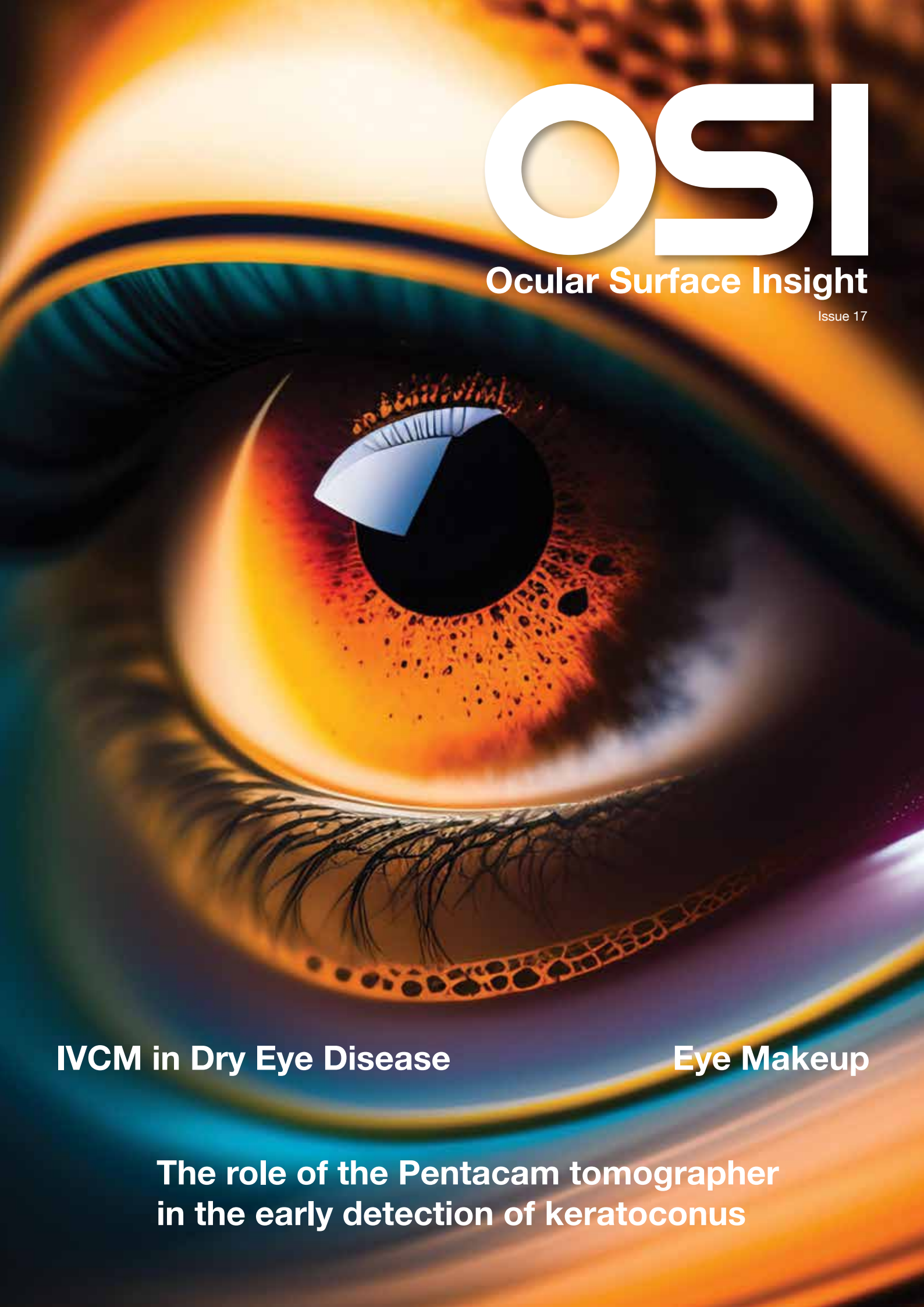

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Ocular Surface Insight

Issue 17

IVCM in Dry Eye Disease

Eye Makeup

The role of the Pentacam tomographer in the early detection of keratoconus

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Ocular Surface Insight

"There are two ways of spreading light: to be the candle or the mirror that reflects it."

Edith Wharton

Welcome to the Winter issue of the OSI Magazine

It is with deep sadness that we learned of the passing of Professor Michael O'Keeffe on January 25th, 2023. Michael was a founding editor of OSI magazine and Symposium, and we all benefited from his kindness both professionally and personally.

In honor of his contributions, OSI will dedicate an annual Professor Michael O'Keeffe lecture and an annual academic Professor Michael O'Keeffe award. Details of these events will be announced at the upcoming Dry Eye Masterclass & Symposium.

As we gear up for the next OSI Symposium & Dry Eye Masterclass, we're thrilled to announce an exceptional lineup of experts who will be sharing their cutting-edge approaches and technologies to enhance the patient experience. With seven interactive workshops led by clinicians and industry experts, this meeting is an invaluable opportunity for ophthalmologists, optometrists, and trainees alike. Be sure to check out the full program on page 20. Join us on March 24-25, 2023, at the Copthorne Tara in Kensington, London, for an unforgettable event.

In this issue, we have several incredible articles that are sure to pique your interest. Colm and Phillip take a deep dive into the PENTACAM's capabilities for early detection of Keratoconus, while Ankur and his colleagues explore In-vivo confocal microscopy's potential in treating severe cases of dry eye disease.

Brian Tompkins has contributed an important reminder of eye-makeup's potential harming effect on the ocular surface. However, there is a growing interest in the industry to put this right and remove harmful ingredients.

Samer Hamada

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We stand with Ukraine!

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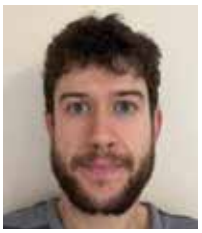

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Editorial Panel:

Contents

What's in the news?

The work-related burden of dry eye

This study set out to investigate the relationship between dry eye disease (DED) and work functioning, unemployment, absenteeism, and worry about job loss.

DED and unemployment, absenteeism, and 'worry about job loss' were assessed in 71,067 subjects (18-65 years, 60% female) from the Dutch population-based Lifelines cohort using the Women's Health study questionnaire and single-item questions, respectively. Work functioning was assessed in 32,475 participants using the Work role functioning questionnaire 2.0. The relationships between DED and work measures were assessed with logistic regression models, corrected for age, sex, BMI, income, educational level, smoking, and 48 comorbidities.

8.3% of participants had DED and had more impaired work functioning compared to those without DED (49.2% vs 41.1%, OR 1.21, 95% CI 1.10-1.32, corrected for demographics, smoking and 48 comorbidities). DED carried a similar risk of impaired work functioning as rheumatoid arthritis. For participants with highly symptomatic dry eye impaired work functioning was even higher (59.1%) and similar to that of depression. The impaired work functioning seen with increasing symptoms were greater in undiagnosed subjects versus diagnosed subjects (P = 0.03). After correction for comorbidities, DED remained tied to absenteeism and increased worry about job loss, but not unemployment.

The authors concluded that DED was linked to impaired work functioning and absence, but not unemployment. DEDs impact on work functioning is comparable to that of other severe chronic disorders, and undiagnosed subjects may be more affected. This highlights the importance of recognizing DED as a severe disorder and of screening for dry eye in the workplace to aid with diagnosis and treatment.

Authors: Mathias Kaurstad Morthen, Morten Schjerven Magno, Tor Paaske Utheim, Christopher J Hammond, Jelle Vehof.
Publication: Ocul Surf. 2023 Jan 21;28:30-36. doi: 10.1016/j.jtos.2023.01.006.

Bilberry-containing supplements on severe dry eye disease in young and middle-aged adults: A 3-month pilot analysis

The purpose of this study was to explore the effect of bilberry and fish oil combination supplement on a small clinical sample patient-base with severe dry eyes.

Twenty-four subjects were recruited with twelve randomly assigned to the intervention and control groups, respectively. Inclusion criteria included severe dry eye symptoms determined by scores >33 from the Ocular Surface Disease Index (OSDI) questionnaire. The intervention group was instructed to take an oral supplement with key ingredients of 600 mg bilberry extract and 240 mg docosahexaenoic acid-refined fish oil once daily for 3 months. The control group did not take any supplements. Mean changes in OSDI score, non-invasive tear break-up time (NITBUT), phenol red thread test (PRT), and percentage of meibomian gland openings were used as outcome measures. Testing was done at baseline, 1-month, and 3-month follow-up. Comparison between the treatment and control groups, and the younger adult and middle-age groups were performed.

The mean baseline values for the treatment and control groups were not clinically different. The OSDI score, NITBUT, PRT, and percentage of meibomian gland openings improved after taking the supplements for 3 months. The OSDI score, NITBUT, and PRT showed clinical improvements between the intervention and control groups. These improvements were consistent between the two age groups.

This study suggested preliminary improvements in signs and symptoms of severe dry eyes that were independent of age after taking dietary supplementation of bilberry extract and fish oil for 3 months. Further studies using more device-based measures and a placebo supplement are warranted.

Authors: Wing Y Yu, Lily Y L Chan, Aden Chung , Paul H Lee, George C Woo.
Publication: Front Nutr. 2023 Jan 19;10:1061818. doi: 10.3389/fnut.2023.1061818.

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What's in the news?

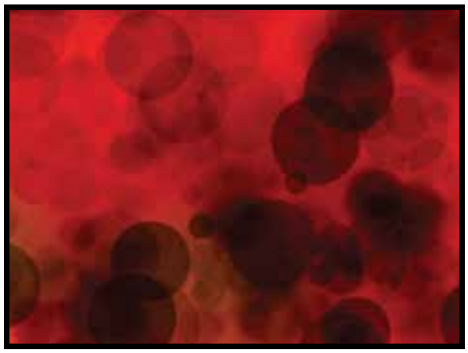
Beneficial Effects of Plasma Rich in Growth Factors (PRGF) Versus Autologous Serum and Topical Insulin in Ocular Surface Cells

In the last few decades, several blood derived products such as platelet-rich plasma (PRP), plasma rich in growth factors (PRGF) and autologous serum (AS) have been used for the treatment of ocular surface disorders. Recently, insulin has been proposed to be used as an alternative for the treatment of ocular surface diseases. The aim of this study was to evaluate the biological potential of PRGF eye drops in comparison with AS and insulin on ocular surface cells.

Blood from three healthy young donors was collected to obtain autologous serum (AS) eye drops and plasma rich in growth factors (PRGF) eye drops. Insulin (Actrapid®) was diluted at 1 and 0.2 IU/mL. The biological potential of PRGF, AS and insulin was assessed by proliferation in HCE, HK and HConF cells. Wound healing assay was performed in HCE cells after incubation with the different treatments. HConF and HK cells were differentiated to myofibroblast after treatment with 2.5 ng/mL of TGF-β1 and then incubated with all treatments.

PRGF eye drops induced significantly higher proliferation rate compared to AS or insulin in HConF and HK cells, but not in HCE cells. In addition, the percentage of wound healing area was significantly reduced after PRGF treatment in comparison with AS or insulin treatment. Furthermore, PRGF significantly reduced the number of myo-differentiated cells compared to AS and insulin at both concentrations analysed.

The results obtained in the present study show that PRGF increases the biological



activity of the ocular surface cells and reduces the expression of fibrosis marker compared to insulin or AS.

The present study suggests that plasma rich in growth factors eye drops are a more effective therapy than insulin and autologous serum eye drops for the treatment of ocular surface diseases.

Authors: Eduardo Anitua, María de la Fuente, Ronald M Sánchez-Ávila, Borja de la Sen-Corcuera, Jesús Merayo-Lloves, Francisco Muruzábal.
Publication: Curr Eye Res. 2023 Feb 7;1-9.doi: 10.1080/02713683.2023.2173237.

The effect of non-ablative thermomechanical skin treatment (Tixel®) on dry eye disease: A prospective two centre open-label trial

The purpose of this trial was to determine the effects of a thermo-mechanical action-based peri-orbital fractional skin treatment (Tixel®) on dry eye disease.

This prospective, controlled, open labelled study was conducted at two study centres: Midland Eye, Solihull, UK, and Vallmedic Vision, Andorra. Participants were screened at the baseline visit (visit-1), received three Tixel® treatments at 2-weeks intervals including further assessment (visits 2, 3 and 4). Participants were followed up for three months post-treatment (visit 5). Vision, intraocular pressure (IOP), dry eye symptomatology was assessed, including the Ocular Surface Disease Index (OSDI) questionnaire, non-invasive tear break-up time (NIBUT) and tear osmolarity as well as detailed ophthalmic assessments.

Seventy-four participants (41 in Birmingham and 33 in Andorra) with periorbital wrinkles and moderate to severe dry eye disease (DED) were enrolled. The mean age was 59.3 ± 13.3 years and 57 were females. No adverse events, no change in vision ($p = 0.310$) or IOP ($p = 0.419$) were observed. Tixel treatment was associated with clinically and statistically significant improvement in the DED symptoms, which was supported by a reduction of 21.40 ± 15.08 ($P < 0.001$) of the OSDI index. Non-invasive tear break-up time improved by 2.10 ± 0.91 s ($p < 0.001$) in the Birmingham cohort and 6.60 ± 2.13 s ($p < 0.001$) in the Andorra cohort. Tear osmolarity reduced from 299.8 ±

13.3 mOsm/L to 298.8 ± 15.6 mOsm/L following the Tixel treatment ($p = 0.271$).

The authors concluded that the thermo-mechanical action-based peri-orbital fractional skin treatment Tixel® could be an attractive, safe, and effective treatment for DED. This treatment is associated with high clinical and statistically significant improvement in DED signs and symptoms with no adverse events.

Authors: Sunil Shah , Debarun Dutta , Ankur Barua , Ludger Hanneken , Shehzad A Naroo.
Publication: Cont Lens Anterior Eye. 2023 Jan 10;101811.doi: 10.1016 /j.clae.2022.101811.

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Netildex® (netilmicin 3mg/ml + dexamethasone 1mg/ml) eye drops Prescribing Information. Consult summary of product characteristics (SPC) before prescribing. Name and active ingredients: Netildex® (netilmicin 3mg/ml + dexamethasone 1mg/ml) eye drops. **Indication:** Treatment of inflammatory ocular conditions of the anterior segment of the eye, including post-operative cases, where bacterial infection or a risk of bacterial infection with netilmicin-susceptible microorganisms exists. Consideration should be given to official guidance on use of antibacterial agents. **Dosage and administration:** One drop four times a day in each affected eye or as prescribed. Safety and efficacy in children and adolescents less than 18 years of age not established. **Contraindications:** Hypersensitivity to active substances, aminoglycoside antibiotics or excipients. Intraocular hypertension. Herpetic keratitis or other herpes simplex ocular infections. Viral, fungal or mycobacterial ocular infections. **Special warnings and precautions for use:** Not for oral use. Should not be introduced into anterior chamber of eye. Monitor intraocular pressure if treatment lasts more than 15 days. Prolonged use may result in ocular hypertension/glaucoma. Prolonged use of corticosteroids may result in posterior subcapsular cataract formation, delayed wound healing, increased hazard of secondary ocular infections. Corticosteroids may mask or exacerbate infection in acute purulent eye infections. Perforation has been reported with use of topical steroids in diseases causing thinning of cornea or sclera. If sensitivity to topical aminoglycosides occurs, discontinue use. Use cautiously in patients with glaucoma and carefully consider those with a family history. Co-treatment with CYP3A inhibitors is expected to increase risk of systemic side-effects. Contains phosphates which may lead to corneal deposits or corneal opacity. Use with caution in patients with compromised cornea or receiving other phosphate containing eye medications. If significant clinical improvement is not reported within a few days, or irritation or sensitization occur, discontinue treatment and start an adequate therapy. Consider referring patients with blurred vision or other visual disturbances to an ophthalmologist for evaluation of possible cataract, glaucoma or central serous chorioretinopathy (CSCR). **Interactions:** No interaction studies have been performed. Significant drug interactions have not been reported. **Fertility, Pregnancy and Lactation:** Avoid use during pregnancy. Do not use during breast feeding. **Effects on ability to drive and use machines:** May cause transient blurring of vision, patients should not drive or use machines until resolved. **Undesirable effects:** Intraocular pressure increased (after 15-20 days of topical administration in susceptible or glaucomatous patients), posterior subcapsular cataract formation, blurred vision, occurrence or worsening of Herpes simplex or fungal infections, impaired healing, ocular hypersensitivity (conjunctival hypereamia, burning, itching), Cushing's syndrome, adrenal suppression. Corneal calcification reported very rarely in association with phosphate containing eye drops in patients with significantly damaged corneas. **Legal Category:** POM. **Basic NHS Price:** £11.29 per pack. **Pack Size:** 20 x 0.3ml single-dose containers. **Marketing Authorisation Number:** PL53941/0009. **Marketing Authorisation Holder:** SIFI Pharmaceuticals Limited, 29/30 Fitzroy Square, London, W1T 6LQ, UK. **Further information is available from:** ParaPharm Development Ltd c/o Draupnir Holdings Ltd, Building 1410 Arlington Business Park, Theale, Reading RG7 4SA, UK. **Date of PI:** January 2022.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard, or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to ParaPharm Development at (+44) 01183 217100 or info@parapharmdev.com

Nettacin® (netilmicin 3mg/ml + dexamethasone 1mg/ml) eye drops Prescribing Information. Consult summary of product characteristics (SPC) before prescribing. Name and active ingredients: Nettacin® (netilmicin 3mg/ml) eye drops. **Indication:** Topical treatment of external infections of the eye and its adnexa caused by netilmicin sensitive bacteria. Consideration should be given to official guidance on use of antibacterial agents. **Dosage and administration:** One to two drops three times a day in the affected eye(s) or as prescribed. Safety and efficacy in children and adolescents less than 18 years of age not established. **Contraindications:** Hypersensitivity to active substances, aminoglycoside antibiotics or excipients. **Special warnings and precautions for use:** Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic aminoglycoside therapy. Caution advised when used concomitantly. Prolonged use of topical antibiotics may determine overgrowth of resistant microorganisms. If no clinical improvement reported within a relatively short period of time or irritation or sensitisation occur, discontinue therapy and start an appropriate treatment. Nettacin is not injectable, therefore it must not be injected subconjunctivally or introduced in the anterior chamber. During a superficial eye infection, use of contact lenses is strongly discouraged. **Interactions:** No significant drug interactions have been reported. Concomitant administration, even topical and particularly intracavitary, of other potentially nephro- and ototoxic antibiotics may increase the risk of such effects. Concurrent or sequential use cisplatin, polymyxin B, colistin, viomycin, streptomycin, vancomycin, other aminoglycosides and some cephalosporins (cephaloridin) or potent diuretics such as ethacrynic acid and furosemide may increase the potential for nephrotoxicity; concomitant use should be avoided. *In vitro*, the association of an aminoglycoside with a beta-lactam antibiotic (penicillins or cephalosporins) may cause reciprocal inactivation. A reduction of half-life or plasma levels of aminoglycoside occurred in patients suffering from renal insufficiency and in some with normal renal activity, even if an aminoglycoside and a penicillin-like antibiotic were administered by two different routes. Patients must be informed that if more than one ophthalmic medicinal product is being used, they must be administered at least 5 minutes apart. Eye ointments should be administered last. **Fertility, Pregnancy and Lactation:** Although preclinical studies show no foetal toxicity with topical administration of netilmicin, during pregnancy the product should be administered only after a careful benefit-risk assessment and under strict medical control. Not recommended during lactation. **Effects on ability to drive and use machines:** May cause transient blurring of vision, patients should not drive or use machines until resolved. **Undesirable effects:** Eye irritation, conjunctival hyperaemia, eyelid rash, eyelid oedema, eye pruritus, hypersensitivity and urticaria. Episodes of eye irritation and hypersensitivity caused by Nettacin are mild and transient. **Legal Category:** POM. **Basic NHS Price:** £9.83 per pack. **Pack Size:** 15 x 0.3ml single-dose containers. **Marketing Authorisation Number:** PL53941/0003. **Marketing Authorisation Holder:** SIFI Pharmaceuticals Limited, 29/30 Fitzroy Square, London, W1T 6LQ, UK. **Further information is available from:** ParaPharm Development Ltd c/o Draupnir Holdings Ltd, Building 1410 Arlington Business Park, Theale, Reading RG7 4SA, UK. **Date of PI:** January 2022.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard, or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to ParaPharm Development at (+44) 01183 217100 or info@parapharmdev.com

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1. Nettacin Summary of Product Characteristics. 2. Netildex Summary of Product Characteristics. 3. Blanco A, *et al. Invest Ophthalmol Vis Sci.* 2009;50(13):2664. 4. Sanfilippo CM, *et al. Curr Eye Res.* 2016;41(5):581-589. 5. Papa V, *et al. J Cataract Refract Surg.* 2016;42:1312-1317. 6. Blanco A, *et al. Curr Eye Res.* 2013;38(8):811-816.

Date of preparation: February 2023. ALT-23-001.

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Eye make-up

Edited by **Mr. Brian Tompkins**

"The moment I wake up,
"Before I put on my makeup,
"I say a little prayer for you…"

It's unlikely that Dionne Warwick was voicing concerns for her eye health in the opening lines of her 1966 chart hit (written by Burt Bacharach and Hal David) but it's possibly something that more of us need to consider when reaching for the mascara in the morning.

Eye health and cosmetics have an uncomfortable relationship.

The importance of makeup usage, in terms of confidence, self-esteem and appearance, is palpable - but there can be downsides, particularly when we see the impact on the eyes, and that is something that we, as eye care professionals, need to recognise and factor into our work.

When we talk to patients we ask them about their days, their hobbies, their working patterns – we build up a picture of their life to gauge the impact that lifestyles have on their eye health and enable us to put together a sustainable treatment model for any condition they may have.

But how many of us are asking a patient about their beauty and skincare routine? How many of us are finding out what brand of eyeliner they use, or how often they replace the product? Are we asking about how those products are applied? We should be. We need to start talking about makeup.

The average woman uses 12 different beauty products each day, the average man uses six. That's a lot of chemicals going on our skin, near our eyes, maybe even in our eyes but how much do we know about those chemicals and, importantly, how they can affect our eye health? The answer, for most of us, is probably 'not much'?

To be honest, that's not good enough. We need to know this and we need to understand it.

A particular chemical or preservative found in everyday cosmetics could exacerbate a patient's dry eye disease, the glue in false lashes could lead to a demodex outbreak or meibomian gland dysfunction, flaking makeup which finds its way onto a contact lens could adversely affect a wearer's vision, or a retinol-laced eye cream could penetrate more than crow's feet (aka the perpendicular pull lines around the eyes). When it comes to the ocular surface, makeup and cosmetics are an important factor and it is high time we recognised that.

Regulation around the cosmetics industry varies greatly around the world. In Europe, about 1,300 chemicals and compounds are banned in the use of cosmetics. In the US, that number falls to just 11.

The need for a new kind of makeup is clear. The industry has made great strides on environmental and sustainability issues but the time has come to upgrade the conversation from 'clean' beauty to 'safe' beauty.

Amy Gallant Sullivan, one of the team behind the ground-breaking TFOS DEWS II report, has been leading on this and here at TK&S Optometrists we are delighted to be among the first practices in the UK to be stocking her new

range of optocosmetics and skincare designed with the ocular surface in mind – Eyes Are The Story.

The range was born following extensive research into the impact cosmetics have on eye health. Amy's research began 20 years ago, when she questioned if there was a correlation between the high prevalence of dry eye disease in women and whether mascara could be causing or exacerbating their condition.

By breaking down the ingredients list she identified a number of chemical components present in mainstream brands that shouldn't be going anywhere near the eye, a seed was sown and we now have an eye-safe brand, uniquely formulated for sensitive eyes, contact lens users, and sufferers of dry eye and digital eye strain.

Amy says: "We've blacklisted toxic ingredients found in mainstream cosmetics and skincare. We not only embrace the safe beauty movement, we're leading a new conversation about optimal eye protection and endocrine health, informed by a science-based platform.

"We have created something that wields pharmaceutical and nutritional science to develop products that support the homeostasis of your eyes. All formulas are based on peer-reviewed research and inspired by world-renowned eye care professionals and vision health."

Of course, it's not just women that need better standards in the cosmetics industry. Male beauty is a huge growth area and we are seeing more and more men who use a range of products in their everyday skincare and grooming regime.

Again, cosmetics are something that eye care professionals need to recognise and talk about. Cosmetics should be a part of the discussion with existing patients to better understand and potentially refine their daily habits and it should absolutely be a talking point with all new patients, male or female.

Learning more about a contact lens patient's daily beauty routine as early as possible can help shape their treatment pathway. It gives us more information on possible causation factors for a multitude of conditions and provides the detail we need to allow us to work smarter and get the perfect lens for the patient, increasing comfort from day one.

A comfortable lens is crucial if we are to build a long-term relationship with patients and minimise drop-outs further down the line. Maybe we need to focus on the make-up to avoid the break-up.

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The role of the Pentacam tomographer in the early detection of keratoconus

By **Sean Phillips**, [1] **Colm McAlinden**[2]

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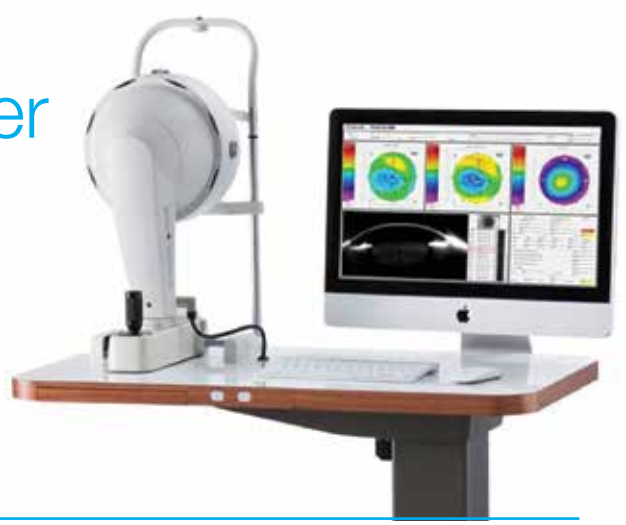
Correspondence: colm.mcalinden@gmail.com



Introduction

Keratoconus is a progressive, bilateral, yet often asymmetrical, eye condition in which the cornea thins and protrudes in an abnormal shape. The cornea plays a vital role in the refractive power of the eye and keratoconus results in reduced vision due to the introduction of irregular astigmatism caused by the change in corneal shape.[1] The estimations of the prevalence and incidence of keratoconus vary between studies,[2] however a recent large meta-analysis by Hashemi et al. estimated the worldwide prevalence of keratoconus to be 1 in 750, which is higher than previously thought.[3] The exact pathophysiology of keratoconus is poorly understood but is believed to be multifactorial. It is thought to be caused by a combination of the up regulation of cellular proteases and down regulation of their inhibitors, combined with oxidative damage and keratocyte apoptosis.[4] The Global Consensus on Keratoconus and Ectatic Diseases agreed that the pathophysiology of keratoconus includes environmental, biomechanical, genetic, and biochemical disorders.[5] Further, it is strongly associated with eye rubbing.[6]

Since its reception, corneal refractive surgery has grown in popularity and in particular, LASIK has become a popular option due to its rapid visual recovery and relatively few adverse effects. However, a well-known, yet rare complication of refractive surgery, is ectasia, with the incidence in the literature predicted as 0.02%, 0.09% and 0.011% for PRK, LASIK and SMILE respectively.[7] One of the major risk factors for the development of ectasia after refractive surgery is a pre-existing corneal ectasia such as keratoconus. It is relatively straightforward to identify moderate to severe keratoconus due to its characteristic tomography, clinical signs and symptomatology. However, the challenge arises when presented with preclinical or forme fruste keratoconus, which can present with normal visual acuity and limited recognisable clinical signs.[8] However, it is understood that the most important risk factor in the development of corneal ectasia following refractive surgery is an abnormal topography.[9] For this reason, it is vital that thorough screening for preclinical keratoconus is undertaken in the hope to prevent iatrogenic corneal ectasia.[10]

The role of the Pentacam in the diagnosis of keratoconus

The Pentacam tomographer (Oculus, Wetzlar, Germany) utilises a rotating Scheimpflug camera which measures elevation points and plots three-dimensional corneal maps.[11] The Pentacam provides a huge amount of information about the variation in elevation of both the anterior and posterior surface of the cornea. The elevation maps are constructed from comparing the anterior and posterior surface to a best fit surface which includes a spherical, toroid, revolutional ellipsoid or non-revolutional ellipsoid.[12] It is relatively straightforward to identify clinical keratoconus with the challenge coming from identifying preclinical keratoconus to better predict the patients that are more at risk of iatrogenic corneal ectasia. Topography is useful in identifying anterior surface changes which are known to be a later sign of keratoconus, with posterior changes known to occur earlier and, more importantly, in preclinical keratoconus. Tomography allows for an in depth analysis of both the anterior and posterior corneal surfaces and gives precise measurements of corneal thickness throughout the cornea.[13,14]

Belin/Ambrosio Enhanced Ectasia Display (BAD)

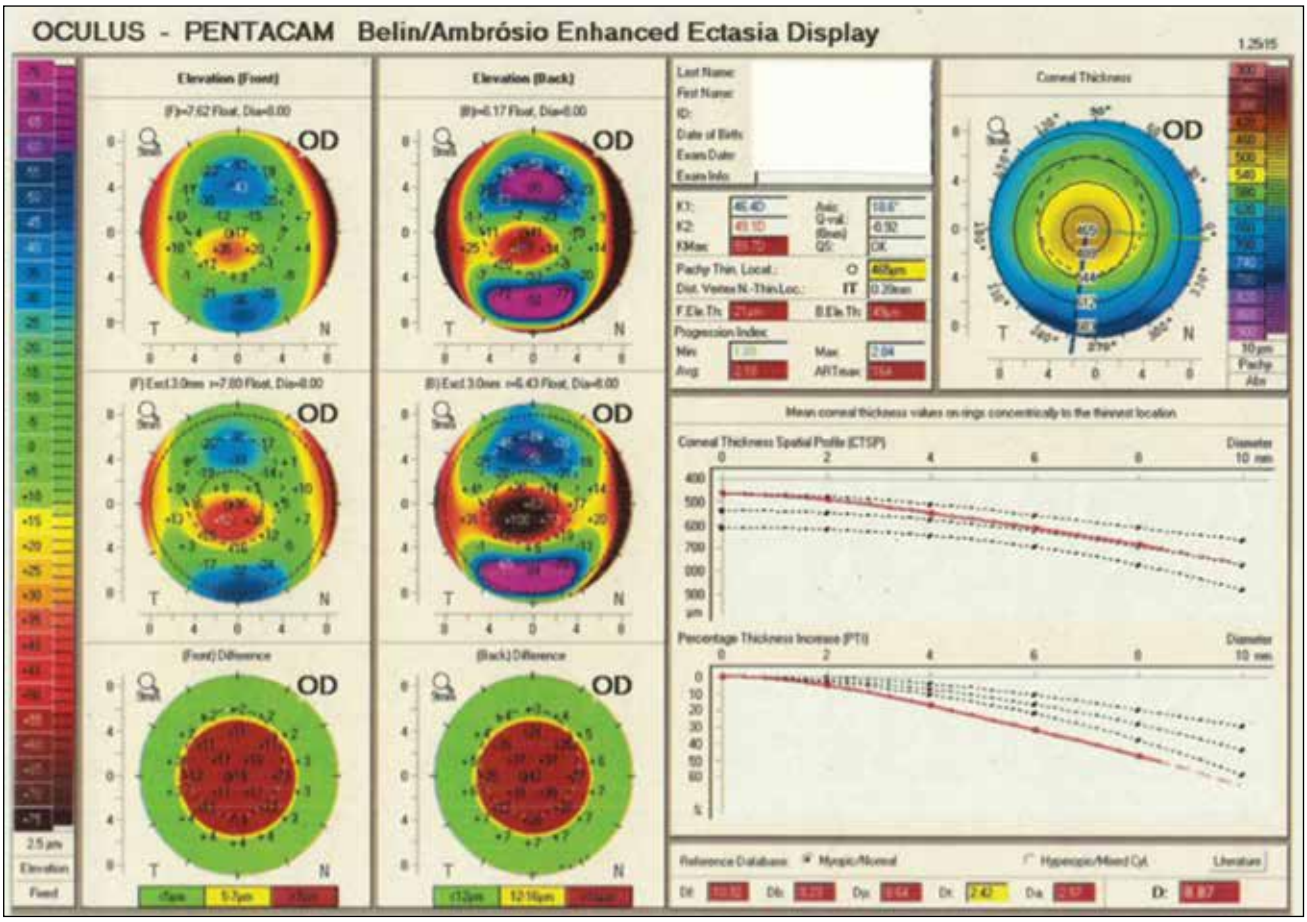
The intention of the BAD was to give clinicians a comprehensive keratoconus screening tool. It combines anterior and posterior elevation as well as pachymetry information. The original software showed anterior and posterior elevation data relative to a standard best fit sphere calculated to a fixed optical zone of 8mm. The original display also showed anterior and posterior elevation values relative to an 'enhanced reference surface' which calculates the best fit sphere from the central 8mm, after excluding all data from a 3.5mm zone centred around the thinnest point. The BAD also calculates the change in elevation values between the standard best fit sphere and the enhanced best fit sphere as described above. The second component of BAD is a display of pachymetry values. It calculates the pachymetry at both the thinnest point and the apex; it then calculates the displacement and direction of the displacement from the thinnest point to the apex.[15,16]

The BAD reports five key indices in terms of D values (standard deviation from the mean). These are: Df (deviation in the difference map of the corneal front surface), Db (deviation in the difference map of the corneal back surface), Dp (deviation of the mean pachymetric progression), Dt (deviation of the corneal thickness at the thinnest point), and Da (deviation of the Ambrosio Relational Thickness [ARTmax] parameter). An overall value is also given in the form

of D (figure 1).[15,16] The literature review by Motlagh et al.[17] showed that BAD had the highest accuracy at identifying both definitive and subclinical keratoconus. Several studies since this review have shown that BAD has excellent capabilities in the screening of keratoconus.[18-28] However, what the studies struggle to agree with is the exact cut off for the D value. The D value represents the standard deviation from the normal average with a value of 0 for the normal population. A range of cut off figures for the D value have been proposed (0.83-2.91).[18-28] The manufacturer suggests a cut off value of 1.6, however if using this cut off value to differentiate between normal high astigmatic eyes and subclinical keratoconus, it would give a false positive rate of 57%.[29]

Belin et al.[30] reported, that although BAD is one of the most used refractive screening displays, it was never intended to be used for this. It is essentially a test to differentiate normal and abnormal corneas. For this reason, BAD is not specific enough in isolation to serve as a sole inclusion criterion and a combination of various Pentacam parameters would be a better approach.

Figure 1: The Belin/Ambrosio Enhanced Ectasia Display (BAD):



Progression pachymetry index

The progression pachymetry index (PPI) is based on the relationship of the corneal thickness to the location and is provided on the BAD screen/printout (figure 2). It evaluates the change in corneal thickness over its entire 360 degrees. The PPI is the progression value at each meridian from the thinnest point. The PPI-Avg is an average of these meridians. PPI-Max is the meridian with maximal pachymetry increase with PPI-Min being the minimal pachymetry increase.[16] The Pentacam interpretation guide suggests a PPI-Avg of more than 1.2 should be considered as ectasia.[15] In the literature review by Motlagh et al.[17] they found that although many studies had excellent diagnostic accuracy for both keratoconus and subclinical keratoconus, the evidence for its use was limited by studies that showed an area under the curve (AUC) less than 0.9, and concluded that there was not a universal consensus that allows for its use for diagnosing subclinical keratoconus. Other studies have found that PPI values have a role to play in the diagnosis of subclinical keratoconus with PPI-Max providing the best combination of sensitivity and specificity.[23,35] Several studies found a cut off value for PPI-Avg was below 1.2 and therefore would be considered normal.[19,20]

Figure 2: The progression pachymetry index (PPI)

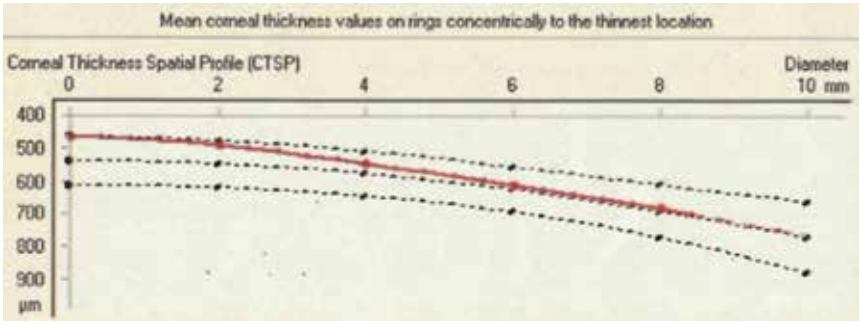
Ambrosio relational thickness

The Ambrosio relational thickness (ART) max is the quotient of the corneal thickness at the thinnest location and maximum progression index, and is provided on the BAD screen/printout (figure 2). ARTavg is the minimum corneal thickness divided by the average PPI.[15,16] The cut off value for ARTmax for a diagnosis of keratoconus is 412µm,[31] however susceptibility is considered with values between 394µm and 412µm. Although ARTmax can be used to successfully distinguish keratoconus from normality, its diagnostic ability for detecting subclinical keratoconus is limited.[17] Koc et al.[18] demonstrated ART has limited capabilities at diagnosing subclinical keratoconus; ARTavg showed a sensitivity of 59.8% and specificity of 61.6%. This is conflicted by Song et al.[19] who showed both ARTmax (sensitivity of 74.29% specificity 92.70%) and ARTavg (sensitivity of 75.71% specificity 86.86%) had good diagnostic ability for differentiating subclinical keratoconus although they did highlight the limited number of participants in their study. Zabaar et al.[28] found that ARTmax produced the leading blend of sensitivity and specificity when differentiating keratoconus from high myopic astigmatism. However, although ARTavg and ARTmax had good diagnostic capabilities of discerning mild keratoconus from normal thin corneas, they showed poor diagnostic capabilities in differentiating between normal thin corneas and subclinical keratoconus.[25]

Corneal thickness spatial profile

The corneal thickness spatial profile (CTSP) is a graph with the x-axis depicting the distance from the thinnest position on the cornea and the y-axis depicting the absolute corneal thickness (figure 3). This is also displayed on the BAD screen/printout. The CTSP starts at the thinnest corneal thickness point and runs 22 imaginary circles around this point in 0.4mm steps. Hence, it graphically displays the progressive thickening of the cornea from the thinnest point towards the periphery. Further, the percentage thickness increase is provided via an index – PTI. The normal PTI is typically between 0.8 and 1.2. Three black lines are displayed on the graph with the central line indicating the population average change in thickness from the thinnest point to the periphery, with the upper and lower black lines indicating the 95% confidence intervals around the average. The measured values are displayed as a red line with ectasia showing a more rapid progression from the thinnest point to the periphery, and may cross the black line(s). A non-ectatic thin cornea would be expected to follow the shape of the black lines. Flatter red lines are seen in thick corneas such as those seen with Fuchs endothelial dystrophy. Hence, lower values for PTI are seen in thick corneas.

Figure 3: The corneal thickness spatial profile (CTSP) graph:



Index of surface variance

The index of surface variance (ISV) is the standard deviation of individual sagittal radii from the mean curvature (figure 4). It gives the clinician an indication of how irregular the corneal surface is.[16] An ISV value >37 is defined as abnormal (depicted as yellow) and a value >41 is defined as pathological (depicted as red). It is a sensitive marker for keratoconus and can also be used to monitor for progression before and/or after corneal cross-linking.
Some authors purport the ISV is the most valuable topometric test for diagnosing subclinical keratoconus.[18]

(See Figure 4 at top of next page).

Index of vertical asymmetry

The index of vertical asymmetry (IVA) is the mean difference in the inferior and superior corneal curvature, with respect to the horizontal meridian (figure 4).[16] The review by Motlagh et al.[17] concluded that although IVA, like many metrics, could be used to distinguish clinical keratoconus from normal corneas, they were unable to conclude its validity in diagnosing preclinical keratoconus. In a more recent study by Donoso et al.,[20] IVA was found to be useful for analysing for subclinical keratoconus. Hashemi et al.[32] found that IVA was the best diagnostic index for keratoconus, suggesting that the likely reason for IVA being good at discriminating keratoconus is that the cone is normally displaced inferiorly along the vertical meridian. Interestingly, Koc et al.[18] found that the IVA had poor diagnostic ability to diagnose preclinical keratoconus with an AUC of 0.685.

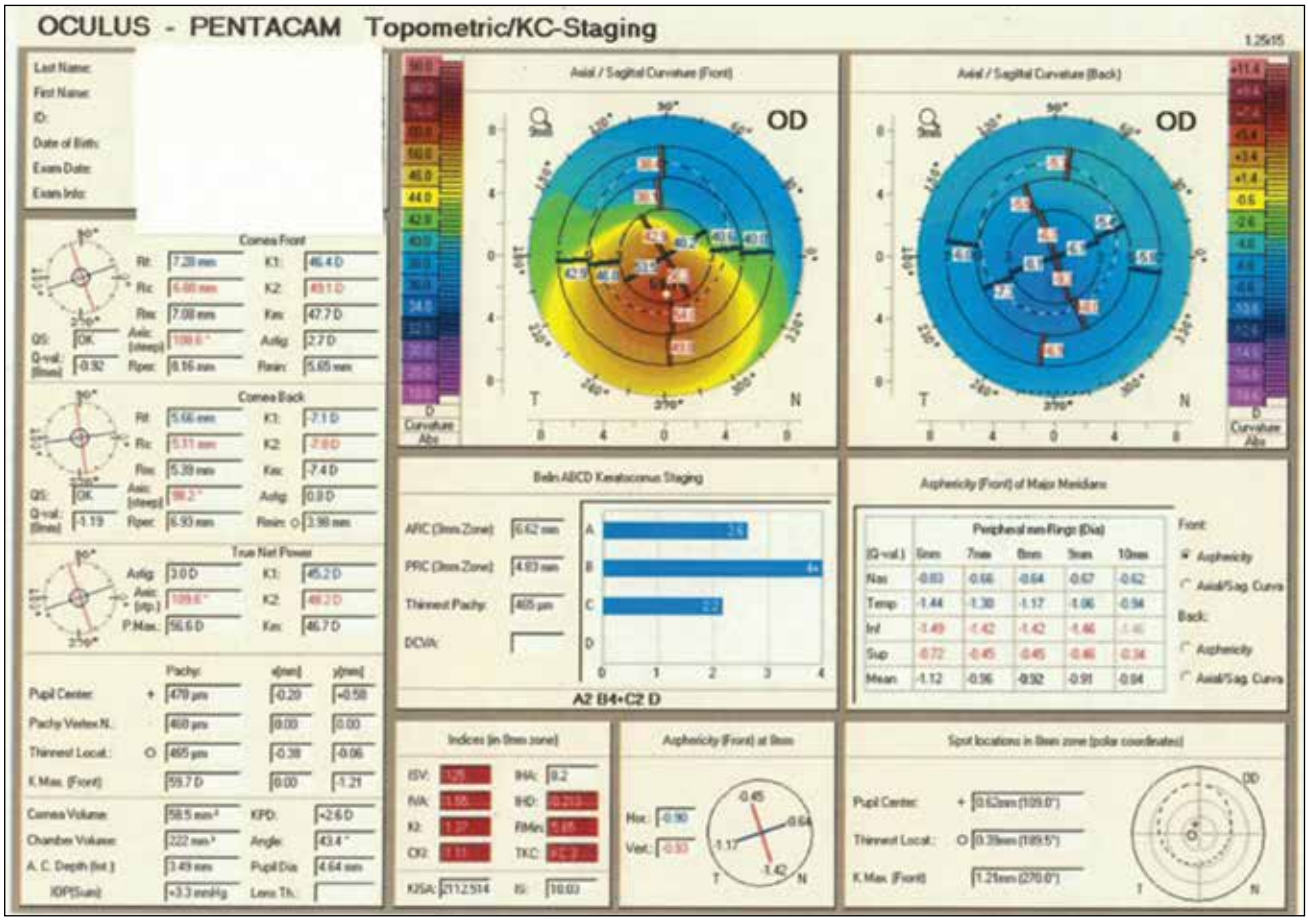
Keratoconus index

The keratoconus index (KI) is the ratio between mean radius values of the superior and inferior cornea (figure 4).[16] Values >1.07 are labelled as abnormal. Like many of the Pentacam indices already discussed, the KI has been found to be reliable for diagnosing keratoconus but is limited in its diagnostic capabilities for subclinical keratoconus.[17] More recent studies found the evidence for KI is mixed. Koc et al.[18] found that KI was not a good predictor for subclinical keratoconus (sensitivity 60.5% and specificity 70.8%). However, this was conflicted by Donoso et al.,[20] who found that KI had the highest discriminatory value for determining subclinical keratoconus (sensitivity 72% and specificity 84%); controversially they found that it was the anterior elevation variables that were most useful in detecting subclinical keratoconus. Although Hashemi et al.[32] found that the KI can be used as a single parameter for diagnosing keratoconus, they advised against this and suggest the use of multiple Pentacam indices.

Central keratoconus index

The central keratoconus index (CKI) is the ratio between the mean radius of curvature in the peripheral Placido ring and the central ring (figure 4).[16]

Figure 4: Indices displayed on the Pentacam (Topometric/KC-Staging display):



Values >1.03 are labelled as abnormal, with increasing numbers representing greater disease severity. It may therefore be a better marker of established keratoconus and used for monitoring progression.
Further, more recent studies have found evidence that the CKI is inferior to the KI as a diagnostic tool for early ectasia.[18,20,23,25,33]

Index of height asymmetry

The index of height asymmetry (IHA) is the mean difference between corneal elevation in the superior and inferior corneal hemispheres (figure 4).[16]
The Pentacam determines that values >19 are abnormal (yellow) and values >21 are pathological (red). The IHA, like many other indices, has a good diagnostic capability in the diagnosis of keratoconus but less useful for the detection of early disease.[17,18,20,23,25]

Index of height decentration

The index of height decentration (IHD) uses Fourier analysis and is the measurement of vertical decentration of elevation on a ring with a radius of 3mm (figure 4).[16] Values >0.014 are marked abnormal and values >0.016 as pathological. There are several papers centred around the ability of the IHD to detect early ectasia.[17] However, Koc et al.[18] showed the evidence is still limited for the use of the IHD for early disease detection (AUC=0.697). It is worth noting that the evidence is conflicting, with Donoso et al.[20] reporting that the IHD was effective as a univariate analysis for the detection of subclinical keratoconus (AUC=0.81).

Minimal sagittal curvature

The minimal sagittal curvature (Rmin) is the smallest radius of sagittal (or axial) corneal curvature (figure 4). It evaluates the maximum steepness of the corneal cone and the cut off value of 6.71mm is used with the Pentacam, with lower values signifying abnormality.[16] Recent studies have found that Rmin has poor diagnostic capabilities as a sole parameter in the diagnosis of early keratoconus.[20,25] However, Rmin did show excellent predictive capabilities at determining keratoconus from high myopic astigmatism when using a Rmin (front) cut off of 7.03mm (sensitivity and specificity of 90%). Comparing this to a Rmin (back) cut off of 5.64mm, the sensitivity and specificity improved to 92% and 90% respectively.[28]
It is important to note the repeatability and repeatability (precision) of these indices. McAlinden et al. found, in a group of normal, non-keratoconic corneas, that the precision for IVA, KI, CKI and IHD was excellent; whereas ISV and IHA were poor.[14] This clearly has implications for the clinical utility of these indices in early detection and also monitoring for progression in established cases.

Other potential diagnostic information

Corneal densitometry, even with normal topography and tomography, has been found to be abnormal in all layers in the 0-2mm zone, and in the anterior and central layers of the 2-6mm zone, suggesting that densitometry may play a role in detecting early keratoconus.[33]
The Pentacam also allows for the evaluation of higher order aberrations,[24,34] with studies suggesting that preclinical keratoconus can be diagnosed using higher order aberrations. In a study by Heidari et al.,[35] the most valuable measurement was anterior vertical coma and this provided good diagnostic predictive value for preclinical keratoconus (AUC 0.857) and may be useful to consider when screening patients for refractive surgery. However, elevated higher order a berrations are not specific to keratoconus and such abnormalities should be considered in the context of the complete clinical evaluation of the patient.

Conclusions

The diagnosis of keratoconus is normally a straightforward process and can be done simply with the wealth of information presented by the Pentacam. The challenge comes when screening patients for potential refractive surgery, in which the detection of susceptibility to ectasia is essential. With several indices comes the challenge as to which are the most appropriate to use when evaluating a patient for refractive surgery. The BAD-D, ART and PPI are particularly useful in screening for detection of subclinical of keratoconus. Other devices and technologies are also important to consider such as the use of epithelial thickness mapping, corneal biomechanics (e.g. the tomographic-biomechanical index [TBI]), and calculations such as the percentage tissue altered (PTA).

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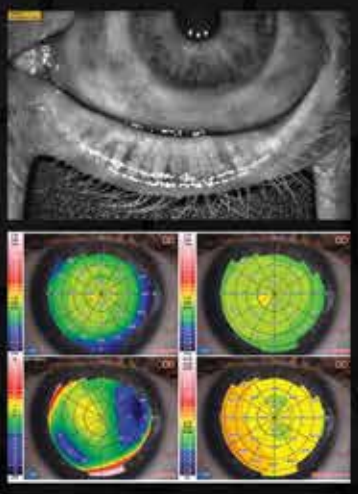

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IVCM in Dry Eye Disease

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As the complexity of dry eye disease becomes more apparent, and the treatment options for dry eye disease are expanding, we are left with the conundrum of diagnosis and management. Dry eye disease presents a significant economic burden (McDonald M, 2016) and while we have more understanding, we also have a lot more treatment modalities to choose from, some of which require time and cost.

The ability to be able to see the pathophysiological mechanisms in-depth may allow more directed and effective treatment when there is so much choice available.

In-vivo confocal microscopy has been a diagnostic tool available for a while for a variety of different corneal conditions, allowing analysis of the corneal layers at a cellular level. Providing a live view of potential pathology means a diagnosis can be made on the spot and furthermore assessment for response to treatment can be made. Not only can each layer of the cornea be analysed, but cellular responses to disease processes and infective agents can be identified and assessed. Deep pathology which may not be isolated by corneal sample/ specimen can be identified by IVCM and collateral indicators of certain disease processed can be identified by IVCM which may not be possible otherwise.

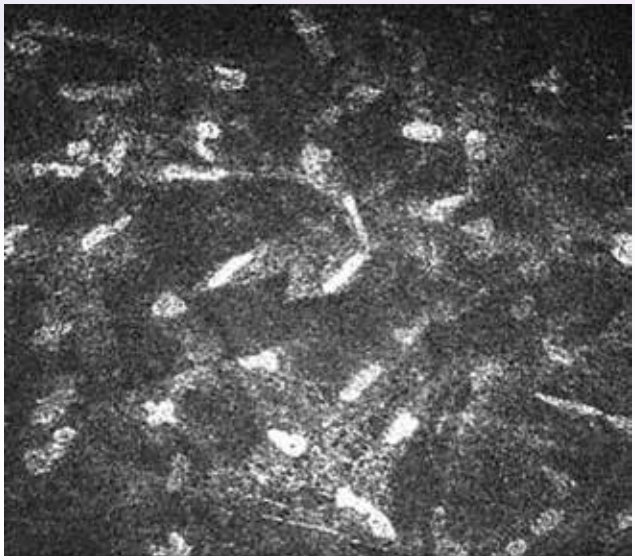
IVCM can be a useful diagnostic tool in dry eye disease. The analysis is not limited to the cornea, as the conjunctiva and meibomian glands also play a crucial role in dry eye disease with useful markers demonstrated by IVCM. (Alhatem A, 2012)

The corneal epithelium, made up of the superficial, suprabasal and basal layers plays a crucial barrier function against outside factors including pathogens. In dry eye disease, IVCM shows evidence of a decreased epithelial cell density, and in Sjogren's the epithelium can show patchy alteration (Tuominen IS, 2003). The decreased epithelial cell density affects all 3 layers in dry eye disease (Zhang X, 2011).

The corneal stroma demonstrates decreased central thickness in dry eye disease with hyperreflectivity from abnormal keratocytes in Sjögren's syndrome (SS) patients (Figure 1). Interestingly, in dry eye secondary to Grave's Orbitopathy, the density of activated keratocytes is significantly higher compared to control subjects. (Villani E, 2010).

Figure 1

SS corneal stromal layer showing increased keratocyte reflectivity (approx. 250 µm of depth).



There is a general consensus that the sub-basal corneal nerve density reduces with age, but the effect of dry eye is less clear. There is literature showing reduced density in SS patients and other types of dry eye including post laser and post corneal infection. (Cruzat A, 2010). The morphology of the nerves including tortuosity and reflectivity may also give a clue to dry eye disease.

Antigen presenting cells of the cornea include Langerhans cells and epithelial dendritic cells which may be increased in dry eye disease and can be another marker point for IVCM. This would represent a sign that the cornea is activating a defence mechanism against such an inflammatory process. (Lin H, 2010). In comparison to infectious keratitis, the increase in density is not as aggressive.

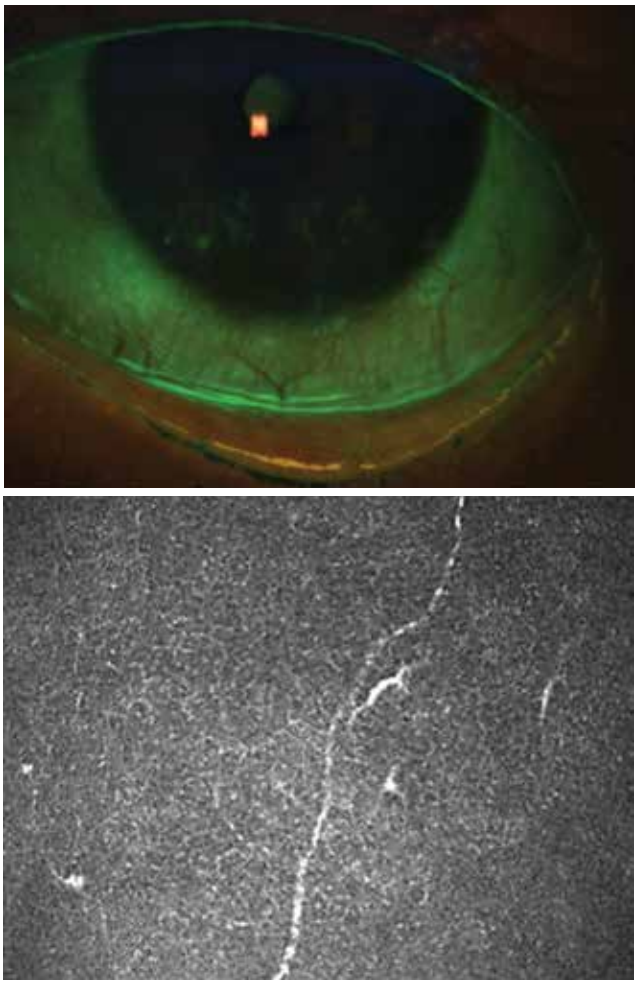
The changes in the meibomian gland structures in meibomian gland dysfunction (MGD) can be used as both a diagnostic marker and as a monitoring tool. The assessment with IVCM looks at acinar density and diameter, orifice diameter, meibum reflectivity and morphology. Morphological features include periglandular inflammation, epithelial cell density, hyperkeratinisation and fibrosis. These are all features found which can help diagnose and monitor MGD. (Ibrahim OM, 2010). While there may be other methods of analysing meibomian gland dysfunction, IVCM may be able to confirm response to treatment with direct visualisation of changes. IVCM has also demonstrated the changes found in rosacea on the cornea, meibomian glands and cutaneous cells on the cheek. (Liang H, 2017).

The conjunctiva also plays a crucial role in dry eye disease, namely but not exclusively related to goblet cell function. The conjunctival epithelial cells and goblet cells are reduced in density in dry eye disease, while epithelial cysts are also found. Compared to impression cytology, goblet cell analysis is comparable with IVCM. (Hong J, 2010).

The exciting development is the ability to assess the corneal nerves and the effect of dry eye on the morphology. This includes bead-like changes, sprouts, irregular branching, tortuosity and neuromas which may all occur from the effect of dry eye on the nerves through inflammation and regeneration via neuropeptides. The corneal nerves are important in ocular healing and this is shown by the challenges in neuropathic ulceration and changes in ocular surface from treatment modalities such as corneal neurotisation. IVCM allows a very effective way of studying corneal nerve structure while being non-invasive and high resolution. There seems to be more nerve abnormalities in aqueous tear deficiency as compared to evaporative dry eye disease. Additionally, corneal nerve sensitivity appears to be decreased in aqueous tear deficiency patients..
This correlates with IVCM findings of lower nerve density. Similarly, lower nerve density is associated with higher symptoms in aqueous tear deficiency, and in turn higher degree of corneal staining. (Patel S, 2021).

Figure 2

SS patient with aqueous tear deficiency dry eye showing central and inferior corneal staining, lid parallel conjunctival folds (LIPCOFs) and irregular lid wiper epitheliopathy marks (top). Same SS patient with reduced corneal nerve density and presence of microneuromas (bottom).



The limitations of IVCM include the lack of built-in software to allow assessment and quantification of nerves. This results in a qualitative assessment which is also user-dependent. Reduced density and tortuosity are known findings in aqueous tear deficiency, while in neuropathic pain nerve fibres may be hyperreflective and have abrupt termination with swelling (microneuroma). However, more research and standardised analytical tools are needed to allow a quantified and measured assessment.

Overall, IVCM provides a noninvasive method of assessment and monitoring in dry eye disease. It would allow for more directed treatment, and allow for justification of higher-cost/ specialised treatments in more severe cases of dry eye disease. It also is an effective method of analysing response to treatment. Having access to IVCM (in particular laser as compared to white light machines) allows an indepth view of the structures involved in dry eye with the benefit of a trained and experienced user. While not accessible to all dry eye services, in those units where IVCM is available, it should be considered as a diagnostic and monitoring tool.

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OSI 6th Annual Symposium and Dry eye Masterclass update

Supported by: SCOPE

Friday 24th of March — Dry Eye Masterclass update

Time	Topic	Speakers
08:00-09:00	*Coffee & Registation*	
08:50-09:00	Welcome & Introduction	
09:00-11:50	**Dry Eye Masterclass - Theory & Discussions**	
09:00-09:10	Classification and Subclassification	Miss Sonia Trave-Huarte
09:10-09:20	How to make the right diagnosis?	Prof. James Wolffsohn
09:20-09:30	Dry eye Masquerades	Mr. Ankur Barua
09:30-09:50	Discussion/Round Table	Moderator: Mr. Arthur Cummings Panel: Prof. James Wolffsohn, Miss Sonia Trave-Huarte and Mr. Ankur Barua.
09:50-10:00	At home therapies	Mr. Connan Tam
10:00-10:10	In-Office therapies	Mr. Brian Tompkins
10:10-10:20	Rosacea blepharitis	Miss Nikolina Budimjila
10:20-10:30	Biologics and Beyond: When and how	Mr. Arthur Cummings
10:30-11:00	Discussion/Round Table	Moderator: Prof. Rohit Shetty Panel: Miss Nikolina Budimjila, Mr. Brian Tompkins Arthur Cummings and Mr. Connan Tam.
11:00-11:30	*Coffee Break*	
11:30- 11:50	Top Tips by the Experts	Moderator: Mr. Samer Hamada Panel: Prof. James Wolffsohn, Mr. Arthur Cummings, Prof. Rohit Shetty, Mr. Ankur Barua and Miss Nikolina Budimjila.
11:50- 17.10	**Dry Eye Masterclass - Interactive Workshops**	
11:50-12:00	Introduction to workshops	Mr. Samer Hamada
12:00-13:00	Workshops Session1	Workshops:
12:00-12.30	Workshop 1	• Diagnostics
12:30-13:00	Workshop 2	• Treatment IPL
13:00-14:00	*Lunch Break*	• Treatment *Others* (Plugs, Debridment and Probing)
14:00-15:30	Workshops Session 2	• Case-Based Discussions
14:00-14:30	Workshop 3	
14:30-15:00	Workshop 4	
15:00-15:30	Workshop 5	
15:30-16:00	*Coffee break*	
16:00-17:30	Workshops Session 3	Workshops will be run by :
16:00-16.30	Workshop 6	Prof. James Wolffsohn, Miss Sonia Trave-Huarte,
16:30-17:00	Workshop 7	Mr. Connan Tam, Miss Nikolina Budimjila,
		Mr. Arthur Cummings, Mr. Samer Hamada,
		Mr. Ankur Barua and Mr. Jack Gormley.
		All workshops are supported by our industry sponsors:
		Scope, Daybreak Medical,
		Hanson Instruments, Vision Matrix, Bodydoctor,
		Trukera and Rayner.
17:00-17:10	*Close*	

This event gives ophthalmologists and optometrists the chance to hear from world-leading experts in ocular surface disease at this new forum for eye health professionals.

REGISTER HERE:

Saturday 25th of March — OSI 5th Annual Symposium

Time	Topic	Speakers
08:00-08:50	*Coffee & Registation*	
08:50-09:00	Welcome & Introduction	
09:00-09:50	**Best Practice: Show me the evidence!**	
09:00-09:10	Impact of diet & nutrition in ocular surface inflammation	Dr. Pooja Khama & Dr. Swaminathan Sethu
09:10-09:20	Tear biomarkers in clinical practice	Prof. Rohit Shetty & Dr. Swaminathan Sethu
09:20-09:30	Vitamin D receptors & it's impact on ocular surface health	Dr. Swaminathan Sethu & Dr. Pooja Khamar
09:30-09:50	Discussion/Round table	Moderator: David Lockington Panel: Prof. Rohit Shetty, Dr. Swaminathan Sethu and Dr. Pooja Khamar.
09:50-10:45	**Ocular surface disease in the community**	**Lead by Miss Sonia Trave-Huarte**
09:50-10:00	Prosthetic CL for amblyopia or trauma, High-power soft CL for aphakia, BCL for wound healing/epithelial protection	Ms. Silvia Gallo
10:00-10:10	Scleral lenses for keratoconus, Therapeutic BCLs after corneal debridement	Mr. Alberto Recchioni
10:10-10:20	Modern empirical methods of scleral fitting including impression moulding	Miss Jennifer McMahon
10:20-10:30	Management of anterior surface conditions (ocular surface disease, post-lasik, dry eye, post-cataract, anterior pole inflammatory conditions, ocular pain). I	Ms. Sarah Farrant Moderator: Miss Sonia Trave-Huarte Panel: Mr. Alberto Recchioni, Ms. Silvia Gallo, Ms. Jennifer McMahon and Ms. Sarah Farrant.
10:30-10:45	Discussion/Round table	
10:45-11:15	*Coffee Break*	
11.15-11:45	**Key Note Lecture 1 : "NOISE" in our judgment of ocular surface disease**	**Prof. Rohit Shetty**
11:45-12:45	**What is new and innovative?**	
11:45-11:55	MMP & Collagen nexus – Can we control it?	Dr. Swaminathan Sethu & Dr. Pooja Khamar
11:55-12:05	Autophagy & Trehalose in inflammation modulation	Dr. Swaminathan Sethu & Dr. Pooja Khamar
12:05-12:15	Desiccation model of dry eye & its translational implication	Dr. Swaminathan Sethu & Dr. Pooja Khamar
12:15-12:25	Genes, ocular inflammation & gene therapy – The future!	Dr. Pooja Khamar
12:25-12:45	Discussion/Round table	Moderator: Mr. Arthur Cummings Panel: Prof. Rohit Shetty, Dr. Swaminathan Sethu and Dr. Pooja Khamar
12:45-13:45	*Lunch Break*	
13:45-14:15	**Memorial Lecture for Prof. Michael O'Keeffe: Making a differnece**	Mr. Arthur Cummings: **Aviation as a model for refractive surgery**
14:15-15:00	**Corneal neuropathy latest developments**	
14:15-14:25	Corneal nerve tracking & it's role in newer refractive procedures	Dr. Pooja Khamar
14:25-14:35	Corneal hypothesia	Mr. Ankur Barua
14:35-14:45	Corneal hyperthesia	Mr. Arthur Cummings
14:45-15:00	Discussion/Round table	Moderator: Mr. David Lockington. Panel: Mr. Arthur Cummings, Mr. Ankur Barua, Prof. Harminder Dua and Dr. Pooja Khamar.
15:00-15:30	*Coffee Break*	
15:30-17:00	**Beyond DED**	
15:30-15:45	The role of functional medicine	Dr. Sharief Ibrahim
15:45-15:55	A message from your patient	Ms. Shakira Elliott
15:55-16:10	Holistic approach to dry eye	Mr. Samer Hamada
16:10-16:25	How to set up a successful dry eye practice?	Mr. David Lockington
16:25-16:50	Discussion/Round table : New horizons in DED managment	Moderator: Mr. Samer Hamada Panel: Mr. David Lockington, Mr. Arthur Cummings, Dr. Sharief Ibrahim and Prof. Rohit Shetty.
16:50-17:00	*CLOSING REMARKS*	

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Clinical relationship between dry eye disease and uveitis: a scoping review

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Abstract

This scoping review examined the relationship between Dry Eye Disease (DED) and Uveitis. We searched Pubmed, Embase, and LILACS databases for articles in which at least one patient had DED and uveitis concomitantly. The search produced 2381 records, and 24 studies were included in the qualitative synthesis. We concluded that DED and uveitis of any aetiology could appear concomitantly in patients of any age. However, both diseases seem to coexist more frequently in middle-aged women and cases of anterior uveitis. Therefore, it is crucial that ophthalmologists actively look for the coexistence of ocular surface abnormalities, especially in patients with these characteristics. Future studies should establish and quantify the risk factors and pathophysiological mechanisms of this coexistence to achieve an early diagnosis of both aetiologies and comprehensive management of these patients.

Background

Inflammation and autoimmunity are pathological processes in many diseases affecting multiple tissues, and the eye is no exception. Dry eye disease (DED) has been recently considered an ocular surface autoimmune disorder [1], where cornea, conjunctiva, eyelids, lacrimal glands, goblet cells, and meibomian glands can be involved. According to The Dry Eye Workshop II (DEWS II), published by the Tear Film and Ocular Surface Society (TFOS), DED [2] can be caused by insufficient tear production or increased evaporation of the tears due to decreased lipid production from dysfunctional meibomian glands or a combination of both. In all cases, inflammation and neurosensorial disorders play an important role. Patients with DED complain of discomfort, visual disturbance, burning and foreign body sensation, conjunctival hyperemia, and photophobia [3]. DED has a prevalence of 6.8% of the US adult population [4] and can affect any gender and age, but the 40-50 age group is the most affected (5-50%) [5–7], and in some studies, female predominance has been reported [4, 8, 9].

On the other hand, uveitis is the term used to describe the inflammation of the eye's pigmented and vascularized middle layer. According to the affected anatomical site, uveitis is classified as anterior, intermediate, posterior, and panuveitis [10]. Although numerous cases are idiopathic, some uveitis are related to autoimmune and infectious aetiologies [11]. Compared to DED, uveitis is a less common problem, with an incidence of 17 to 52 per 100,000 inhabitants/year and a prevalence of 38 to 714 cases per 100,000 inhabitants. It can be present in any age group, but adults from 20 to 50 years old are the most affected (60-80%) [12]. Uveitis can share symptoms with DED, such as photophobia, blurred vision, and decreased vision; nevertheless, they differ in the pattern of ocular pain, described as neuropathic pain for DED [13] and dull pain around or in the eye, which may worsen when focusing on uveitis. Additionally, the pattern of redness is described as a ciliary injection in uveitis and diffuse hyperemia in DED [14]. Some severe or longlasting uveitis complications are glaucoma, cataract, cystoid macular edema, chorioretinal neovascularization, epiretinal membranes, and blindness [15].

Experimental studies have shown that DED and uveitis share some pathophysiological aspects (molecular signalling pathways), such as the role of Th1 lymphocytes in diseases initiation, IL 17 and Th17 expression, metalloproteinases elevation and activation, and infiltration of innate immune cells, such as macrophages and dendritic cells [16]. Likewise, the role of NLRP1, NLRC4, AIM2, and NLRP3 inflammasomes have been studied in the pathogenesis of DED, uveitis, and other diseases, with promissory findings until now [17]. Moreover, patients with uveitis have elevated concentrations of inflammatory cytokines and chemokines as IL-1RA and IL23 in tear samples compared to

controls without uveitis ($p < 0.05$), and these cytokines' profile differs according to the anatomical location of uveitis with higher concentrations when inflammation comprises the anterior segment, suggesting that the intraocular inflammation could have a negative impact in the ocular surface [18].

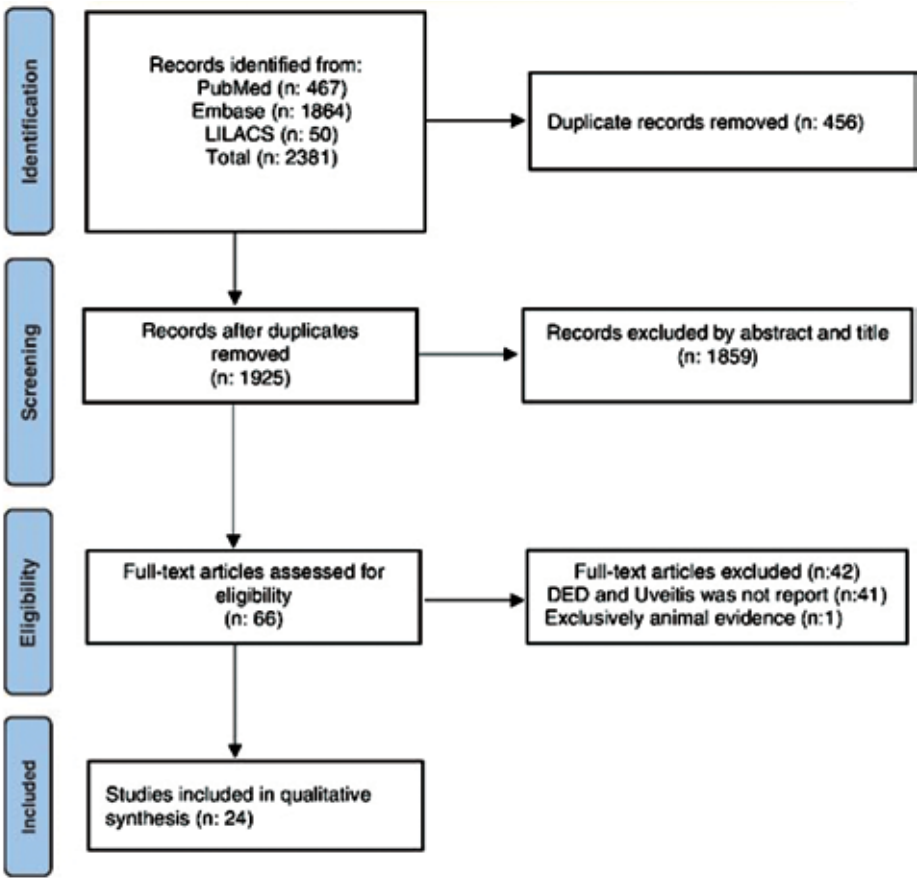
Although studies have shown that DED and uveitis share some pathophysiological mechanisms and suggest that these diseases could coexist, few studies explore the implication this phenomenon could have in clinical practice [18]. Therefore, this scoping review aimed to summarize the current literature regarding the clinical relationship between DED and uveitis.

Materials and methods

We performed a scoping review of the literature to assess the relationship between DED and uveitis. First, we systematically searched the literature to identify original articles, case reports, case series, crosssectional, and case-control studies. The search was performed using PubMed database (https://pubmed.ncbi.nlm.nih.gov accessed on 24 of September 2021) with the following MeSH terms ((“Uveitis” [All Fields] OR “Intraocular inflammation” [All Fields]) AND (“Dry eye” [All Fields] OR “Dry eye syndrome” [All Fields]’)); Embase database (https://www.embase.com) where Entree terms were adapted to ((“Uveitis” [All FIelds] OR “Intraocular inflammation” [All Fields]) AND (“Dry eye” [All Fields] OR “Dry eye syndrome” [All Fields]’)), and LILACS (https://lilacs.bvsalud.org/es/) using the following search ((“Uveítis” [words] OR “inflamación intraocular” [words]) AND (“Síndrome de Ojo Seco” [words] OR “Ojo Seco” [words]). After the exclusion of duplicated records, three pairs of review authors (WRC, GMS, CCG, VVM, NDB, and DV) independently examined the titles and abstracts identified by the electronic searches and decided if the record would be included or not. If there were discrepancies, a third reviewer made the decision (ADLT). Then, the same reviewers' groups read the full text and included the articles in which at least one patient had reported DED and uveitis concomitantly. We excluded narrative reviews and articles related to animal evidence exclusively. Due to the diversity in the terms related to dry eye (keratoconjunctivitis sicca (KCS), dry eye, dry eye syndrome, DED, and dry eye symptoms) and considering the long period of observation of studies (1975 - 2021), we decided to homogenize using the term DED if any of the terms were reported in the studies [19, 20].

We extracted the following data from the included articles: type of study, number of patients included in the study, number of patients with uveitis, number of patients with uveitis and DED, mean age of uveitis presentation, gender, anatomical localization, aetiology, ocular examinations findings, and DED test. Finally, we performed a narrative synthesis of the studies found (Fig. 1).

Fig. 1 Identification of studies via databases and registers



Results

The initial search retrieved a total of 2381 articles. After removing duplicates, 1925 articles were reviewed for title and abstract, obtaining 66 articles for full-text review. After that, we obtained 24 studies that were included in the qualitative synthesis. We divided these articles according to the uveitis aetiology reported as non-infectious and infectious. Then, we grouped the articles by type and summarized them.

Non-infectious aetiology

We found six case series and three case reports between 1987 and 2021 describing an association between DED and autoimmune uveitis. One case report and one case series described patients with Sjögren Syndrome (SS) that developed anterior and/or posterior uveitis [21, 22]. Four studies describe a relationship between ocular sarcoidosis (OcSar) and SS [23, 24, 26, 28]. The other three describe cases of IgG4-related disease [27], Zinsser- Egman-Cole syndrome [25], and Blau syndrome [45], in which patients presented uveitis and clinical features of DED. Interestingly, most patients were women with anterior uveitis. The age range of uveitis presentation was 10 to 70 years old.

Additionally, there were eight cross-sectional studies (one analytic, seven descriptive), uveitis was more common

in females, and the mean age of presentation ranged from 3.3 to 52.5 years old. Anterior uveitis was the most frequent anatomic localization, even though some studies involved cohorts of patients with only one type of uveitis (anterior, intermediate, or panuveitis). The most commonly related autoimmune disease was Juvenile idiopathic/rheumatoid arthritis (JIA) (25 patients) [30, 31, 37], followed by Fuchs' heterochromic uveitis (FHU) (15 patients) [32], undetermined (9 patients) [36], Sarcoidosis (2 patients) [33, 34] and Rheumatoid arthritis (RA) (1 patient) [35].

We found three case-control studies that evaluated the ophthalmological manifestations in patients with JIA [39], Psoriatic Arthritis-Related Uveitis (PsA-related uveitis) [40], and Vogt-Koyanagi-Harada syndrome (VKH) [38], the mean age of uveitis presentation ranged from 41 to 52.5years, with a proportional sex ratio in JIA but with female predominance in VKH. Anterior uveitis was the most common localization, followed by posterior, panuveitis, and intermediate. Interestingly, DED was present in 13.3% of patients with JIA (2/15) [39] and 17.9% PsA-related uveitis (21/117) [40], and 100% of VKH cases

(16/16) had abnormalities in ocular surface suggestive of KCS [38].

Rosenbaum et al. [21] described eight patients with SS and uveitis with a Schirmer test positive below 10 mm; all of them were women between 29 and 55years. Likewise, Ramos Casals et al. [23] presented a case series of patients with Sarcoidosis and SS who all had sicca syndrome (5 with xerophthalmia, 4 with xerostomia). Among them, 2 patients had anterior uveitis with abnormalities on the Schirmer test suggestive of DED. Tahvildari et al. [36] characterized the corneal, conjunctival, and eyelid margin abnormalities in patients with panuveitis and found a prevalence of 44.5% of ocular surface abnormalities and 48.5% had Meibomian gland dysfunction. Interestingly, 20% had dry eye signs, and the most common cause of uveitis in patients with ocular surface disease was idiopathic (26.8%) and sarcoidosis (24.4%), concluding a higher incidence of ocular surface, corneal, and eyelid margin disease in patients with panuveitis. Similar findings were described by Aoki et al. [46], who compared the tear function in OcSar, VKH, and healthy subjects to elucidate the association between OcSar and DED. The Schirmer 1 Test values were significantly lower in the OcSar patients than in the VKH patients ($P = 0.004$) and control subjects ($P = 0.001$). They conclude that the neural reflex arc and lacrimal gland system, which attenuate the vicious cycle between the tear film and ocular surface epithelium in DED, are significantly impaired in OcSar cases, indicating a possible association between OcSar and DED.

Degirmenci et al. [37] performed a case-control study in patients with JIA and chronic bilateral uveitis compared with controls, evaluating the presence of DED and Meibomian gland dysfunction. They found no significant differences between groups regarding age, mean intraocular pressure, mean Schirmer 1 test value, tear film breakup time (TBUT), and Oxford staining score. However, they found that patients with oligoarticular JIA had higher meiboscores than normal subjects, which indicates a possible evaporative dry eye tendency in these patients. Similarly, Akinci et al. [39] studied patients with JIA, of which 23.4% of patients had uveitis, and did not find a significant difference in the Schirmer test and TBUT in this group of patients.

Other less common autoimmune diseases, such as FHU, VKH, and Behçet, have also been related to tear deficiency. Mastropasqua et al. [32] found that 15 out of 30 patients with FHU had tear deficiency noted by abnormal Schirmer 1 test, tear film BUT, and Ferning's test. There was a significant difference in the test results between the affected eyes and the fellow unaffected eyes ($P < 0.001$). Piveti et al. [38] performed tear function tests (BUT, Schirmer test, fluorescein, and rose bengal staining) in 16 VKH patients compared with 16 control with diffuse uveitis. They found that patients with VKH syndrome had a higher incidence of DED when compared to controls. Karaca et al. [47] evaluated the ocular surface and meibography of 25 right eyes of patients with inactive Behçet's uveitis (Group 1), and 25 right eyes of 25 healthy individuals (Group 2). They did a Schirmer 1 test, tear film BUT, ocular surface staining with fluorescein and Oxford scoring, and ocular surface disease index (OSDI) score assessment. Also, lower and upper eyelid Meibomian glands were examined with the infrared filter of the slit-lamp biomicroscope. Schirmer test and film breakup time were significantly lower in group 1 in comparison with group 2. Oxford scale and OSDI scores were higher in group 1. There was no significant difference in the upper and lower meiboscores. They conclude that despite the tendency toward DED, Behçet's uveitis is not associated with quantitative meibomian gland changes, which is demonstrated by gland dropout with meibography.

Infectious and other aetiologies

Regarding infectious aetiologies, we found two case series and one cross-sectional study. All uveitis were viral, caused by Human T-cell Lymphotropic Virus Type 1 (HTLV-1) [41], Herpes Virus [42], and SARS-CoV-2 [43]. The mean age of uveitis ranges between 9.4 and 55.6 years old, anterior uveitis was the most common localization of inflammation, followed by panuveitis, and women were the most affected. In a cross-sectional study, Kalpana et al. [29] compared ocular characteristics between uveitis secondary to sarcoidosis and tuberculosis, finding that patients with a low Schirmer test had a higher risk of OcSar.

Merle et al. [41] studied 200 patients infected by HTLV- 1, 77 (38.5%) were seropositive, and 123 (61.5%) had HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/ TSP). Uveitis was found in 29 cases (14.5%). For diagnosing DED, at least 2 out of 3 tests of the followings had to be positive: Schirmer 1 test < 10 mm; BUT <10seconds, pink bengal test >3 points. DED existed in 74 patients (37%). In patients with HAM/ TSP, uveitis was more frequent among younger patients, patients with earlier onset of HAM/TSP, and patients with severe motor disabilities. The sicca syndrome related to HTLV-1 virus differs from primary or secondary Sjögren syndrome because it does not reveal any of the immunologic anomalies generally seen in this disease. Finally, Ozturk et al. [42] described the case of 5 paediatric patients with bilateral non-granulomatous acute anterior uveitis secondary to the multisystem inflammatory syndrome in children (MIS-C) due to COVID-19 infection, and of those, 60% (3/5) with abnormalities in ocular surface and tear function test.

Discussion

Understanding the pathophysiological mechanisms of diseases is a primary requirement when proposing diagnostic and therapeutic strategies [16]. In the case of eye diseases, many share clinical signs and symptoms that make their approach complex and even more when two conditions are found in the same patient. A clear example is a relationship between glaucoma and DED, diseases known to coexist,

mainly because glaucoma medications are a risk factor for developing DED [48]. However, the relationship between DED and uveitis has been poorly explored, a relationship that has a pathophysiological theoretical basis, considering that both are diseases in which the immune system plays an important role [16].

Molecular relationship between both entities: a hypothesis

Even though DED and uveitis are not specific nosological entities alone, both entities share an inflammatory pathway by definition and can coexist. Based on the current literature, we draw some hypotheses and inferences in the pathophysiology that can underlie in patients with uveitis and DED overlapping. It has been demonstrated that HLA-DR expression by conjunctival cells is increased in patients with uveitis and DED compared with those with vernal keratoconjunctivitis and normal subjects [49]. Likewise, it is known that high HLA- DR expression in conjunctival epithelial cells associated with high conjunctival staining may identify a subgroup of DED patients prone to epithelial disease that possibly need a different approach from current treatment standards [50]. These results suggest an involvement of the Th2 system on the ocular surface in uveitis; thus, exploring the ocular surface in uveitis may represent a new way to understand better the immune pathways involved in this complex disease [49].

Other studies have evidenced that uveitis can modify the cytokine and chemokine profile in aqueous humor and tears. Patients with uveitis have higher tear levels of IL-1β [18], a well known immune marker of DED [51]. Likewise, these patients have higher tear levels of IL-23 compared with controls [18]. This interleukin plays an essential role in the long-lived memory of T-helper 17 (Th17), which actively mediates chronic inflammation in autoimmune disorders, including DED [52, 53].

Another crucial cytokine in the inflammatory mechanism of diseases is IFN-γ. Hill et al. [54] investigated differences in the T cells in aqueous humor between several types of uveitis and correlated it with clinical phenotype. However, they just found increased percentages of IL-10+−, but not interferon IFN-γ+T lymphocytes in aqueous humor compared with peripheral blood in patients with acute anterior uveitis (AAU), FHU, or chronic panuveitis. As the authors mention, “this could be due to the fact that some patients had a higher baseline expression of IFN-γ + T cells due to their disease being active and stimulation with phorbol myristate acetate failing to augment fully or any further the number of cytokine-positive T cells.” In the same way, Carreño et al. did not find significant differences in tear levels of IFN-γ between uveitis patients and healthy controls [18]. However, they found an increase in the IP-10/CXCL10; this chemokine is often released in the context of inflammation by many cells, including leukocytes, neutrophils, eosinophils, monocytes, and stromal cells, in response to IFN-γ [55].

Additionally, there was a trend towards elevated levels of IL10+ T cells in aqueous humor from patients with FHU compared with those from acute uveitis and panuveitis patients. Increased levels of IL10+ T cells in aqueous humor compared with peripheral blood were also found in samples from patients with isolated uveitis but not those with associated systemic disease [54].

Interestingly, IL-10 has been related to the disease onset and activity in SS [56–58], a disease that can present both DED and uveitis.

Another relevant cytokine in the pathophysiology of both entities is IL6, related to the intraocular immune response in several types of uveitis and involved in DED pathology, even correlated with eye pain in the latter [59]. Also, it has been evidenced that epithelial cells produce and release chemokines, tumor necrosis factor-alpha (TNF-α), IL-1, IL-6, and IL-8, which amplify the immune response and attract inflammatory cells in DED [60]. Undoubtedly, the action of a single cytokine or chemokine cannot wholly explain the pathophysiology of the uveitis/DED overlapping, and more complex molecular regulators such as inflammosomes may play a fundamental role, as they have emerging importance in regulating ocular surface and anterior segment health and disease [17].

Non-infectious aetiology

The multiple published case series and case reports make us think that coexisting DED and uveitis could be more common than we suppose. This is backed by the crosssectional studies appraised that showed a relationship between DED and uveitis, especially with anterior chamber compromise, considering that the most common anatomic localization of uveitis in patients who concomitantly had DED was anterior, followed by panuveitis. Tahvildari et al. reported DED in 8.9% (9/101) of patients with panuveitis [36]. Likewise, Caimmi et al. described a cohort of 92 RA patients with ocular inflammatory disease, of which 14 patients had anterior uveitis and one patient had DED concomitantly, with a Schirmer test < 5 mm in 5 minutes and positive staining [35]. These results coincide with previous studies where higher levels of inflammatory markers have been found in patients with anterior and panuveitis compared with intermediate and posterior uveitis [18]. This suggest that inflammation of the anterior chamber might spread locally to the ocular surface, supporting that intraocular inflammation could generate corneal and conjunctival changes.

Regardless of localization or aetiology, women were the most frequently affected by concomitant DED and uveitis. This is expected, considering that the Pacific Ocular Inflammation Study reported that although there are no significant differences in incidence rates of uveitis between genders, there is a higher prevalence in females [61], and multiple studies have evidenced that DED is most common in women. Additionally, it is crucial to consider that gender is a common risk factor for autoimmune diseases, such as in JIA, the most frequent systemic disease found in the cross-sectional studies evaluated in the present review [62].

Regarding tear function tests, 50% (15/30) of patients with FHU had impaired tear production, evidenced by the Schirmer test [32]. Moreover, JIA-related uveitis patients had a higher median meiboscore (p =0.041), abnormal Schirmer test results (< 5 mm in 5 min) [30, 35], and ocular surface staining [31] compared to healthy subjects. Thus, patients with uveitis can present both evaporative or aqueous deficiency DED. However, there is a lack of information regarding the risk factors for presenting either.

Case-control studies identified similar information to the previously described, where most patients were women with anterior uveal compromise. For example, a study comparing patients with VKH versus other types of uveitis found that all VKH patients had altered tear function tests,

with a statistically significant difference in DED proportion between both groups [38]. However, in another cohort of children with JIA, there were no sig nificant differences in TBUT and Schirmer test results between those with or without a history of uveitis [39]. Therefore, the current literature is controversial, and further research is needed with prospective studies to characterize the risk factors associated with DED in patients with specific aetiologies of uveitis.

Infectious aetiology and others

The observational studies that assessed the relationship between DED and infectious uveitis found similar associations. Merle et al. described a cohort of 200 patients infected by the Human T-cell Lymphotropic Virus Type 1 (HTLV-1), where a slightly higher prevalence of DED was observed in the uveitis group (11/29, 37.9%) vs. non-uveitis group (63/171, 36.8%). There was a female: male ratio of 7:4. Four patients had panuveitis, of which three were female. Five had anterior and intermediate uveitis, of which three were female. And two had intermediate uveitis, with a 1:1 relationship [41]. Similarly, in herpetic uveitis, DED was described as the third most common complication (25/73, 34%) after keratitis (43/73, 59%) and elevated IOP (55/73, 75%) [43]. Additionally, abnormalities in ocular surface and tear function tests in paediatric patients were observed in 60% (3/5) of cases with anterior uveitis due to MIS-C secondary to COVID-19. Three patients were female and presented with corneal punctate epitheliopathy [42]. These results suggest a relation between viral infectious uveitis and DED. Infectious mechanisms seem to be involved in dysfunction in tear production or preservation. Additionally, we found an interesting multicenter study performed by Babu et al. that aimed to look at clinical and radiological markers to differentiate OcSar from ocular tuberculosis. They described significantly lower Schirmer test results in patients with sarcoidosis (36/42, 85.7%) than in ocular tuberculosis (7/42, 16.6%), proposing it as a marker that could help differentiate OcSar in a high TB endemic population. Patients with uveitis and low Schirmer test had higher odds of OcSar than TB (OR- 30, CI-95% 9.168 - 98.173) [44].

In general, most studies only describe the frequency of coexistence of both entities, which can vary between 1.58% and 100% depending on the characteristics of the cohort studied. Only one study compared patients with and without uveitis, finding DED more common in patients with uveitis [41]. Another study in patients with Inactive Behçet's uveitis found a "trend" towards DED as these patients had lower levels of Schirmer 1 test (18.68 vs. 23.69, p =0.017) and mean tear film BUT (10.76 vs. 13.36, p = 0.026) compared to healthy controls [47].

Furthermore, it is essential to consider that uveitis is not always an organ-specific condition. In fact, non-infectious uveitis is associated with a systemic autoimmune disease in up to 33% of cases [63]. And it has been shown that these diseases can also be related to alterations of the ocular surface and DED in up to 53% of cases [64], regardless of the presence or not of uveitis. Likewise, it is essential to consider the role that treatment may have since, generally, uveitis and its complications are treated with topical and systemic medications that cause DED, such as corticosteroids, anti-glaucoma agents, cycloplegics, and NSAIDs [65, 66].

This scoping review summarizes the literature regarding the clinical relationship between DED and uveitis; however, many questions remain open. For example, most studies are cross-sectional, so the question of which came first: the DED or the uveitis? Is still unanswered. This is the first step in understanding the coexistence of both diseases. It encourages researchers to continue studying this phenomenon to understand the link between them, their clinical implications, and the need for effective diagnostic mechanisms and treatment approaches in cases where both diseases present concomitantly.

Conclusion

Observational studies showed that uveitis and DED could appear concomitantly in patients of any age and with any uveitis aetiology. However, it seems that middle-aged women are the ones in whom the two diseases coexist more frequently. This could represent clinical evidence of the common pathophysiological pathways found between these inflammatory diseases or maybe just a coincidence because both disorders are more common in adult women. Anyway, it is essential that ophthalmologists actively look for the coexistence of DED, both aqueous and lipo deficient, in patients with uveitis, especially if anterior.

Further research about these disorders' risk factors and pathophysiological mechanisms is essential, considering that several studies have shown that intraocular inflammation might expand to the ocular surface, evidenced by the increase in cytokines in the tears of patients with uveitis. Therefore, longitudinal studies will allow us to know which of the two diseases appears first and the clinical implications of this association. By increasing our knowledge of this coexistence phenomenon, we could develop diagnostic methods that allow timely diagnosis and therapeutic strategies that will enable the comprehensive management of these patients.

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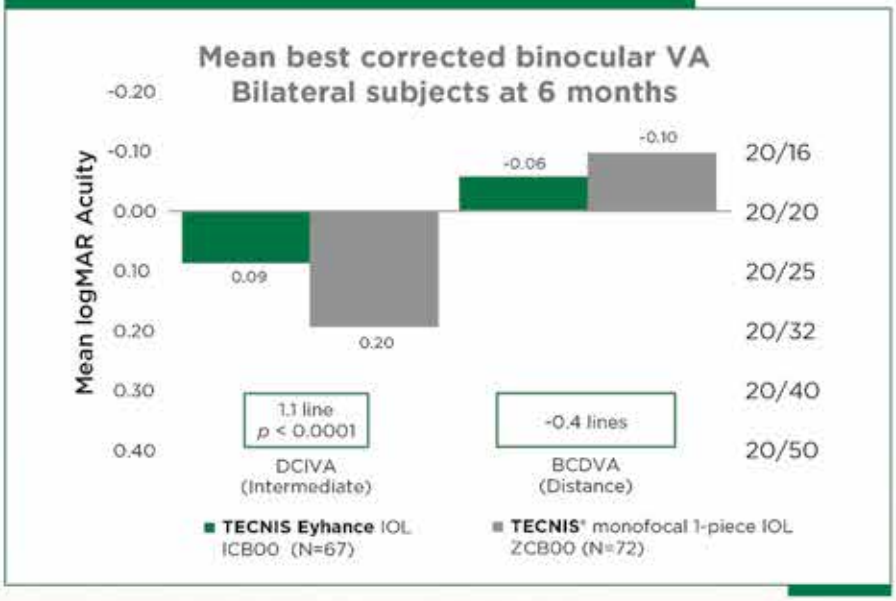

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A patient's perspective

- an update from Shakira

Edited by **Åsa Baudin**

Shakira shared a patient perspective with OSI in the autumn of 2020, what her whole patient journey had been like up until that point. It had been an extremely challenging time for Shakira, with the pain being so bad that she would rarely leave her home. Shakira was diagnosed with Meibomian Gland Dysfunction, possible Ocular Rosacea and evaporative dry eye in 2016 after visiting an optician and then a specialist in a hospital through the NHS. She was sent home with a set of instructions, but the condition did not improve, and she tried various treatments without much success. She felt that her condition has taken away many things from her life, hobbies like horse-riding and water-skiing but determined to find new treatments to improve her condition.

Shakira eventually went to a private clinic and was recommended to see a specialist in London who had extensive knowledge about dry eyes. In this new clinical setting Shakira received gland expressions and microflow treatment every 3-4 weeks, Doclycycline 100mg/day, cyclosporine eye drops and preservative-free ocular lubricants. Shakira started to notice some improvement after the third session of IPL treatment.

It's now February 2023, and Shakira is busy preparing for a social gathering with friends. A few years ago, such an event would have been impossible due to debilitating pain. However, Shakira's current treatment plan has improved her symptoms and enabled her to enjoy a better quality of life. She's eager to share the details of her regimen, which includes regular IPL courses tailored to her needs, followed by manual gland expression, Autologous Serum Eyedrops (ASE), and PRP injections in the ocular area. She also takes Doclycycline, uses Finacea cream for rosacea on the eyelids, low-dose Naltroxane, and vitamin supplements, including Vitamin C, Vitamin D, and Omega 3. Shakira's diet avoids refined sugars, includes a lot of fish, and emphasizes hydration. She also wears Blue light blocker glasses when using electronic devices. Shakira credits ASE with being a game-changer for controlling inflammation and pain, allowing her to regain some of her social life. She hopes that sharing her experience will help clinicians and other patients get the right treatment faster.

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References: 1. Product Leaflet. 2. Jones, L. *et al.* Ocular Surface 2017; 15: 575–628. 3. Lee, SY. & Tong, L. OptomVis Sci 2012; 89:1654–1661. 4. Aragona, P., *et al.* ISOPT 6th, Berlin, 2006 Medimonds S.r.l. ed pg81–86. *Install TheaLipid® 15 minutes before inserting contact lenses.

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