue to explore these important topics together.

Samer Hamada

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We stand with Ukraine!



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What's in the news?

Topical Tacrolimus in Anterior Segment Disorders in Ophthalmology: A Review

The purpose of this study is to emphasise topical tacrolimus's role in treating anterior segment diseases in ophthalmology. The present study analysed research papers and publications from international databases, including Pubmed, MedLine, Google Scholar, Cochrane Library, Embase, China National Knowledge Infrastructure (CNKI), and Scopus to highlight the significance and advantages of topical application of tacrolimus and its efficacy in treating allergic eye disorders, immune-mediated diseases, and other ocular surface disorders.

Tacrolimus and cyclosporine are the two most commonly used topical immunosuppressants in ophthalmology. Tacrolimus is a selective calcineurin inhibitor administered for the prevention and treatment of allograft rejection in solid organ transplant recipients and has a similar mechanism of action to cyclosporine. Management of immune-mediated inflammatory anterior segment requires intense immunosuppression and studies have shown that tacrolimus is ten to hundred times more effective than cyclosporine.



Abbreviations: IL-2 = interleukin-2, FDA = Food and Drug Administration Agency, GvHD = graft versus host disease, (Ig)E = immunoglobulin E, SAC = seasonal conjunctivitis, PAC = perennial allergic conjunctivitis, VKC = vernal keratoconjunctivitis, AKC = allergic keratoconjunctivitis, GPC = giant papillary conjunctivitis, PKC = phlyctenular keratoconjunctivitis, DED = dry eye disease, TBUT = tear break up time.

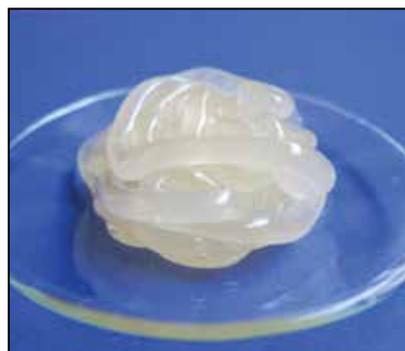
Author: Sultan Hornoud Alrashidi

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Scleral Lenses for Managing Dry Eye Disease in the Absence of Corneal Irregularities: What Is the Current Evidence?

Scleral lenses (SLs) are large-diameter rigid contact lenses that are a mainstay treatment for eyes with corneal irregularities. In recent years, there has been increased interest in the role of managing dry eye disease (DED) with SLs, as many patients with DED have reported symptomatic relief with SL wear.

The role of SLs for DED management when there are associated corneal irregularities is supported by individual case reports and studies. This has prompted practitioners to begin advocating using SLs in DED cases, even in the absence of associated corneal irregularities and other ocular surface diseases (OSDs). There have also been discussions on potentially placing SLs earlier in the treatment hierarchy of DED, where it currently sits



at a more advanced level of intervention (Step 3) in the TFOS DEWS II Report.

This review will present the currently available, albeit sparse, evidence that supports and suggests this practice, as well as ancillary evidence supporting the purported benefits of SL wear in DED. The advantages of SL wear,

such as corneal healing, absence of tear evaporation and contact lens dehydration, and improved visual acuity with associated increased wear comfort, and how this will benefit DED patients will be explored. Conversely, the challenges associated with fitting SLs in DED patients, including increased midday fogging, poor wettability, and subjective patient satisfaction, will also be presented, as well as a discussion on the key considerations for SL fitting in this population. Overall, while more research is needed to support the use of SLs in DED patients without associated corneal irregularities and other forms of OSD, the use of these lenses may prove to have a potentially wider role given their reported ancillary benefits in these populations.

Authors: Sharon X Qiu , Daddi Fadel , Alex Hui

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A Review of Intense Pulsed Light in the Treatment of Ocular Rosacea

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Introduction

Ocular rosacea is an underdiagnosed form of rosacea that may occur with or without typical cutaneous signs of rosacea. One of the common manifestations is dry eyes. Although the use of intense pulsed light (IPL) in the treatment of rosacea-related dry eyes has been reported, a recent review is lacking.

Methods

A scoping review was performed to summarize the efficacy of IPL in the treatment of ocular rosacea.

Results

Five articles were included, representing 108 patients, with a mean age of 58.4 years. Based on available data, 59.2% (n = 58/98) were female. The studies detailed the use of IPL in combination with meibomian gland expression treatment. Overall, 91% (n = 89/98) of patients with ocular rosacea treated with IPL had a partial response and 9% (n = 9/98) had no response. IPL therapy did not lead to complete recovery in any of the included patients. One participant experienced an adverse event across the included studies.

Conclusions

IPL is a promising treatment modality for ocular rosacea, as demonstrated by its ability to relieve dry eye symptoms with limited adverse events. Further research into this novel treatment is necessary to ascertain its role in the management of ocular rosacea.

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Introduction

Rosacea is a chronic, inflammatory skin condition characterized by flushing, erythema, papules, pustules, and telangiectasia.¹ The prevalence of rosacea has been estimated to be about 10% of the population, with a higher incidence in those with fair skin.² It is 3 times more common in women than men.² The pathogenic mechanism of rosacea is multifaceted, with factors such as genetics, as well as exposure to environmental triggers such as ultraviolet light, temperature changes, spicy foods, and stress all linked to its development.³

Ocular symptoms are present in an estimated 58% to 72% of rosacea patients.⁴ Ocular rosacea may occur with or without facial symptoms of rosacea, making it difficult to diagnose.^{2,5} Common clinical findings include conjunctival hyperemia, meibomian gland dysfunction, and corneal vascularization.⁴ Meibomian gland dysfunction manifests in the form of itching and dry eye sensations. Mild ocular rosacea primarily involves the eyelid margin and meibomian gland, moderate disease involves the ocular surface, and severe disease includes corneal involvement.⁴ When severe cases are left untreated, ocular rosacea may lead to poor irreversible outcomes, such as vision loss.⁴

Current guidelines for the treatment of ocular rosacea outline the use of 50 to 100 mg of doxycycline twice daily.⁶ The use of light-based therapy in the treatment of ocular rosacea is an emerging avenue and could potentially be a safe and noninvasive mode of therapy. In addition, the use of light-based treatment avoids microbiome alterations associated with antibiotic use, contributing to the promotion of antimicrobial stewardship. Intense pulsed light (IPL) therapy devices use flashlamps to produce pulsed light of

different wavelengths, durations, and fluences.⁷

The treatment protocol demonstrating the use of IPL for dry eyes was first outlined by Dr Ronaldo Toyos.⁸ The process begins with the use of IPL eye pads over closed eyes.⁸ Then ultrasound gel is applied on the patient's face from tragus to tragus, and overlapping flashes are delivered over the area to encompass one full pass.⁸ Subsequently, more ultrasound gel is applied, and a second pass is performed.⁸ Next, the gel is removed and 1% proparacaine is administered prior to beginning gland expression.⁸ Using a sterile cotton tip, it is placed on the area of the palpebral conjunctiva, and the physician places a finger over the skin adjacent to this gland.⁸ With the patient looking up, a gentle consistent pressure is applied with both the cotton tip and finger, and the gland is expressed for 30 seconds.⁸ This process is repeated across the span of the lower lid bilaterally.⁸ Gland expression of the upper eyelid is performed using finger pressure while the patient is instructed to look down.⁸ If finger pressure does not suffice, a sterile cotton tip can also be used.⁸ On completion of gland expression, a drop of topical steroid or a nonsteroidal anti-inflammatory drug can be administered.⁸ The protocol encompasses 4 IPL treatments followed by meibomian gland expression (MGX) 4 to 6 weeks apart.⁸

Although the exact mechanism of action of IPL in ocular rosacea is unknown, it is proposed to employ the benefits of heat-inducing ablation.⁹ One proposed mechanism highlights the warming effect produced by IPL as integral to increasing the expression and subsequent outflow of viscous meibum found in conditions causing dysfunctional meibum glands.⁹ The increased outflow of meibum reduces the proliferation of bacteria typically seen in meibum stasis, therefore decreasing ocular inflammation and irritation.⁹ Another potential explanation is the targeting and subsequent reduction of

Demodex mites which have been found to contribute to inflammation.⁹ Finally, IPL may have a role in altering the levels of inflammatory mediators, specifically through the downregulation of pro-inflammatory cytokines and upregulation of anti-inflammatory cytokines.⁹ IPL may also induce changes in the microcirculation, through the eradication of abnormal small vessels surrounding meibomian glands, ultimately decreasing the availability of inflammatory mediators and reducing inflammation.⁹

IPL is a promising avenue of treatment and warrants further investigation to determine its impact on ocular rosacea outcomes.

Methods

A scoping review of the literature was conducted.

Search Strategy

A literature search was conducted on January 12, 2022, using the MEDLINE (1946 to January 11, 2022), Embase (1980 to January 11, 2022), and PubMed databases using the search terms “rosacea” and (“treatment” or “therapy” or “management” or “IPL” or “light”). No date, geographical, or language restrictions were applied.

Study Eligibility Criteria

Eligibility criteria for this review were established using the population, intervention, comparator, outcomes, and study design (PICOS) framework. Studies were included if they met the following predetermined criteria:

- Population: individuals aged ≥ 18 years old diagnosed with ocular rosacea by a healthcare professional, including individuals with any disease severity, treatment history, or comorbid conditions
- Intervention: any treatment regimen involving light therapy
- Comparator: untreated individuals with ocular rosacea or in the absence of a comparator, open-label studies where outcomes were assessed in treated individuals
- Outcomes: clinical response (patient or physician reported) on dry eye symptoms, length of delay to diagnosis, timing of ocular, and cutaneous symptom presentation
- Study design: randomized control trials, cohort studies, cross-sectional studies, and case series (excluded if < 3 subjects).

Data Screening

Title and abstract screening were completed by 3 independent researchers (S.K., S.A., and I.M.) using Covidence online systematic review software (www.covidence.org). Conflicts were resolved by consensus and ties were broken by a third researcher (I.M.). Full-text review was completed independently by 3 researchers (S.K., S.A., and I.M.) and conflicts were resolved by consensus. References of included studies were manually checked to identify any additional relevant studies.

Data Extraction

Data extraction was completed in duplicate by 3 reviewers (S.K., S.A., and N.K.) using a predetermined extraction form including study characteristics (publication year, country, sample size), patient characteristics (age, biological sex of participants), intervention type, and outcomes (clinical response and length of follow-up).

Data Synthesis

To aid in pooling results from heterogenic outcomes, outcomes from each study were coded into 3 categories: complete response (CR), partial response (PR), and no response (NR).

Definitions

Complete response: complete or near complete response based on criteria established by each included study.

Partial response: partial or moderate response based on criteria established by each study.

No response: no response or worsening symptoms based on criteria established by each study.

Results

Five articles met the inclusion criteria and are summarized in this review (Supplemental Table S1).

<https://journals.sagepub.com/doi/full/10.1177/12034754241254051#supplementary-materials>

The mean age of participants was 58.4 years. All the included studies were conducted in adult populations, and the follow-up period ranged from 10 weeks to 12 months.

Overall IPL therapy led to a PR in 91% ($n = 89/98$) of included patients, and 9% ($n = 9/98$) had NR. IPL therapy did not lead to complete recovery in any of the included patients. The Sagaser et al study was included in our review but was excluded from the pooled analysis as it did not provide information on response per participant.

Summary of Included Studies

All included studies reported an improvement in ocular rosacea symptoms. A study investigating the use of IPL and MGX in chronic graft versus host disease (GVHD) patients with ocular rosacea noted a decrease in the Standard Patient Evaluation of Eye Dryness Questionnaire (SPEED2) score measuring the severity of dry eye disease.¹⁰ This study used the treatment protocol first developed by Dr Rolando Toyos, which outlines a total of 4 IPL treatments followed by MGX 4 to 6 weeks apart.⁹ Among 8 patients, where the baseline score was 20.7, a statistically significant mean improvement of 8.0 points in the SPEED2 score was noted and this improvement was maintained after 12 months.¹⁰ However, meibomian gland evaluation did not reveal any change in the number of meibomian glands producing liquid secretions over the 12 month period.¹⁰ One adverse event was reported, where the patient withdrew from the study due to the development of active GVHD.¹⁰ Similarly, in another study where participants received an average of 3 IPL sessions, SPEED2 measurements found that 62.3% of participants experienced a greater than 50% reduction in SPEED2, and overall, 85% of patients reported a positive SPEED2 response to IPL therapy.¹¹

In contrast to the previous study, this study observed an increase in MGX, where 71% of patients had improvement in the number of glands with liquid secretions in the lower eyelid.¹¹

In a group of 20 patients with dry eye disease associated with ocular rosacea, a statistically significant improvement in subjective symptom score was noted, from a median value of 8 to 2.12 Tear breakup time, a metric of tear film stability, changed from a median of 4 to 10 following therapy.¹² Other statistically significant changes included the Schirmer test result from 13.5 to 15, and the Van Bijsterveld score remained at 3.12 The treatment algorithm comprised

of 3 sessions including warm eyelid compresses for 7 minutes, manual MGX, administration of 5 flashes of xenon light, and ending with a second manual MGX.¹²

In a study investigating the use of IPL in rosacea-associated meibomian gland dysfunction, the Ocular Surface Disease Index (OSDI) score was used to characterize treatment outcomes.¹³ A total of 82.4% of the participants reported an improvement in symptoms between the baseline and final examination, and the remaining participants described improvement within the follow-up period.¹³ The OSDI is a validated and reliable tool used to measure the severity of dry eye disease.¹⁴ It is scored on a scale from 0 to 100, where higher scores correspond to greater severity of disease—a score of 0 to 12 is characterized as normal, 13 to 15 is mild disease, 23 to 32 as moderate, and 33 to 100 as severe.¹⁴ The baseline OSDI score was noted to be 50.0, and at 12 months was <40.0.¹³ Other outcome metrics also described improvement, where tear film instability and ocular surface epithelial damage resolved during treatment and 3 weeks posttreatment.¹³ A study by Sagaser et al. also found that while the mean OSDI scores between the IPL-MGX and MGX treatment groups were comparable at baseline (55.7 vs 43.5, $P = .212$), following 4 visits, the OSDI scores in the IPL-MGX group were significantly improved compared to the MGX only group ($P = .030$).¹⁵ Similar to previously described studies, these studies used the Toyos treatment protocol.

Discussion

Our review summarizes studies reporting on the use of IPL for the treatment of ocular rosacea. Available data suggest that IPL can lead to an improvement of symptoms associated with ocular rosacea, particularly dry eyes, with limited adverse events, as evidenced by the PR to treatment demonstrated in 91% ($n = 89/98$) of included patients. Given the chronic nature of rosacea and lack of curative treatment, the results similarly demonstrate no CR. PR was variable, but primarily encompassed decreased frequency and severity of dry eye symptoms such as dryness, irritation, burning, watering, and eye fatigue, as well as reduced redness of the eyelid margins. Interestingly, this treatment effect is demonstrated despite no direct application of IPL to the eyelids. Furthermore, though IPL application is limited up to the margins of the lower eyelid shields, there is improvement in both the lower and upper eyelids. This could be due to the increase in anti-inflammatory mediators and antioxidants that are being propagated through the orbital vasculature.¹⁶ There are updated protocols treating the upper eyelid as well, specifically using a Jaeger lid plate beneath the conjunctival sac as the IPL is pulsed, or using an internal eye shield as a means to protect the cornea and conjunctival sac and to mitigate adverse effects secondary to the IPL.^{17,18} There are also published studies on the use of external adhesive eye shields that can be placed to protect the upper and lower lashes, exposing the upper lid and using a handpiece with a smaller surface area to directly target the upper meibomian glands.¹⁷

The literature demonstrates that IPL applied to the eyelids in addition to MGX is a relatively safe procedure with low risk of adverse effects. Some adverse events reported are epidermal keratoconjunctivitis, floaters, herpes simplex keratitis, glaucomatocyclitic crisis, and iridocyclitis. IPL is not recommended for children <10 years of age or patients who have underlying uveitis or glaucomatocyclitic crisis. Caution is advised in those with a history of herpes simplex keratitis.¹⁹ There are no studies to compare efficacy between treating lower eyelids and treating both upper and lower eyelids.

Caution should be used when treating the upper eyelid as partial eyelash loss has been reported.¹⁷ Conflicting evidence exists regarding the potential increase in MGX with IPL; therefore, more research is warranted to determine whether IPL can lead to consistent physical changes and symptom improvement.

A correlation between ocular rosacea and the presence of bacteria associated with *Demodex* mites has been described in the literature.¹⁵ *Demodex* mites are parasites that normally colonize human hair follicles and sebaceous glands, but a greater density of these mites has been associated with the pathophysiology of rosacea and other inflammatory skin conditions.²⁰ A study of 59 participants by Li et al²⁰ found that positive serum immunoreactivity to *Bacillus oleronius* was significantly associated with lid margin inflammation ($P = .040$) and ocular *Demodex* infestation ($P = .048$). *Demodex* infestation can lead to ocular surface inflammation, causing blepharitis, meibomian gland dysfunction, and conjunctivitis.²⁰ Given the pathogenic role of *Demodex*, it is plausible that IPL targets the eradication of mites for symptomatic relief.⁹

Demodex mites and their associated bacteria have also been linked to meibomian gland pathology.²¹ These organisms enhance the production of lipases and esterases degrading the lipid content of meibum, a key component of the tear film.²² This causes the meibum to become more viscous, causing stasis of the meibum which subsequently leads to lowered secretion.²² The compromised tear film lipid layer causes tear film instability and dry eyes.²² Thus, IPL could heat the meibum, improving stasis and increasing MGX.⁹

Though the number of sessions and time between sessions varied across studies, 3 to 4 treatments were most commonly administered and spaced 4 to 6 weeks apart. The IPL application methods used are summarized in this review (Supplemental Table S2).

<https://journals.sagepub.com/doi/full/10.1177/12034754241254051#supplementary-materials>

Many of the included studies described the Toyos protocol, encompassing 4 IPL treatments followed by MGX 4 to 6 weeks apart.⁸ This protocol describes that candidates for IPL must have Fitzpatrick skin types 1, 2, or 3, where sometimes type 4 can tolerate treatment.⁸ Clinicians should exercise caution in administering IPL in patients with Fitzpatrick skin types 4 to 7. IPL treatment intensity ranges from 8 to 20 J/cm², where higher intensities may be employed based on increasing age and lid margin disease severity.⁸ The number of sessions required for maintenance was not reported in the included studies and more research is needed before the development of recommendations.

There are limitations to this review. Our study categorized participant outcomes as producing a CR, PR, or NR as an aggregate measure allowing for the pooling of heterogeneous modalities. A limitation of this method is the variability of PRs, due to the spectrum of strong to weak PRs being grouped together. There is also variability in the patients of included studies and their comorbidities. Given the relatively novel nature of IPL as a form of therapy for ocular rosacea, there are few studies investigating its efficacy, and these studies often use small groups of participants.

Conclusion

Our review highlights the potential for IPL in the management of dry eyes associated with ocular rosacea. Although a framework for treatment has been developed, further research is necessary to ascertain a treatment algorithm outlining the number of IPL sessions necessary depending on factors such as Fitzpatrick skin type, symptom severity, and age. Overall, IPL remains a potential treatment modality for symptom management in combination with appropriate lid hygiene and massage.

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What's in the news?

The roles of neural adaptation and sensitisation in contact lens discomfort

The purpose of this study was to investigate the roles of neural adaptation and sensitisation in contact lens discomfort (CLD).

The methods used included Cooling stimuli (20 °C) that were applied to the cornea in a group comprising 24 symptomatic and 25 asymptomatic contact lens (CL) wearers as well as 15 non-CL wearing controls, using a computerised Belmonte esthesiometer. The adaptation paradigm consisted of 20 repetitive stimuli at threshold, sub- and supra-threshold levels. The sensitisation paradigm involved five levels of suprathreshold stimuli ranging between 1x to 2x threshold. Following each stimulus, participants rated the sensation magnitude regarding intensity, coolness and irritation. Measurements were taken with habitual CL (BL_CL), after 2 weeks of no-CL (No_CL) and after restarting habitual CL wear (ReSt_CL).

The results showed that the symptomatic subjects exhibited a lower threshold but reported enhanced sensations during the adaptation and sensitisation paradigm, compared to the asymptomatic and control groups (all $p \leq 0.021$). At the BL_CL and ReSt_CL visits, they showed increased ratings to repeated subthreshold stimuli ($p = 0.025$) and greater irritation during the sensitization paradigm ($p \leq 0.032$). Ratings in asymptomatic and control groups were relatively unchanged over time ($p \geq 0.181$). Logistic regression revealed a link between the augmented sensory responses and increased likelihood with CLD.



The authors concluded that the maladaptive sensory responses seen in CLD subjects, with reduced adaptation and heightened sensitization to ocular surface stimulation, suggest an imbalance between sensitisation and adaptation in CLD. As CLD may represent a reversible subcategory of dry eye, it can serve as a human dry eye model for studying the neurosensory effect of ocular surface stimulation.

Authors: Ping Situ, Carolyn Begley, Trefford Simpson

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The Toyos Dry Eye Diet

by Rolando Toyos

My discovery of Intense Pulse Light (IPL) and Low-Level Light (LLLT) treatments for dry eye disease (DED) over 23 years ago put me on the path of becoming an expert in the field. Malcolm Gladwell famously wrote that it takes ten thousand hours of work to master your trade. I surpassed ten thousand hours long ago. What I learned concentrating on this disease is that we need to spend more time on diet and lifestyle. There is a place for medications and technologies but if you rely on just these treatments the epidemic will continue and we don't have enough specialists to keep up with the demand.

I am a DED patient and always volunteer to be the first to try different treatments. I flashed IPL over my whole body to help me develop useful protocols that provided the most efficacious results. I spent many hours tinkering with many wavelengths of light to finally develop the at home LLLT device, The Q. If you added up the number of eyedrops that I have tried over the years you could fill up a swimming pool. But you know what has been the biggest factor in maintaining my DED under control, diet. During my consultation with a DED patient I always go over their diet and lifestyle. Patients want to go straight to the IPL or other technologies we have but I always slow them down and talk about their diet. I am often met with resistance because most of my patients feel that they eat a well-balanced diet. But when we study their current diet we find that most of the foods that they are eating are making their DED worse.

DED is an inflammatory disease so we need to eliminate the foods that are inflammatory like meat, poultry, eggs, and dairy. If we really want our foods to decrease inflammation then we have to deal with any imbalances in our gut bacteria. I used to have my DED patients submit stool samples for testing. I quickly realized that all my DED patients had acidic guts. I tried probiotics to improve these acidic guts to no avail. Then I worked with nutritionists and experimented with various diets to improve gut bacteria. I developed a 2-month starter diet that I utilize for all my DED patients. The diet was so successful that it led to my current book, The Toyos Dry Eye Diet. In the book I cover diet, lifestyle, and update my first DED book, Dry Eye Treatment in the Year 2020. (All proceeds from my books go to free care for the underserved.)

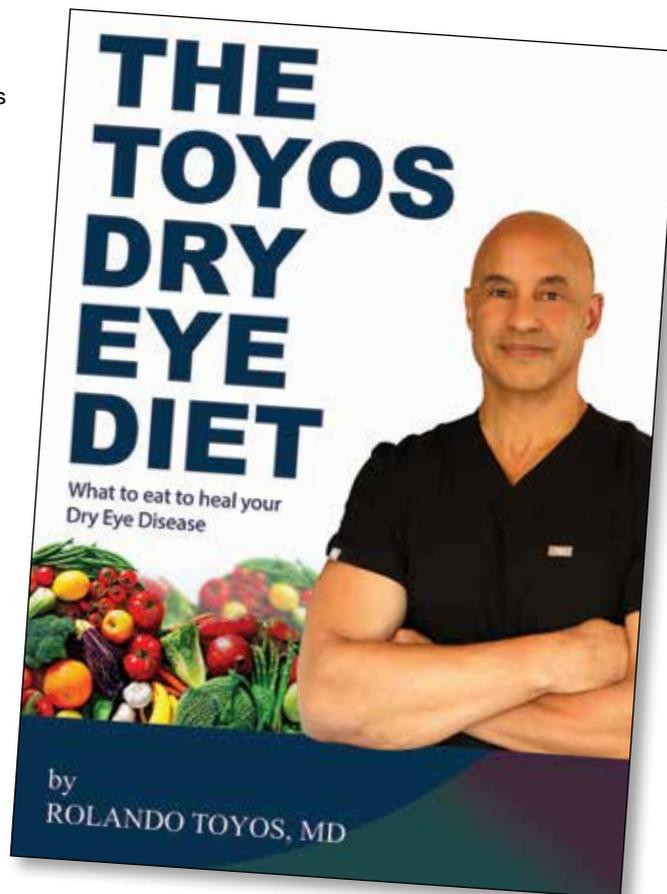
In the 2-month starter diet not only do we eliminate all inflammatory foods but we incorporate foods that are pre and probiotic. I take into account some patients with dietary restrictions, like Inflammatory Bowel Disease. Once we improve the patient's gut we allow them to incorporate a wider variety of foods. I find that complete restriction leads to non-compliance so I educate patients on the 90/10 rule. Ninety percent of what patients eat is within our guidelines and ten percent falls outside the recommended diet. It allows patients the freedom to have their favorite cake at a party without feeling guilty.

I don't encourage cheat days because that gives patients the freedom to completely go off the diet and can lead to cheat weeks.

We want to be deliberate in what we eat but also what we put on our skin. Recently many manufacturers are including retinoids in their skin care products to stimulate fibroblasts to produce collagen and elastin. The problem with retinoids is they can exacerbate meibomian gland dysfunction. I actually tell my patients that there are now many other skincare products that are effective on stimulating fibroblasts but do not negatively affect DED. (IPL stimulates fibroblasts). I also tell patients that they should look at all the ingredients in the products that they use for skin care. Many non-active ingredients can also be detrimental to the DED patient like phthalate,

kathon, limonene, linalool, parabens, and propylene glycol to name a few.

Patients understand that another key component to improving their eye health is modifying their lifestyle. When we are on cellphones and computers our blink rate decreases and that leads to increase in evaporative dry eye. Many of our patients are spending hours focused on screens. One of the best ways I have found to relieve the problem is a technique taught by Japanese eye doctors to their patients. For every hour that a patient is on a screen they are to take a break and close their eyes, block out the light with their hands, and think of their happy place. The Japanese patient will think of a rock garden or Mt. Fuji but I tell my patients to think of the place that they enjoyed their last vacation (most think of a beach). The thought is not focusing on your work allows you to relax accommodation.

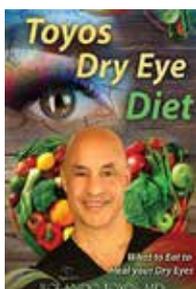


Since the release of my book many people will ask me to give them a couple of quick tips. It is really hard to summarize 3 years of research but I will give you some information to whet your appetite. I believe that DED patients should increase their mushroom intake. Over 60% of our DED patients also have seasonal allergies. Many of the treatments for allergies, like anti-histamines, dry the eyes. Mushrooms are a natural mast cell stabilizer helping patients control their allergy symptoms without resorting to anti-histamines.

I also encourage certain supplements like CoQ10. CoQ10 is a coenzyme needed to power our mitochondria. It is also an antioxidant that regenerates vitamin C and E. I believe DED patients can benefit from supplementation

because we are trying to jump-start the cells responsible for making natural tears. Certain medicines, such as statins, rob us of CoQ10. Several studies show the neuroprotective effect of CoQ10 for diseases such as Alzheimer's, Parkinson's, and ocular nerve damage in glaucoma and DED.

I believe to improve signs and symptoms of DED we have to not only utilize all the technologies and medicines available for DED but we must spend time with patients educating them on diet, lifestyle, and the products that patients are using. If you need proof that patients are receptive to my holistic form of treatment realize that my book has been a best seller on Amazon for over a year. As you read the book remember to take a vision break every hour.



Extensive knowledge is packed into Dr Toyos' book which is highly recommended for anyone who suffers with symptoms of dry eyes. The well researched information, based on decades of first hand experience of treating those with dry eye disease, has led to a book that may finally bring relief to sufferers of this frustrating condition.

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<https://teamtoyos.com/product/toyos-dry-eye-diet-book/?wmc-currency=GBP>

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Dry Eye Disease: An Update on Changing Perspectives on Causes, Diagnosis, and Management

Monitoring Editors: **Alexander Muacevic** and **John R Adler**

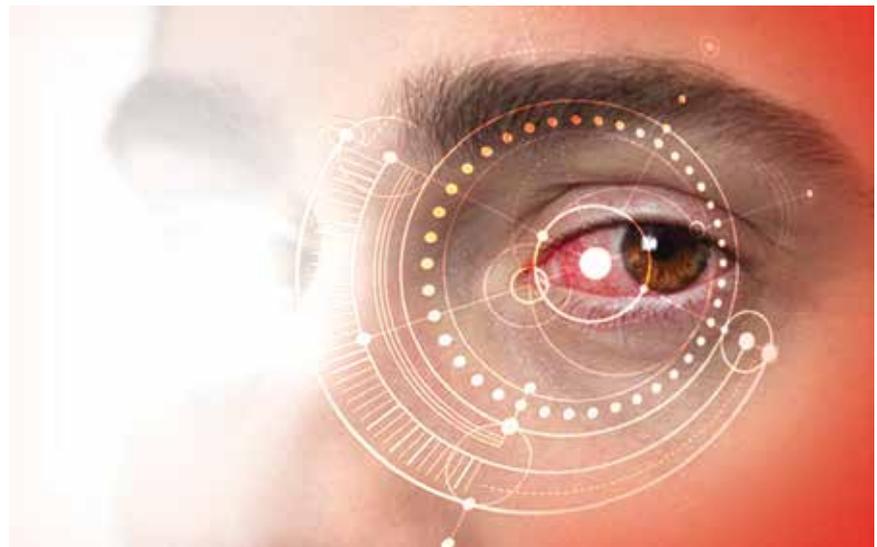
Authors: **Nikita Dash** and **Deepak Choudhury**

Abstract

Dry eye disease is a common clinical problem encountered by ophthalmologists worldwide. Interest in this entity has increased in recent years due to the consequences it has on the ocular surface after any surface procedure. With changing times, several new factors have come to light that can influence this disease. The effect of the COVID-19 pandemic has also been greatly felt, with a range of causes, starting from increased screen work to inflammatory processes, exacerbating the condition in many. With changes in the concepts of the etiopathogenesis of the disease, a paradigm shift has taken place in the approaches to treatment. More researchers are in favor of a new tear film-oriented approach that tries to localize the disease to a single component in the tear film. Innovation of newer techniques for the treatment of meibomian gland disease has also made its foray into clinical ophthalmology. Newer drug formulations and molecules are underway to better treat the inflammatory component of the disease. Many other receptors and targets for the treatment of dry eyes are being researched. This review hopes to provide a succinct, narrative summary of the relevant research on dry eye disease to date to increase awareness about the nature and future course of this disease and its management.

Introduction and background

Dry eye disease (DED) is commonly encountered by ophthalmologists worldwide. In 2017, the Tear Film and Ocular Surface Society International Dry Eye Workshop II (TFOS DEWS II) defined dry eye as “a multi- factorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear-film instability and hyperosmolarity, ocular surface



inflammation and damage, and neurosensory abnormalities play etiological roles”^[1]. While there has been extensive discussion about the etiopathogenesis of DED, recent consensus in Japan and Asia has attributed tear film instability as the core mechanism behind the disease. The concept of clarifying each cause by focusing on every layer of the tear film is referred to as a tear film-oriented diagnosis^[2]. Treatment based on such a diagnosis is referred to as tear film-oriented therapy^[3,4]. Recent research has changed the understanding of DED; thus, this review attempts to shed light on newer concepts related to its risk factors and diagnosis as well as changing perspectives on the management of DED.

Review

Risk factors and their role in disease development

Tear film hyperosmolarity and subsequent inflammatory changes remain the core mechanisms of DED; thus, factors affecting these play an important role in the development of the disease^[1]. A recent literature review confirmed the role of increased tear film

osmolarity in the pathogenesis of DED and outlined various causes behind it^[5].

Environment and Its Contribution

Although the role of environmental factors (e.g. humidity) in DED is often debated, exposure to certain pollutants is known to exacerbate the disease^[5,6]. Pollutants such as nitrogen dioxide (NO₂), sulfur dioxide (SO₂), ozone (O₃), and particulate matter (PM) can cause ocular surface symptoms^[6]. Both outdoor and indoor pollutants have been found to be associated with the symptoms of DED. The effect of reactive gases on DED has not been studied in detail^[7].

In general, high outdoor humidity has been shown to be protective against dry eye symptoms^[8]. However, exposure to sunlight, windy conditions, and high altitude can negatively impact the ocular surface^[9,10].

Various ocular conditions have been known to cause or aggravate dry eye due to their effect on tear film osmolarity. Sjogren’s syndrome is an autoimmune disease that is largely associated with aqueous-deficient dry eye. The involvement of the lacrimal gland and underlying meibomian gland

dysfunction (MGD) play major roles in its pathogenesis. Increased inflammatory markers, such as interleukins and changes in tear film glycoproteins, have also been noted [11-13].

MGD is a type of posterior blepharitis that results in unbalanced lipid secretion, which leads to tear film instability and evaporative dry eye. Many factors, including age, sex, microbial infections, parasitic infestations, and topical medications, are known to influence MGD [14,15]. Ocular surface disorders, such as pterygium and graft-versus-host disease (GVHD), can cause changes in tear composition. A recent proteomic analysis found higher levels of increased expression of keratin proteins in pterygium and GVHD tears, which may be related to increased epithelial keratinization. Similarly, tears from keratoconus-affected eyes showed increased expression of proteins related to immune responses [16]. Pseudoexfoliation syndrome can alter goblet cell activity and mucin production, leading to increased tear osmolarity [17].

Systemic Diseases and Dry Eye

Diabetes is commonly associated with DED, and the prevalence of DED in diabetics may be underestimated. Pathogenesis can be attributed to several factors. Injury to the lacrimal gland, its blood vessels, and/or the corneal nerve following prolonged hyperglycemia can lead to a decrease in aqueous production [18,19], resulting in increased tear osmolarity and blinking abnormalities. The severity of dry eye is often related to the duration of diabetes. Studies have also found that dry eye is more prevalent in patients with diabetic retinopathy and that the severity of DED has a positive correlation with retinopathy [20-22].

Thyroid dysfunction is another cause of dry eye. A mixed mechanism of evaporation and aqueous deficiency has been proposed. Palpebral fissure widening, eyelid retraction, and incomplete blinking lead to inadequate tear distribution and excess tear evaporation [23]. In addition, a wider palpebral fissure results in a shorter tear film break-up time (TBUT), leading to an unstable tear film [24]. Autoimmune mechanisms cause decreased tear production. Autoantibodies against thyroid-stimulating hormone receptors bind to similar receptors on the lacrimal gland, leading to its impairment and aqueous deficiency [25].

Recent studies have found decreased tear volumes in patients suffering from metabolic syndrome. Metabolic syndrome encompasses a group of risk factors for diabetes, hypertension, hyperlipidemia, and other lifestyle diseases. Increased oxidative stress remains the major underlying mechanism of metabolic syndrome [26,27]. Apart from Sjogren's syndrome, other connective tissue and immune-mediated diseases such as rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, and fibromyalgia can present with dry eye [28,29]. Autonomic dysfunction in patients with Parkinson's disease can also cause dry eye [30].

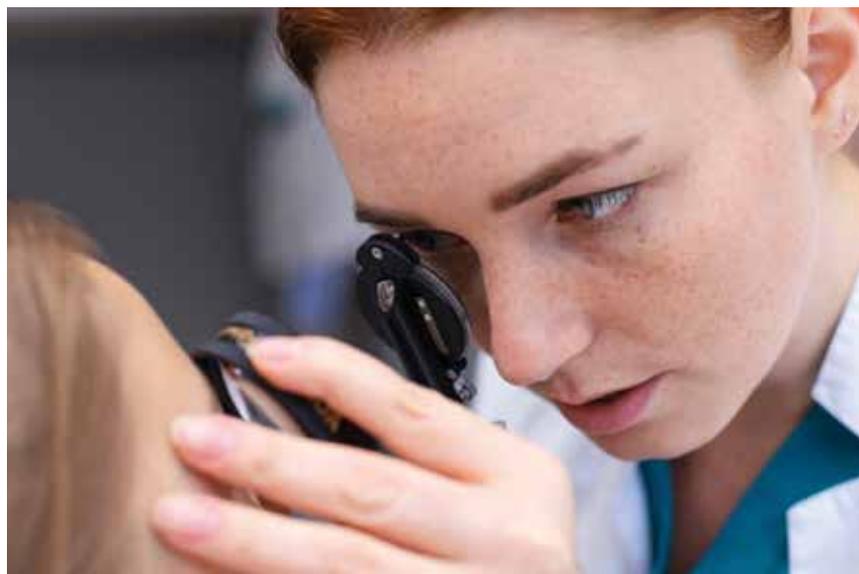
Lifestyle and Mental Health

Recent studies have found a significant association between TBUT and a sedentary lifestyle, reinforcing the idea that DED is more prevalent among those who exercise less. Prolonged periods of inactivity can predispose individuals to other risk factors and systemic diseases associated with DED [31,32]. In addition, office workers often spend the majority of their time in

decreased sleep duration (less than or equal to five hours/night), symptomatic DED patients are more likely to experience psychological stress and have a history of depressed mood [37]. Galor et al. proposed a mechanism of central sensitization in patients with depression and anxiety that may affect how pain is perceived [37]; these patients may react more sensitively to ocular sensations as compared to the control group [38,39]. Subjective happiness has also been found to be positively correlated with dry eye symptoms [40].

Ocular Surgeries

Cataract surgeries have long been considered to aggravate dry eye symptoms. It is believed that corneal incisions made during cataract surgery can release inflammatory mediators (HLA-DR and CD3), similar to the inflammatory process in a dry eye subject [41]. While phacoemulsification cataract surgery does not induce or exacerbate DED in the general population, it can transect the corneal nerves, which may lead to reduced reflex tearing [42]. Preexisting comorbidities, such as MGD and



front of visual display terminals, which results in sympathetic dominance and decreased tear production [33,34], and prolonged visual tasks can result in incomplete or decreased blinks, thereby causing tear film instability and DED [35].

Several studies have found an association between sleep disorders and DED. It is thought that ocular discomfort and inflammatory processes may lead to pain, causing sleep disruption that aggravates symptoms [36,37]. However, it has yet to be established whether poor sleep leads to DED or vice versa. In addition to

diabetes, play a major role in increased dry eye symptoms following cataract surgery [42]. Manual small-incision cataract surgery results in more symptoms due to the size of the incision involved, which results in the denervation of a greater part of the cornea [43].

Recently, Ju et al. have demonstrated that femtosecond laser-assisted cataract surgery (FLACS) can lead to tear film instability by changing the corneal curvature prior to surgery, which can damage the limbal stem cells and conjunctival goblet cells [43].

Photorefractive surgeries often lead to iatrogenic corneal nerve damage, changes in corneal shape, and damage to conjunctival goblet cells, all of which cause decreased tear production, impaired wettability, and increased tear osmolarity, thus resulting in dry eye symptoms [44,45]. Although dry eye symptoms have been reported with the implantable collamer lens technique, it is moderate compared to laser vision correction [46]. Small incision lenticule extraction (SMILE) reported better TBUT and Ocular Surface Disease Index (OSDI) scores as compared to laser-assisted in situ keratomileusis (LASIK). Significant differences in neuromediators and proteomics of the tear film have been observed between the two groups even when ocular surface signs are comparable [47,48].

restrictions imposed by the pandemic [51]. Besides, the use of screens doubled, leading to increased eye strain and dry eye symptoms [52]. Moreover, the mandatory usage of masks contributed to worsening dry eye symptoms, especially in females and subjects with prior DED [53].

Changes to the ocular surface after a COVID-19 infection can also cause DED. Compared to healthy eyes, in vivo confocal microscopy (IVCM) in COVID-19 survivors has established the loss of small corneal nerve fiber and increased dendritic cell density at a mean of 3.7 months after diagnosis [54]. Moreover, the ocular surface also serves as an entry point for SARS-CoV-2, since angiotensin-converting enzyme 2 and transmembrane protease serine 2 were

culpable [58]. The report also acknowledges the role of hormones in the development of DED. Androgens are an important regulator of the ocular surface and adnexa, especially the meibomian gland; thus, their deficiency may trigger a non-autoimmune type of DED known as primary lacrimal gland deficiency, with associated MGD [58]. Other hormones, such as thyroid hormones, hormones of hypothalamic pituitary axis, and steroid hormones, have also been shown to influence the ocular surface and adnexa, although a clear mechanism is yet to be established [58].

The use of contact lens and topical medications with preservatives can also prove detrimental to the ocular surface, leading to increased tear osmolarity and subsequent dry eye symptoms [5,59]. Other risk factors include Asian race, allergies, vitamin A deficiency, and essential fatty acid deficiency [60].

Changing concepts in diagnosis and advancements in diagnostics

Traditionally, dry eye has been diagnosed based on clinical findings from Schirmer's test, TBUT, staining of cornea and conjunctiva, and standardized scoring systems. However, recent research on tear film break-up analysis patterns, tear film osmolarity, and biomarkers has provided deeper insights into the diagnosis of DED.

Tear-Film-Oriented Diagnosis and Fluorescein Break-Up Patterns

The Japanese and Asian dry eye societies consider an unstable tear film at the core of dry eye mechanisms; thus, the concept of tear-film-oriented diagnosis was introduced to clarify the cause by focusing on each layer of the tear film. Yokoi et al. have described fluorescein break-up patterns that not only aid in diagnosis but also detect which tear film layer is responsible for DED. The break up patterns judge the abnormalities in the tear film using a physical theory [3,4]. When there is upward movement of the eyelid during eye opening, capillary suction from the upper tear meniscus sucks the aqueous tears up leading to the spread of aqueous layer on the cornea. However, the surface pressure gradient on the tear-film lipid layer pulls the aqueous tear layer resulting in the formation of the precorneal tear film. The various tear-film break-up patterns are area break, spot break, line break, dimple break, and random break, which are described in Table 1 [3]...

Changes in corneal sensitivity, tear film instability, and goblet cell loss have been attributed to the DED symptoms in strabismus patients post-surgery. Exposure to a larger area of bulbar conjunctiva opposite the side of deviation and distortion of the normal relationship between the lids and the globe leads to microtrauma, which can cause symptoms prior to surgery [49]. A recent study showed an increased concentration of inflammatory tear mediators (IL-6 and TNF- α) in concomitant exotropia, which explains the prevalence of dry eyes and tear film instability in squint patients before surgery [50].

Effect of COVID-19

The COVID-19 pandemic heralded a new era of DED, primarily due to increased screen usage and lifestyle changes. Napoli et al. coined the term "quarantine dry eye" while discussing lifestyle factors such as diet, hydration, sleep deprivation, and other psychological aspects pertaining to

detected in conjunctiva and cornea, probably upregulated by the inflammatory process [55]. Patients with long COVID may also present with worsening MGD and ocular surface staining scores, with higher viral loads and supplementary oxygen use being major risk factors in them. Bilateral dacryoadenitis, wherein fibrosis and obliteration of lacrimal gland ducts have been observed, has been reported as a post-COVID complication [56]. This may play a role in the pathogenesis of DED in COVID-19 survivors.

Other Causes of DED

While advancing age is a well-known risk factor for DED, sex and hormones also play important roles [57,58]. The recent TFOS DWES II report not only agrees with the fact that females are more affected than males but also establishes that DED is more likely to affect women at a younger age than men. Several anatomical and psychological factors, such as pain perception and mental health, are



Table 1**A summary of different patterns of tear-film break-up and their mechanisms as described by Yokoi et al.**

Type of break	Description
Area break	Fluorescein break-up is observed during eye opening when aqueous tear volume is severely reduced
Spot break	Characteristic spot-like shape noted immediately after eye opening. This is a result of impaired wettability due to mucin deficiency
Line break	It occurs after eye opening due to drag and suction mechanisms. It is characterized by a linear break in the lower part of the cornea in mild-to-moderate aqueous deficiency
Dimple break	A vertical line-like break in the tear film towards the end of the upward movement of fluorescein-stained tears. It is caused by a mild-to-moderate impairment of wettability due to mucin deficiency
Random break	It is caused by the increased evaporation of tears. This results in the thinning of the aqueous layer that causes a random break after the movement of the fluorescein-stained tear film is complete.

This is a very basic interpretation of DED types based on fluorescein break-up patterns. Yokoi et al. described more complex and modified forms based on physical theory and the forces involved [61]. It is believed that the practical use of such a classification might make it popular in the years to come.

Tear Film Osmolarity and Its Measurements

The osmolarity of the tear film explains homeostasis involving tear production, drainage, absorption, and evaporation. Presently, a threshold of 316 mOsm/L is used to differentiate between mild and moderate/severe dry eye, whereas a threshold of 308 mOsm/L is considered sensitive enough to distinguish normal eyes from those with DED [62]. The tear film osmolarity measurements show great variability in patients with DED. Therefore, an average reading is considered more reliable than a single measurement [63].

There are three primary techniques for the measurement of tear film osmolarity: electrical impedance, vapor pressure, and freezing pressure osmometry [64]. Devices such as the TearLab osmometer and I-Pen® use the electrical impedance technique, which measures tear film osmolarity based on the number of charged particles therein. The Wescor 5520 Model follows the concept of vapor pressure; an advantage is the ability to measure osmolarity in small tear film samples. Freezing pressure osmometers are the gold standard, as they can accurately measure osmolarity in very small tear volumes. However, they are highly operator-dependent and require extensive apparatus, and a single

measurement takes about 15 minutes [64].

Concept of Functional Visual Acuity

Dry eye patients usually complain of visualization difficulties despite good visual acuity. This has led to the idea of dynamic measurement of visual acuity in such patients. Goto et al. first proposed the measurement of visual acuity by forced eye opening under topical anesthesia and termed it “functional visual acuity” (FVA) [65]. They concluded that FVA decreased despite good conventional visual acuity. Manual measurements, however, resulted in inter-test variations and drawbacks associated with the timing of measurements [64].

Presently, the FVA measurement system provides a non-invasive alternative to continuous visual acuity monitoring under natural blinks without the use of topical anesthesia. In addition to its use in the diagnosis and screening of DED, it has been of great help in judging the effect of dry eye treatments, as improved FVA has been noticed in those undergoing treatment [66]. However, numerous factors can influence FVA assessment, and future research in this matter is required to explain abnormal FVA measurements [66].

Non-invasive Imaging Modalities

To avoid disturbances caused by fluorescein instillation, lipid layer interferometry, a grid xeroscope, and a tear film stability analysis system have been used to study tear film stability. The tear film stability analysis system uses corneal topography. Goto et al. proposed

capturing images immediately and 10 seconds after eye opening to study the changes in surface regularity and asymmetry. Later, analysis using aberrometry was introduced to detect higher-order aberrations in DED [65,66]. Newer instruments, such as the Oculus Keratograph 5M, not only measure TBUT but can also evaluate meibomian glands and measure tear meniscus height (TMH) [67].

Anterior segment-optical coherence tomography (AS-OCT) has also emerged as a valuable tool for measuring TMH and assessing tear volume. A dry eye diagnosis is made with a sensitivity of 67% and a specificity of 81% when 0.3 mm of the inferior AS-OCT meniscus height is the cut-off. Its use in the assessment of TMH following therapeutic procedures has also been described [68,69].

Another instrument that has been developed for the measurement of tears is the strip meniscometry tube. The commercially available Strip meniscometry tube (SMTube, Echo Electricity, Fukushima, Japan) uses a non-woven rayon and pulp material sandwiched between polyethylene material as the absorber. It can measure the retained tear volume in the tear meniscus in five seconds. Its cut-off value for diagnosing dry eye is considered as 4 mm, with 93% sensitivity and 73% specificity. The validity of the measurements has been correlated alongside AS-OCT values [66,70].

While impression cytology has been used to study the cellular morphology of the ocular surface in the past, today, IVCM provides a non-invasive

alternative. The histological trademark of DED in a typical conjunctival epithelium is squamous metaplasia, which has been detected by both impression cytology and IVCN without any significant differences. Although a morphological study of goblet cells did not yield consistent results, certain parameters related to MGD that could aid in the diagnosis and study of the disease have been detected with greater sensitivity and specificity with IVCN [66].

Advances in MGD Diagnosis

In addition to meibography and confocal microscopy for MGD diagnosis, recent developments in lipid layer interferometry have further expanded the armamentarium for MGD diagnosis. These include the LipiView® (TearScience Inc., Morrisville, NC, USA) and DR-1α® (Kowa, Nagoya, Japan). LipiView quantifies lipid layer thickness in the lower one-third of cornea, while the DR-1α assesses the lipid layer and evaluates the entire cornea, including the central region and tear film dynamics. In addition to facilitating MGD diagnosis, these devices help assess disease severity and create treatment plans for subjects with MGD [66].

Tear Film Biomarkers

Because inflammation lies at the root of DED pathogenesis, several studies have attempted to find a suitable biological marker that can be measured and quantified to aid in the diagnosis and/or prognosis of the disease. Proteins such as S100A8, S100A9, lipocalin, and α-1 antitrypsin have been observed in greater quantities in the tears of dry eye patients than those of controls. Increased expression of interleukins, protease inhibitors, and tumor necrosis factor-α has also been detected. It has also been found that matrix metalloproteinase-9 (MMP-9) found in ocular inflammation can cause DED. One study has established that certain chemokine levels are positively correlated with TBUT, basal tear secretion, goblet cell density, tear clearance rate, and keratoepitheliopathy score [64]. However, no consensus on the ideal biomarker has been reached.

Advances in dry eye treatment

Following a tear-film-oriented diagnosis, therapy to treat DED caters to the patient needs and is tear-film-oriented. The therapeutics already in use is outlined in Table 2 below.

Progress in research and development of new drugs has added to the arsenal against DED.

Advances in Therapeutics Targeting Meibomian Gland

Devices for warm compresses: While conventional warm compresses have been proven to be effective for the treatment of MGD by liquefying meibum and changing lipid layer composition, several modifications have been attempted. Some studies have suggested the addition of menthol to improve TBUT; however, the amount of improvement could not be clearly attributed to menthol. The wetness of warm compresses has also been debated, with Arita et al. theorizing that increased wetness leads to a cooling effect that can undermine the benefits of warm compresses. Other devices, such as MGDRx eye bags, EyeGenie masks, and Blephasteam, have also shown better results compared to conventional towel compresses. Their success has been attributed to their ability to maintain an appropriate warm temperature of the eyelids for a longer duration [71].

Table 2
Treatment options in use for DED.

DED: dry eye disease; MGD: meibomian gland dysfunction. Table credit: Author Nikita Dash.

Aqueous layer treatment	Mucin layer treatment	Anti-inflammatory
CMC 0.5% or 1%	Rebamipide	Cyclosporine A 0.05%
Sodium hyaluronate 0.1 or 0.3%	Diquafosol sodium 3%	Autologous serum drops
Diquafosol sodium 3%	-----	Preservative-free corticosteroids
Polyvinyl alcohol	-----	MGD treatment
Punctum plugs	-----	Omega-3 fatty acids

Thermal pulsation technique: LipiFlow™ (TearScience Inc., Morrisville, NC, USA) is a device that combines meibomian gland expression with heat in an in-office MGD treatment technique known as vector thermal pulse therapy. The device applies heat to the palpebral conjunctiva of the upper and lower eyelids, while providing pulsatile external pressure. Studies have shown that this device can alleviate symptoms for up to three years [66,71]. The MiBo Thermoflo (MiBo Medical Group, Dallas, TX, USA) also uses the same principle, but ultrasound energy is used for massaging. However, it does not raise the temperature to more than 40°, which is optimum for meibum liquefaction. Randomized trials are awaited in this regard [72,73].

Probing of meibomian gland: A novel technique of meibomian gland probing using a bevelled, 2 mm stainless steel probe into meibomian orifices was first described by Maskin in 2010. Patients reported immediate relief that lasted for four weeks. In 2018, post-probing meibography revealed the lengthening of shortened glands and the partial restoration of faded glands with the possibility of new gland growth [74,75]. Syed and Sutula described a new method using an operating microscope [76]. While the symptoms of MGD have been found to be relieved by both methods, they tend to reappear after an average of 38.2 weeks after initial treatment. Therefore, multiple sessions of probing are necessary for long-term success [71].

Intense pulsed light therapy: It helps to liquefy the meibum for easy expression, retard bacterial and parasitic growth on eyelids, induce thermolysis of telangiectatic vessels around the gland, and stimulate cell activity in meibomian glands that promotes wound healing [71]. Studies have shown that IPL treatment is effective against MGD-associated dry eye of varying severity, although at least three treatment sessions two to four weeks apart are required for desired results. It has recently been approved by the United States Food and Drug Administration for dry eye treatment. Topical and oral medications: Topical and oral azithromycin formulations have been effectively in use for the treatment of bacterial colonization and inflammatory processes associated with MGD. Research has shown that the differentiation of human meibomian gland epithelial cells (HMGECS) is induced by the cationic amphiphilic nature of azithromycin. Similarly, solithromycin, a newer macrolide, has been found to be more potent in

stimulating HMGECS; however, clinical trials are pending. Oral tetracyclines also show anti-inflammatory property owing to their bacteriostatic nature and ability to reduce MMP-9 on the corneal surface [71]. Other topical medications that have been studied include Manuka honey, lipid-containing eye drops, and perfluorohexyloctane eye drops, all of which have been shown to be effective as adjunctive therapy for MGD-related dry eye with few local side effects [71]. They act by improving meibum quality, gland expressivity, and alleviating the symptoms of blepharitis [71].

Other devices treating MGD: BlephEx™ and TearCare® System (Sight Sciences, Menlo Park, CA, USA) are two recently developed in-office treatment devices that aim to provide symptomatic relief against MGD. The BlephEx™ is a handheld device that spins a disposable, single-use medical-grade microspoon to remove debris from lashes and lids and helps in the treatment of blepharitis. Although Connor et al. demonstrated improvement in symptoms four weeks after treatment, a trial is yet to be conducted [77,78]. The TearCare® System (Sight Sciences, Menlo Park, CA, USA) places single-use, flexible iLid™ applicators over each tarsal plate, which deliver constant, regulated heat at 41-45°C over a 12-minute treatment time. This helps in meibum liquefaction and effective expression. A randomized controlled trial is awaited; however, manufacturer-sponsored trials have shown improvement in symptoms [78].

Newer Drugs and Potential Therapeutics

Lifitegrast: In July 2016, lifitegrast 5% became the second FDA-approved topical ocular anti-inflammatory medication for the treatment of DED. It blocks interactions between intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-1 (LFA-1), which are instrumental in T-cell activation and migration. The results of phase III clinical trials (OPUS 1-3) demonstrated improvement in both signs and symptoms of DED. Improved primary symptom outcome of change from baseline eye dryness score (EDS) within 14 days and effect sustained till study endpoint of 84 days. Further study is needed to determine which patients respond best to lifitegrast and whether concomitant use of lifitegrast with topical corticosteroids or cyclosporine can result in faster symptomatic relief [78,79].

Lacritin: Ocular-specific glycoproteins secreted primarily by acinar cells of the lacrimal gland increase basal tear secretion. Studies have shown that lacritin levels are significantly decreased in patients with Sjogren's syndrome as compared to healthy controls [80]. The efficacy of lacritin in humans was established in 2021, although dosing and duration of administration have yet to be finalized.

Lubricin: Lubricin (PRG4) is a mucin-like glycoprotein that is expressed by the normal ocular surface and suppressed by inflammatory cytokines. It reduces friction between the cornea and the conjunctiva and eyelid. With regard to symptomatic relief, research has shown that lubricin (150 mcg/mL) significantly outperformed sodium hyaluronate (0.18%) in moderately DEDs [81]. A phase-II trial was completed in the United States by Novartis. Thymosin β4: Thymosin β4 is a G-actin-binding protein that improves epithelial healing and downregulates pro-inflammatory cytokines. Sosne et al. first reported the use of topical thymosin β4 (RGN-259) for the treatment of DED [82]. In 2018, a head-to-head comparison of RGN-259 versus prescription agents including cyclosporine, lifitegrast, and diquafosol was done in a murine model. The RGN-259 drops performed comparably or better [83]. RGN-259 is currently the subject of a 700-patient phase 3 clinical trial in the United States and has demonstrated safety in the treatment of DED consistent with previous clinical trials [84].

Higher concentration cyclosporine: Eye drops with a higher concentration of cyclosporine (CsA) than Restasis® have been approved in Europe, Japan, and other countries. Phase II/III results, reported by Tauber et al., demonstrate an earlier onset of action in the 0.09% formulation with similar safety and tolerability profiles. A phase III clinical trial is currently underway for Seciera™ (Sun Pharma, Mumbai, India), which has a CsA concentration almost twice that of Restasis® (0.09% vs. 0.05%) [78,85].

Amniotic membrane extract eye drops: Amniotic membrane extract eye drops (AMEED) are proposed to have growth factors, cytokines, and collagens that promote corneal wound healing, inhibit fibroblast activity, and decrease inflammation on and within the ocular surface. A variety of products that are marketed for the treatment of DED are available without FDA regulations, and clinical trials are ongoing for use in patients with GVHD and post-PRK dry eye [86].

New Devices for DED

Thermosensitive collagen plugs: The thermosensitive atelocollagen punctal plug is initially liquid; when inserted from the punctum, it solidifies with the body temperature and the punctum is occluded. In order to maximize the effect of this thermosensitive atelocollagen punctal plug, a pre-heating method has been described where the plug is preheated to 41°C and injected in a somewhat stiffened state [87].

Modified moisture chamber spectacles: Modified moisture chamber spectacles have a cover integrated with the frame of the glasses and a tank for containing water to increase humidity around the eyes. Furthermore, ultrasonic moisture glasses can be used to actively control humidity [88,89].

Scleral lenses: The most well-known scleral lens used to treat ocular surface disease is the BostonSight® PROSE (Prosthetic Replacement of the Ocular Surface Ecosystem) lens (Boston Foundation for Sight, Needham, MA, USA), which can significantly improve dry eye signs and symptoms due to Stevens-Johnson syndrome, chronic GVHD, and even neurotrophic keratopathy following skull base tumor resection. Other innovations include the EyePrintPro™ lens, which converts an imprint of the ocular surface into a 3D digital model [78,90].

Tear neurostimulation: TrueTear® stimulates the intranasal nerve endings of the afferent nasolacrimal reflex pathway in the nasal mucosa with

small electric currents to increase tear production. Improvements in Schirmer scores were observed after using the device four times a day for 180 days. Common side effects include nasal discomfort, burning, pain, nosebleeds, transient electrical discomfort, nasal congestion, facial pain, and headaches. They are contraindicated in patients with implantable metallic or electronic devices and in those with a hypersensitivity to hydrogel that coats the device probes [91].

Antioxidants and Probiotics

Anthocyanin-rich berries and berry extracts are food supplements that have been used for the treatment of eye diseases based on the findings of animal and human studies. A recent trial concluded that the maqui berry has the maximum effect against reactive oxygen species in the lacrimal gland. Similarly, probiotics like *Enterococcus faecium* WB2000 have reportedly improved dry eye symptoms in human subjects and murine dry eye models [66].

Future Research

The potential for future research remains targeted at anti-inflammatory mechanisms for the treatment of DED. Proposed therapeutic targets include interleukin-20, corneal lymphangiogenesis, the PI3K/AKT signaling pathway, and microRNA-328 [92-95]. Newer drugs, such as IL-1 receptor antagonists, serine protease inhibitors, resolvins analogues, and integrin antagonists, are under research [96]. The therapeutic role of pituitary adenylate cyclase-activating polypeptide

is also being explored, and drug delivery systems, such as liposomal rebamipide, are being considered [97,98].

Conclusions

Despite being a very common clinical problem, several aspects of DED are poorly understood and require further research. The role of environmental conditions needs to be studied in depth for a better understanding of the disease pathophysiology and its significance in inciting the inflammatory processes that result in dry eye. Future research could also include the role of the genetic profile of an individual in the causation of DED. With the advent of artificial intelligence, there is a probability to screen DED using algorithms in the future. With newer imaging modalities and interesting research in the pipeline, it remains to be seen what more can be done for DED patients.

Notes

The authors have declared that no competing interests exist.

Author Contributions

Nikita Dash:

- **Concept and design**
- **Drafting of the manuscript**

Deepak Choudhury:

- **Acquisition, analysis, or interpretation of data**
- **Critical review of the manuscript for important intellectual content**
- **Supervision**

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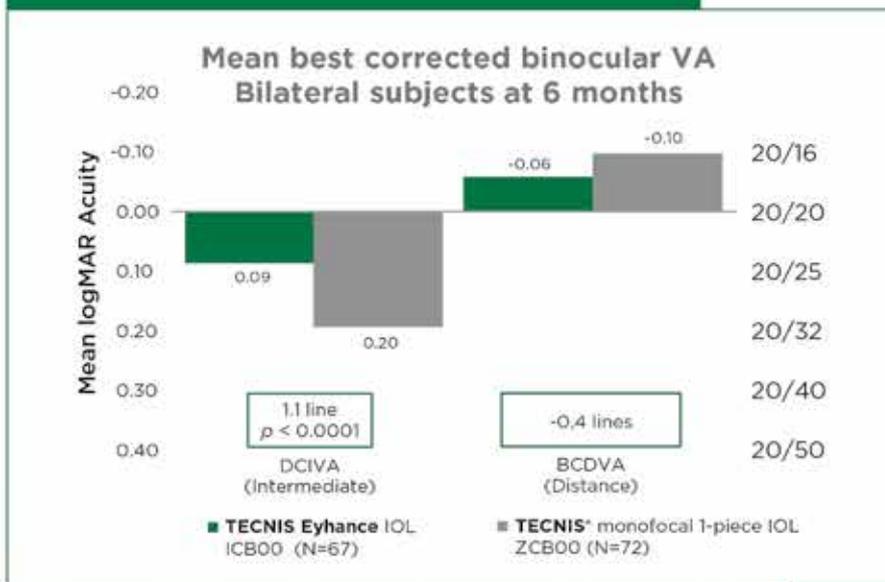
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What's in the news?

Exploring the relationship between oxidative stress status and inflammatory markers during primary Sjögren's syndrome: A new approach for patient monitoring

Primary Sjögren's syndrome (pSS) is a chronic inflammatory disease primarily affects exocrine glands dysfunction. Oxidative stress (OS) is a phenomenon occurring because of an imbalance between the generation of free radicals and antioxidant defence system. Hence, we aimed to establish the status of OS and inflammatory response according to the pSS disease activity index. In this context, the authors investigated malondialdehyde (MDA), and antioxidant enzymes during pSS. The possible association between MDA and nitric oxide (NO) levels and between MDA and some pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α , and IL-33).

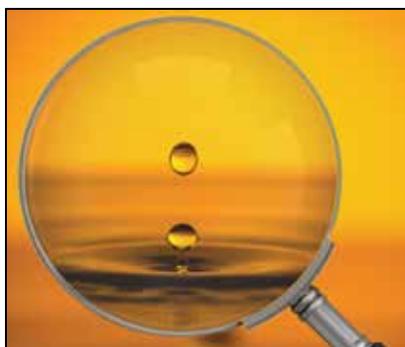
The study has been conducted on 53 pSS patients. The antioxidant enzymes, represented by glutathione peroxidase (GSH-Px), catalase (CAT) and superoxide dismutase (SOD), were estimated by a colorimetric activity kit.

Whereas, MDA value was assessed by measuring thiobarbituric acid reactive substances. Moreover, pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α , and IL-33) and NO were respectively quantified by enzyme-linked immunosorbent assays (ELISA) and the modified Griess.

Interestingly, they report a notable reduction in our pSS patients' antioxidant enzyme activity, while NO, MDA and proinflammatory cytokines

values were significantly increased. pSS patients with higher disease activity had much stronger increases in NO and MDA levels. No significant difference was assessed in CRP level. Additionally, substantial significant correlations between plasmatic NO and MDA levels and between MDA, NO and IL-1 β , IL-6, TNF- α cytokines were reported. However, no significant association was found between NO, MDA and IL-33 concentrations.

The authors concluded collectively; their data showed altered oxidant-antioxidant balance in pSS patients. MDA, NO, IL-1 β , IL-6, TNF- α seem to be good indicators in monitoring disease activity. Oxidative stress was closely related to inflammation in pSS. Exploiting this relationship might provide valuable indicators in the follow-up and prognosis of pSS with a potential therapeutic value.



Authors: Sarah Benchabane , Souad Sour , Sourour Zidi , Zohra Hadjimi , Lyazidi Nabila , Dahbia Acheli , Amel Bouzenad, Houda Belguendouz , Chafia Touil-Boukoffa

Publication: : Int J Immunopathol Pharmacol. 2024 Jan-Dec;38:3946320241263034.doi: 10.1177/03946320241263034

Obesity, body fat distribution and eye diseases

The prevalence of obesity, a chronic disease, is increasing, and obesity is now considered a global epidemic. Eye diseases are also increasing worldwide and have serious repercussions on quality of life as well as increasingly high costs for the community. The relationships between obesity and ocular pathologies are not yet well clarified and are not pathologically homogeneous: they seem to be somehow linked to excess body fat, especially to the distribution of adipose tissue and its ectopic deposits.

Our objective was to examine the associations between obesity and anthropometric indices, including body mass index (BMI), waist circumference (WC), and the waist/hip ratio (WHR), and the risk of most widespread eye

diseases, with particular attention given to the most significant metabolic mechanisms.

This article provides a narrative overview of the effect of obesity and anthropometric measurements of body fat on prevalent eye diseases. We used the MEDLINE/PubMed, CINAHL, EMBASE, and Cochrane Library databases from 1984 to 2024. In addition, we hand-searched references from the retrieved articles and explored a number of related websites. A total of 153 publications were considered.

Results: There is significant evidence that obesity is associated with several eye diseases. Waist circumference (WC) and the waist/hip ratio (WHR) have been

observed to have stronger positive associations with eye diseases than BMI.

Conclusions: Obesity must be considered a significant risk factor for eye diseases; hence, a multidisciplinary and multidimensional approach to treating obesity, which also affects ocular health, is important. In the prevention and treatment of eye diseases related to obesity, lifestyle factors, especially diet and physical activity, as well as weight changes, both weight loss and weight gain, should not be overlooked.



Authors: Francesca Bosello , Angiola Vanzo , Chiara Zaffalon , Luca Polinelli , Filippo Saggin , Erika Bonacci , Emilio Pedrotti , Giorgio Marchini , Ottavio Bosello

Publication: [t Disord](#). 2024 May 6;29(1):33.doi: 10.1007/s40519-024-01662-8.

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Descemet Membrane Endothelial Keratoplasty: A Short Report of Surgical and Visual Outcomes at a District General Hospital in the United Kingdom

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Introduction

An intact cornea provides a refractive power for high quality vision; corneal diseases are thus a major cause of visual impairment and blindness worldwide.¹ In the United Kingdom, approximately 2500 corneal transplantations are undertaken each year, with a variety of indications and techniques.² Penetrating keratoplasty (PK) and Descemet membrane endothelial keratoplasty (DMEK) are two such techniques.

PK is a full-thickness corneal resection and transplantation, which enables treatment of disease in the epithelial, stromal, and endothelial layers. Full-thickness grafting also prevents stromal interface issues between donor and recipient tissues. However, shortfalls of PK include long post-operative recovery time and a higher chance of considerable refractive error due to graft astigmatism requiring contact lenses.³

DMEK is a new alternative to PK as a corneal transplantation technique for corneal endothelial diseases such as Fuchs' endothelial dystrophy (FED) and bullous keratopathy (BK). DMEK is a partial-thickness posterior endothelial corneal graft which involves transplantation of the Descemet membrane and endothelium without stromal tissue, thereby avoiding degradation at the donor-recipient interface. The procedure is surgically challenging and involves difficulties in donor preparation, although the majority of comparative studies between DMEK and PK have found rapid visual rehabilitation following the procedure, lower rejection rate, fewer complications, and better visual outcomes.

Corneal endothelial transplantation guidance, published June 2009 by the National Institute for Health and Care Excellence (NICE), sets out a number of standards for outcomes in endothelial keratoplasty (EK).⁴ A randomised controlled trial of thirteen EK-treated eyes reported an improvement in mean uncorrected visual acuity (UCVA) of 0.21 LogMAR from 0.81 to 0.60 at 6-months follow-up. Regarding surgical outcomes, adverse events reported in the literature included graft dislocation, graft failure, and interface opacity. Studies reported total detachment requiring repeat operation rates of 2.0% to 8.5%. The interventional guidance committee noted that as techniques and experience for this procedure evolve, thorough data collection is required to allow ongoing review of outcomes. In this clinical audit, outcomes of patients who underwent DMEK at the Royal Shrewsbury Hospital (RSH) were compared to an external standard selected for its comparable size, cohort, and outcomes; a retrospective case series of patients who had DMEK at a Tertiary Eye Hospital (TEH) - Moorfield's Eye Hospital between 2013 and 2014.⁵

Aims

The aim of this clinical audit was to assess the early surgical and visual outcomes of patients who underwent DMEK at the RSH between August 2020 and July 2021 compared to a retrospective case series of DMEK-treated patients at the TEH between July 2013 and August 2014.

Materials and methods

13 patients who underwent DMEK were included. DMEK alone, as well as triple procedure (keratoplasty combined with phacoemulsification/extracapsular-cataract-extraction followed by intraocular lens (IOL) implantation for coexistent cataract) were included. All surgeries were performed by two experienced surgeons (TJ and EC) with comparable techniques between August 2020 and July 2021 at the Ophthalmology Department of the Royal Shrewsbury Hospital, Shrewsbury and Telford Hospitals NHS Trust, United Kingdom.

Demographic information obtained from medical records included age, gender, and clinical indication. Main outcomes were intra-operative and post-operative complications, baseline best-corrected visual acuity (BCVA), post-operative BCVA, and three months post-operative BCVA. Values are given as mean \pm standard deviation (LogMAR).

Surgical success was evaluated by comparing short-term complications including partial Descemet membrane detachment requiring air re-injection into the anterior chamber (rebubbling), total detachment requiring repeat operation, and primary graft failure. Functional success was measured by comparing visual outcomes in patients including pre-operative BCVA, post-operative BCVA, and three months post-operative BCVA. Surgical and visual outcomes were extracted from the TEH's DMEK case series for comparison to this study, which included 14 DMEK-treated patients by a single surgeon between July 2013 and August 2014.

Ethical approval

No ethical approval was required for this original brief report.

Results

Patient characteristics

A total of 13 patients who underwent DMEK surgeries between August 2020 and July 2021 with sufficient follow-up information were included in the audit for further analysis. Mean age was 70.2 ± 6.7 years (60 to 86). 9/13 (69.2%) were female and 4/13 (30.8%) were male subjects. The main indication for DMEK was 10/13 (76.9%) patients who had

FED. In comparison, the 2013-2014 TEH's study included 14 DMEK-treated patients, with a mean age of 66 (49 to 80). 8/14 (57.1%) were female and 6/14 (42.9%) were male. The clinical indication for all subjects was FED.

Table 1. Patient characteristics and aetiological distribution for DMEK-treated eyes at the RSH (2020 – 2021).

Total patients	13
Mean age ± SD (range)	70.2 ± 6.7 years (60 to 86)
Gender	9/13 (69.2%) F, 4/13 (30.8%) M
Fuchs' endothelial dystrophy (FED)	10/13 (76.9%)
Other	3/13 (23.1%)

Surgical outcomes

At the TEH's, partial Descemet membrane requiring rebubbling occurred in 5/14 (35.7%) of cases. There was 1/14 (7.1%) instance of total detachment requiring repeat operation, which occurred due to displacement of the bubble through a superior iris defect into the posterior segment within an hour of the DMEK procedure. Primary graft failure occurred in 1/14 (7.1%) case due to insertion of the graft into the anterior chamber complicated by raised IOP which occurred in 1/14 (7.1%) case in total. There were no cases of corneal oedema, corneal endothelial pigments, or anterior scarring after surgery.

In contrast, at the RSH, partial Descemet membrane detachment requiring rebubbling occurred in 1/13 (7.7%) eye which underwent inferior detachment. There were no instances of total detachment requiring repeat operation. Primary graft failure also did not occur. Other complications included 3/13 (23.1%) eyes with corneal oedema following surgery, 2/13 (15.4%) cases of corneal endothelial pigment on grafts, 1/13 (8.0%) instance of anterior scarring, and 1/13 (7.7%) case of raised intraocular pressure (IOP) requiring corneal paracentesis. Overall, there was a reduction in incidence of serious complications such as partial detachment (35.7% to 7.7%), total detachment (7.1% to 0.0%), and primary graft failure (7.1% to 0%) when comparing 2013/14 outcomes to 2020/2021.

Visual outcomes

At the TEH, seven patients were included in the visual analysis. Mean pre-operative BCVA was 0.30 (0.20 to 0.50). Mean BCVA at 3 months post-operatively was -0.03 (-0.20 to 0.20). Mean difference in BCVA between pre-operative assessment and at 3 months post-DMEK was an improvement of 0.33. In patients who underwent DMEK at the RSH (2020 – 2021), mean pre-operative BCVA was 0.79 ± 0.58 (0.00 to 1.78). Mean post-operative BCVA was 0.79 ± 0.62 (0.00 to 2.30), and mean BCVA at 3 months post-operatively was 0.39 ± 0.22 (0.00 to 0.78). Mean difference in BCVA between pre-operative assessment and at 3 months post-DMEK was an improvement of 0.40. Overall, although the TEH case series had a better pre-operative (0.30, 0.79) and post-operative (-0.03, 0.39) BCVA, there was a greater mean improvement in visual acuity in patients who underwent DMEK at the RSH (2020 – 2021) compared to TEH (2013 – 2014) (0.33 to 0.40).

Figure 2a. Mean BCVA (LogMAR) pre-op and 3 months post-op.

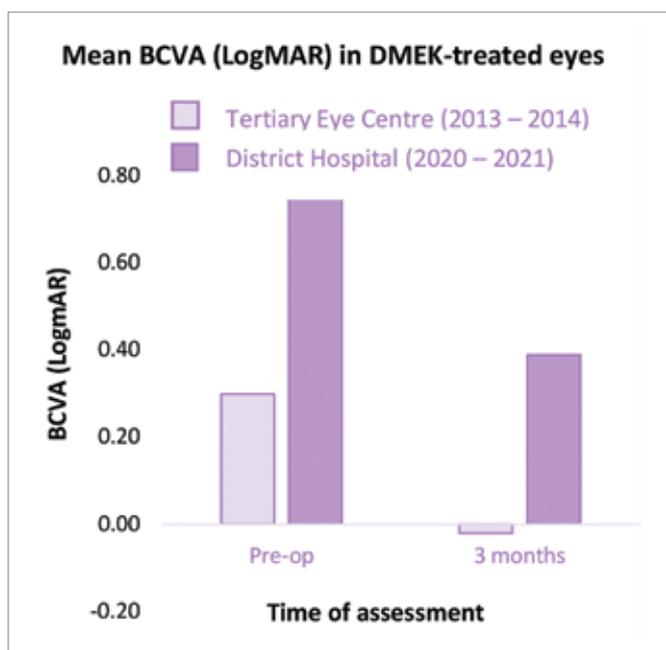


Figure 1. Incidence (%) of DMEK complications at the RSH (2020 – 2021).

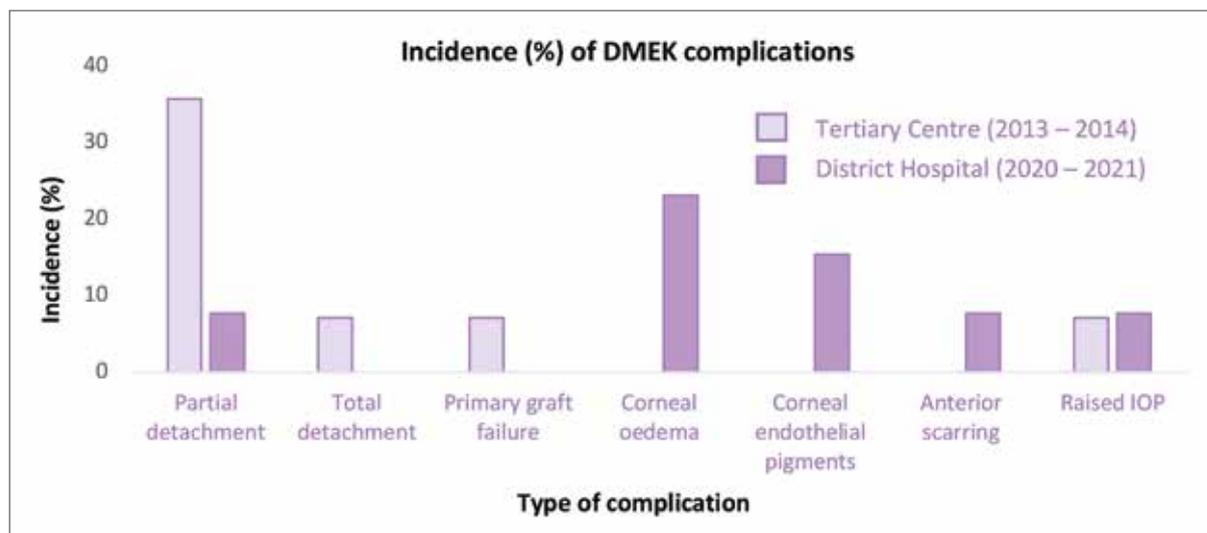
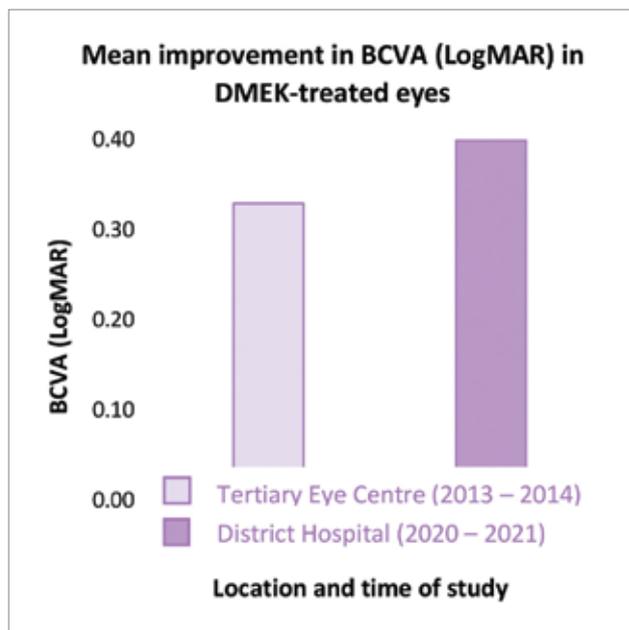


Figure 2b.
Mean improvement in BCVA (LogMAR) at the RSH (2020 – 2021).



Discussion

DMEK is a corneal transplantation technique involving a partial-thickness posterior endothelial corneal graft. As noted by the corneal endothelial transplantation guidance set out by NICE, as techniques and experience for this procedure evolve, thorough data collection is required to allow ongoing review of outcomes. Thus, the aim of this clinical audit was to assess the early surgical and visual outcomes of patients who underwent DMEK at the RSH between 2020 and 2021 compared to a retrospective case series of DMEK-treated patients at the TEH between 2013 and 2014. A retrospective review of 13 patients who underwent DMEK by two surgeons was carried out, and compared to the external standard.⁵ Outcomes included demographic information, surgical outcomes, and visual outcomes at a 3 months follow-up.

The results of this audit have shown a reduced incidence of serious complications and a greater mean improvement in visual acuity when comparing the RSH (2020 – 2021) to TEH (2013 – 2014). Overall, there was a reduction in incidence of serious complications including partial detachment (35.7% to 7.7%), total detachment (7.1% to 0.0%), and primary graft failure (7.1% to 0%). Mean improvement in visual acuity in DMEK-treated eyes increased from 0.33 in 2013/14 to 0.40 in 2020/21. The NICE interventional guidance⁴ set out a standard of improvement in mean UCVA of 0.21 at 6-months follow-up, and a total detachment rate of 2.0% to 8.5%. Although not directly comparable due to differences in VA measurement and timescale, both the TEH and this RSH study exceeded this improvement in VA over a 3 months follow-up. Additionally, the 2020/21 review found a total detachment rate better than that set out by NICE (0.0% compared to 2.0% - 8.5%).

In 2013/14, one case of total detachment requiring repeat operation occurred due to displacement of the bubble through a superior iris defect into the posterior segment. Primary graft failure occurred in one case due to insertion of the graft into the anterior chamber complicated by raised IOP. There were no cases of corneal oedema, corneal endothelial pigments, or anterior scarring reported at the TEH. At the RSH, however, 3/13 (23.1%) eyes had corneal oedema following surgery, 2/13 (15.4%) cases of corneal endothelial pigment on grafts, 1/13 (8.0%) instance of anterior scarring, and 1/13 (7.7%) case of raised intraocular pressure (IOP) requiring corneal paracentesis. The TEH case series had a better pre-operative (0.30, 0.79) and post-operative (-0.03, 0.39) BCVA, although a greater mean improvement in visual acuity was seen in 2020/21.

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Dry Eye and Menopause

by **Nikolina Budimlija**. Consultant Ophthalmologist, Oculoplastic surgeon, Institute of Eye Surgery Ireland.

Dry eye disease (DED) is a disorder with multifactorial aetiology, and endocrine anomalies are one of the inciting factors. The endocrine anomalies that cause DED include physiological conditions such as menopause, menstrual cycle variations, pathologies such as polycystic ovarian syndrome, androgen resistance, iatrogenic conditions such as contraceptive use, and antiandrogen treatment.

Menopause represents the end of a woman's reproductive years and generally occurs when women are in their late 40s or early 50s. Many hormonal changes occur during this time. As a result, women undergoing menopause stop having periods for at least 12 months. However, these hormonal changes can also affect other areas of the body— including the eyes.

The ovaries produce two major female hormones: estrogen and progesterone. As a woman enters menopause, the ovarian production of these hormones declines and fluctuates until it eventually stops. In postmenopausal women, the ovaries produce significant amounts of androgens for many years after the menopause.

Androgens

Androgens are quantitatively the predominant sex steroid in women. Plasma levels are measured in micromolar and nanomolar levels compared with picomolar levels of estrogens. The major circulating androgens in descending order of concentration are; dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione (ANDR), testosterone (T) and dihydrotestosterone (DHT). ANDR and T are produced by both the adrenal gland and the ovary and the ovarian production is regulated by luteinizing hormone (LH). In normal healthy women with intact ovaries, all androgens, including DHEAS,

DHEA, ANDR and total and free T decline with age. The decline is steepest in the early reproductive years and levels out in midlife.

Androgens stimulate the genes involved in the production, transport, and secretion of lipids in the meibomian gland⁴. Androgen deficiency has been pointed out as an important etiological factor in the pathogenesis of evaporative dry eye in women with Sjogren's syndrome.⁵

Testosterone regulates the expression of several genes in the lacrimal gland including those involved in cell growth, proliferation, metabolism, cell communication and transport, nucleic acid binding, signal transduction, and receptor activities. Testosterone provides trophic support to lacrimal glands and increases lacrimal glands' tissue growth and activity. In a study by Sullivan and Hann, androgens were demonstrated to increase the lacrimal gland production and secretion of IgA.⁶

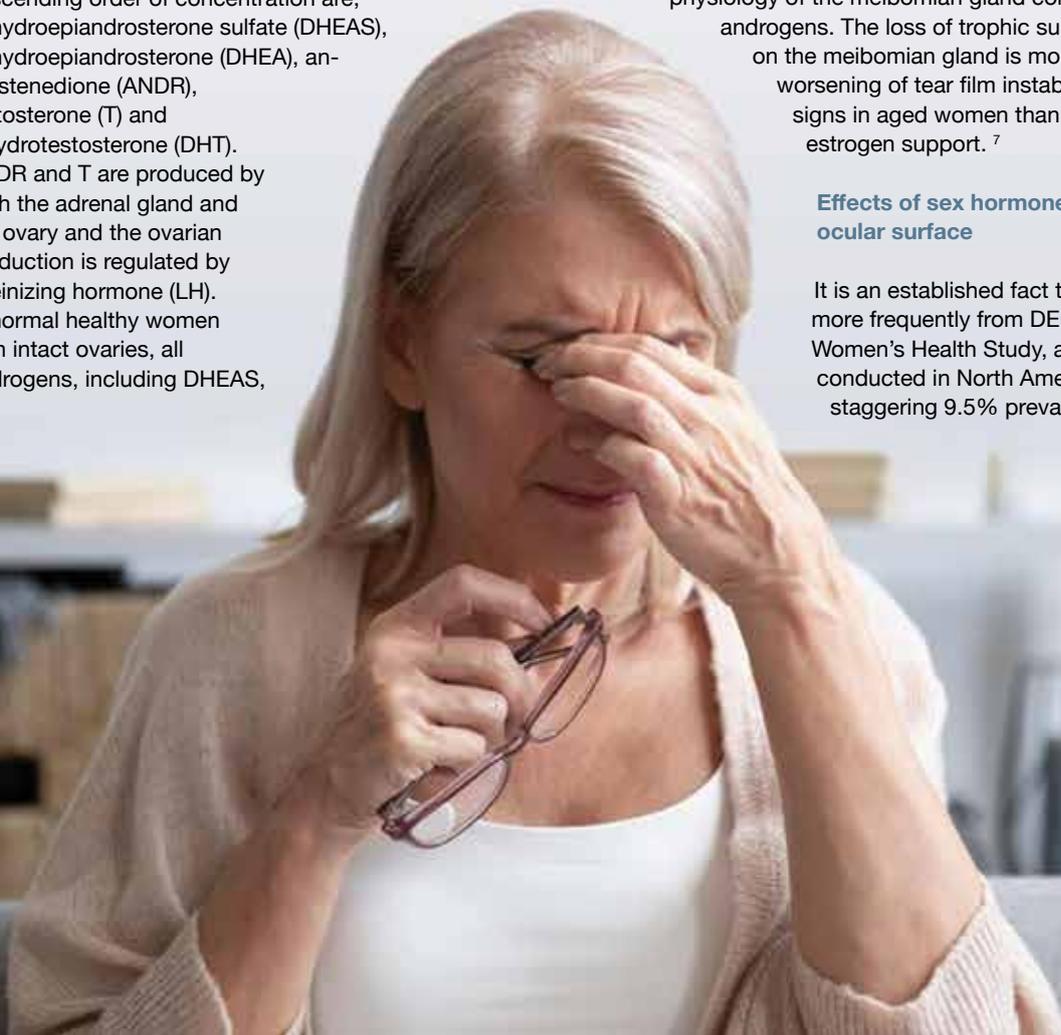
Estrogen and Progesterone

Estrogen and progesterone receptors are present in various ocular surface structures including the cornea, conjunctiva, meibomian gland, and lacrimal gland, and many ocular surface structures. Hence, it can regulate key cellular events on the ocular surface.

Estrogens appear to have antagonizing effects on the physiology of the meibomian gland compared to androgens. The loss of trophic support of androgens on the meibomian gland is more critical to the worsening of tear film instability and other DED signs in aged women than the reduced estrogen support.⁷

Effects of sex hormones on the ocular surface

It is an established fact that women suffer more frequently from DED than men.¹ Women's Health Study, a large health survey conducted in North America, reported a staggering 9.5% prevalence of DED in



women aged more than 75 years. ² The same study group (Schaumberg et al.) assessed the prevalence of DED in men with a similar methodology and reported a 70% higher prevalence of DED among women compared to men in the 50 years and older age group ³

The ocular surface shows cyclical changes in its structure and function that mirror the cyclical variations in the circulating estrogen and progesterone hormone levels. The cornea shows variations in thickness, biomechanical strength, and sensitivity during different phases of the menstrual cycle. The cornea is thinnest at the beginning of the cycle and becomes thicker toward the end of the cycle. ⁸

Estrogens were suggested to upregulate pro-inflammatory cytokines including MMP9 in human corneal epithelial cells. ⁹ Although the role of estrogen in relation to the ocular surface appears controversial, the hypothesis has recently been advanced that during menopause, evaporative DED is not so much due to the reduction in estrogen, but rather to the reduction in androgens ¹⁰.

Unlike estrogens, androgens promote the activity of the meibomian glands, stimulating the lipogenesis and maturation of acinar cells and have an anti-inflammatory role, favoring the synthesis of TGF- β and inhibiting that of interleukin-1 β and TNF- α . On a clinical level, in fact, there is an alteration in the functioning of the meibomian glands and an increase in the risk of DED in all cases in which there is a reduction in circulating androgens, a dysfunction or insensitivity of the androgen receptors, or anti-androgen therapy ¹¹



Menopause is a physiological change not just the endocrine system but the entire human body itself. There are three pertinent changes in a systemic endocrine milieu that should be kept in mind when we try to understand the concept of DED in postmenopausal women. There is aging-associated decrease in androgen levels in these women, along with a reduction in circulating estrogen levels and possible reduction in the ocular surface synthesis of estrogen from its precursors (intracrine pathways). As mentioned earlier, DED is more prevalent in postmenopausal women compared to men of similar age. Endogenous estrogen levels are critical in the maintenance of ocular surface homeostasis in postmenopausal women. But the existing reports showed conflicting results, few authors suggested low estradiol levels

correlated with severe dry eye, while others suggested higher concentrations of estradiol were predictive of worse meibomian quality.

Lifestyle modifications for managing dry eyes during menopause

- Avoiding irritants: air conditioning, allergies, wind, contact lens overuse
- Replace makeup every 2 months and use optocosmetics, only eye makeup developed by ophthalmologists for dry and sensitive eyes (Eyes Are The Story)
- Reduce screen time
- Blink more
- Diet: Omega-3 fatty acids found in fish oil and flaxseed oil, Vitamin D, high quality proteins, low fat dairy products, phytoestrogens
- Lubricant drops and ointments

Hormone replacement therapy treatment

The clinical effects of estrogen and progesterone replacement therapy in women are complex and depend on the age, pre-treatment sex hormone levels, ovarian physiology, and the mode of treatment. The influence of hormone replacement therapy in menopausal women remains unclear, as some authors support the idea that it improves

the quality and the volume of the tear film, whereas others have shown that it increases the risk of dry eye. Health surveys with large sample cohorts and smaller clinical studies demonstrated that SHRT in postmenopausal women increased the prevalence of DED. ¹²

The effect of estrogen replacement on the lacrimal gland is controversial as well. Few reports show restoration of lacrimal gland morphology and activity, ¹³ while Data from the Women's Health Study suggests a 69-percent increased risk of dry eye associated with post-meno-pausal estrogen therapy and a 29-percent higher risk for women taking estrogen plus progesterone therapy. ¹²

There is a need for increased collaboration between

ophthalmologists, who treat dry eye and gynecologists, who treat menopause. With improved communication and joint management, we can provide better care for menopausal patients with dry eye.

Potential innovations in the treatment of menopause-related dry eyes

Topical application of DHEA (precursor of testosterone) improves the TBUT through stimulatory and trophic effects on the production and secretion of lipids by the meibomian gland. Topical androgen therapy in the form of testosterone eye drops is shown to improve tear film stability. ¹⁴

In contradiction to the clinical effects of systemic replacement, topical estrogen therapy improves dry eye symptoms, Schirmer test, and TBUT values.¹⁵

There are still many promising areas of research to find better treatments for dry eye during menopause by exploring alternate routes like oral pills or skin patches.



Conclusion

Alteration of sex hormones plays an important role in the pathophysiology of DED in perimenopausal and menopausal age group. DED remains very underrecognized in this group. Often, simple measures such as lubrication may provide relief. In more severe cases, anti-inflammatory, immunomodulatory, and rarely surgical interventions are required. Novel hormonal replacement treatments, both systemic and topical, are also evolving.

It is important for all healthcare providers to understand DED to recognize, treat, and seek ophthalmologic intervention where applicable but also educating menopausal women about dry eye changes empowers them to seek treatment and improve eye health.

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