Contact Lens Update
CLINICAL INSIGHTS BASED IN CURRENT RESEARCH

Eyelids and Contact Lens Discomfort

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Approximately 35% of contact lens wearers discontinue contact lens wear, with the majority reporting 'discomfort' and 'dryness' as significant reasons, particularly at the end of the day.[1] Approximately, 30 to 50% of contact lens wearers report comfort problems as dry eye symptoms.[2-5] This report briefly reviews the published literature on clinical, microbiological and biochemical aspects of eyelids, their association with ocular and contact lens comfort and offers management strategies for patients reporting contact lens discomfort.

Associations between clinical characteristics of eyelids and contact lens comfort

The eyelid margin

Tribological principles have been applied to model the dynamic interaction between the lid-wiper epithelium and the ocular or contact lens surface, during normal and abnormal blinking and dry eye situations.[6] The lid-wiper epithelium has a conjunctiva-mucosal morphology,[7] that contains goblet cells which produce mucin, mostly likely used for lubrication and to reduce the friction between the eyeball and eyelid margin during the blink. In contact lens wear, the coefficient of friction of the surface of the contact lens may play a dominant role, since the friction occurs during small movements and low velocities.[6] In contrast to symptomatic contact lens wearers, asymptomatic wearers may adapt to this wear, or more likely due to highly hydrated brushes formed by mucins in the form of the glycocalyx coating the surface of the cornea and conjunctival region, may reduce mechanical forces between the ocular surface and the back surface of contact lenses.[6] The lid-wiper region also has the highest neural sensitivity compared to other parts of the ocular surface such as the bulbar or palpebral conjunctiva and other parts of the eyelid margin and is comparable to the central cornea.[8] It is of obvious importance during contact lens wear.[9-12]

Korb et al. linked changes in the lid-wiper region of the eyelid margin in subjects who experience symptoms of ocular dryness.[9-12] A disturbance in the integrity of the lid-wiper region (called 'epitheliopathy') can be viewed clinically by staining the marginal conjunctiva with common ophthalmic dyes such as fluorescein and/or rose bengal.[9] Several studies have explored the relationship between lid-wiper epitheliopathy and symptoms of dryness and discomfort in contact lens wearers. Lid-wiper epitheliopathy was more common in symptomatic lens wearers (67–80%) compared to asymptomatic lens wearers (13-32%),[10,13] with more signficant differences observed in the upper eyelid[14] compared to the lower eyelid.[15] However, a large multi-centre study that assessed subjective comfort in 253 habitual contact lens wearers showed that 85% of participants presented with lid-wiper staining.[16] The authors found lid-wiper epitheliopathy to be independent of age, sex, race and refractive error but dependent on the habitual soft lens type that was worn. In that particular study there was no relationship to contact lens comfort.[16] Clinical observations of the lid-wiper region in silicone hydrogel wearers has revealed different patterns of staining such as vertical streaks, short horizontal bands, speckled or comb appearances and broad horizontal bands.[17] These patterns change with contact lens type.[17] Lens surface wettability, tear film

evaporation rate and quality of the tear film lipid layer may impact the different patterns of lid margin staining.[17] Efron[18] conducted a literature review of staining agents, staining techniques, grading scales and pathologies that were associated with lid-wiper epitheliopathy. The meta-analysis relating to various aspects of soft contact lens wear was unable to demonstrate a significant relationship between grades of lid-wiper epitheliopathy and contact lens user experience (CLUE) score.[18]

Histology has revealed that cells with para-keratinization increase in number and extend from the natural stainable line of Marx over the surface of the lid-wiper epithelium.[7] Norn *et al.*[19] performed vital staining of the eyelid margin with fluorescein, lissamine green and Sudan III, concluding that the stained line represented the border between tear fluid and the skin corresponding to a mucocuntaneous junction. Findings from this study suggested that eyes with abnormal meibomian gland secretions or morphology had significantly higher (antero-retro displacement) of line of Marx scores. Scoring of location of the line of Marx has been demonstrated to be a rapid, efficient and less-invasive screening test for assessing meibomian gland function.[20] Further research needs to be conducted to clearly elicit changes in the mucocutaneous junction and their association with discomfort in contact lens wearers. Studies have shown improvements in the symptomatology of contact lens wearers after treatment of anterior blepharitis and meibomian gland dysfunction.[21]

Conjunctiva

Lid parallel conjunctival folds (LIPCOF) are parallel folds of the lower bulbar conjunctiva parallel to the lower lid margin easily observable with the slit-lamp biomicroscope. They remain unaltered after forced blinks, and have been found to be present in dry eye but are not age-related.[22,23] Several factors have been hypothesized to cause LIPCOF, including conjunctival looseness, inflammatory processes, a decrease in elastic fibres and lymphatic dilation by mechanical forces between the lower eyelid and conjunctiva.[24] Decreased mucin production is associated with the severity of LIPCOF, and LIPCOF are also significantly correlated with lid-wiper epitheliopathy.[14] Experienced contact lens wearers with an increased number of LIPCOF with their habitual contact lenses, have significantly lower numbers of LIPCOF three months after having been refit with silicone hydrogel lenses.[25] There is also a suggestion that LIPCOF may have an impact on tear meniscus volume and tear drainage, leading to discomfort due to dryness.[26] In contact lens wearers, both lid-wiper epitheliopathy and LIPCOF correlated with dryness, but other clinical factors such as corneal staining, bulbar redness, or tear break-up time, did not.[25] This suggests that both lid-wiper epitheliopathy and LIPCOF may arise from a similar etiology of friction,[27] and may also be secondary to a reduction in lubrication, leading to a cascade of events relating to dryness.

Associations between palpebral conjunctival changes and symptoms of dryness have been previously reported.[10,28] However, it is not completely clear whether these physiological changes are also the underlying cause of reduced comfort. Allansmith et al. reported that 14% of non-contact lens wearers had a satin-smooth conjunctival appearance of the upper tarsal plate, 85% had small uniform papillae and 1% had non-uniform papillae,[29] while Korb *et al.* reported 0.6% of healthy non-lens wearers showing conjunctival papillae of more than 0.3 mm on the upper tarsal conjunctiva.[30] The papillary reaction on the upper tarsal conjunctiva is accompanied by discomfort and mucous production and can lead to intolerance and discontinuation of contact lens wear.[28,31,32] Participants with obvious contact lens papillary conjunctivitis will be symptomatic, but there have been no reports directly linking contact lens discomfort with general, non-pathological changes to the palpebral conjunctiva.[33]

Meibomian glands

Clinical and cytological evidence suggests that meibomian gland dysfunction in contact lens wearers is due to obstruction of the meibomian orifices by desquamated epithelial cells that tend to aggregate in keratotic clusters, resulting in changes in the meibomian gland and contributing to the primary complaint of contact lens intolerance.[34,35] A comparative cross-sectional study to determine the effect of contact lens wear on the

meibomian glands found gland dysfunction in 49% of lens wearers and 39% of non-lens wearers.[36] A recent review of the literature[37] on the impact of contact lens wear on meibomian glands concluded that, although there is some evidence suggesting that contact lens wear affects the morphology and function of meibomian glands, it is difficult to demonstrate a relationship between contact lens discomfort and meibomian glands due to a lack of specificity of the applied questionnaires. Longitudinal studies with appropriate questionnaires to monitor comfort changes in a population of neophyte contact lens wearers would provide useful insights in this regard.

Tear film

When meibum reaches the gland orifices, it spreads out over the anterior surface of the pre-ocular tear film.[38,39] A contact lens when placed on the ocular surface divides the tear film into a pre- and a post-lens tear film and creates new interfaces with, and within, the ocular environment. This partition and new interactions have been shown to lead to biophysical changes of the tear film properties, such tear film stability, pre-lens lipid layer thickness, tear volume as well as tear evaporation rate. To date, the effect of many of these biophysical properties on comfort are inconclusive.[40]

Compared to the tear meniscus volume (approximately 1.5 µL) on the ocular surface,[41] a reduced tear meniscus volume (approximately 1 µL) on the contact lens surface was evident.[42] In contact lens wear, tear volume reduces with time,[43] which corresponds to the gradual decrease in ocular comfort towards the end of the day.[44,45] A significant positive association between upper and lower tear meniscus volume with comfort has been noted following 10 hours of contact lens wear.[44] Stability of the tear film is not constant throughout the day and upon insertion of contact lenses.[46] Tear film thinning occurs significantly more rapidly (5-6 seconds) over the surface of contact lenses than on the corneal surface.[47,48]

In contact lens wearers, reduced pre-lens break-up times have been associated with discomfort.[45,49-55] Non-invasive tear break-up time is a significant predictor of symptoms as measured by the Ocular Surface Disease Index (OSDI).[56] Tolerant wearers averaged a non-invasive tear break-up time of around 20 seconds in comparison to 13 seconds for intolerant wearers.[45] The pattern of pre-lens tear film drying on the contact lens surface has been shown to vary with tolerance to contact lens wear, with all intolerant contact lens wearers exhibiting a streak pattern of break-up in comparison to tolerant wearers, in whom more spot break-up patterns were observed.[45,57] Non-invasive tear break-up time after 6 hours of lens wear was found to be shorter in the intolerant group, and pre-lens break-up time deteriorated gradually over the six-hour wear period in the tolerant group only.[58] However, another study could not confirm non-invasive tear break-up time as a predictor of contact lens tolerance.[59]

The grade of the lipid layer recurrently deteriorates over the contact lens surface, indicating a thinning lipid layer due to lack of a sufficiently thick aqueous layer.[60] Lipid layer spread has been found to become much slower after 8 hours of soft contact lens wear.[61] This impairment in lipid spread correlates with the thinner aqueous layer formed over the soft contact lens surface, especially silicone hydrogel lenses.[44,62] Tear film evaporation is believed to be the main determinant of tear film thinning and is a key component in tear dynamics,[63] compared to absorption and drainage.[64,65] Excessive tear evaporation may cause tear hyperosmolarity, triggering a cycle of ocular surface inflammation.[66] With one exception,[67] most of published literature report increased tear evaporation rate in dry eye,[68-72] typically in association with a loss of integrity of the lipid layer.[73] Tear evaporation rate increases with a contact lens *in situ,*[63,74,75] but there are no consistent differences in the tear evaporation rate with different lens materials, even between rigid and soft lenses under constant environmental conditions. The increase in tear evaporation rates ranged from a 1.23 to 2.63 times relative to the non-lens wearing eye, with no clear pattern relating to either the type of lens or its water content.[74,76,77]

Tear hyperosmolarity is likely to be a key pathogenic factor causing ocular surface inflammation leading to discomfort.[40] The electrolytes of the aqueous phase, predominantly sodium and potassium cations and chloride and bicarbonate anions, are major contributors of tear osmolarity, while proteins and sugars play a negligible

role.[78] Tear film osmolarity in the normal eye ranges between 283 and 318 mmol/kg, with an average value of approximately 302 mmol/kg.[78,79] Tear film osmolarity may return to, or remain at, its pre-contact lens insertion level,[80] or may increase post-lens removal compared to baseline.[81,82] Reduced tear production due to reduced corneal sensitivity and/or excessive tear evaporation due to a disrupted tear film and reduced tear stability could be the two main reasons for increased osmolarity in contact lens wear.[83,84] Significantly higher osmolarity values in participants with contact lens induced dryness have been observed.[85] However, in a study by Stahl and colleagues,[82] an association between tear osmolarity and ocular comfort during contact lens wear could not be established.

There is some evidence suggesting a link between reduced blink frequency or increased percentage of incomplete blinks,[48,86-89] tear turnover rate,[90] tear pH,[91-97] and comfort in contact lens wearers. The best evidence points towards a link between decreased stability, increased evaporation, reduced tear turnover and contact lens discomfort.[40] However, the effects of these tear properties on comfort are inconclusive.

Associations between biochemical characteristics of eyelids and contact lens comfort

The level of cholesterol (cholesteryl ester + free cholesterol) in tears decreased immediately with lens wear (1.91±1.9 mg/ml) compared to no lens wear (1.95±1.5 mg/ml), but recovered to habitual levels within two weeks of ceasing soft contact lens wear.[98] Higher levels of cholesteryl esters have been significantly associated with thin lipid layer patterns and increased dryness symptoms in symptomatic contact lens wearers.[99]

In meibum samples of dry eye patients there were higher levels of triacyl glycerides that increased with disease severity,[100] whereas lower levels of triacyl glycerides were found in patients with obstructive meibomian gland dysfunction (2.2%) compared to healthy individuals (3.1%).[101] Differences were observed in iso and anteiso fatty acid groups of triacyl glycerides of meibum in contact lens wearers compared to non-lens wearers.[102] In the same study, lower levels of unsaturated and branched fatty acids of the triacyl glycerides were observed in patients with meibomian keratoconjunctivitis. However, in one study, lower levels of triacyl glycerides in the tear lipidome in symptomatic contact lens wearers were associated with reduced tear film stability.[99]

Due to their amphiphilic and surfactant properties, *(O-acyl)-ω-hydroxy fatty acids* (OAHFAs) are likely to play an important role in maintaining the structural stability of the tear lipid layer along with phospholipids.[100,103] Lam,[100] reported reduced concentrations of OAHFAs in meibum with increased disease severity in a dry eye population. The effect of contact lenses on OAHFAs in tears has not been reported to date to the best of our knowledge.

Wear of daily disposable hydrogel lenses reduced tear phospholipid concentrations (162 ± 33 µg/ml) in tears after 12 hours of lens wear compared to tears of the same subjects when not wearing lenses (220 ± 35 µg/ml).[104] Reduced tear phospholipids have also been associated with shorter tear break-up times among soft contact lens wearers.[99] Phospholipase enzymes cleave the ester bond of glycerophospholipids at their sn-2 position, yielding free fatty acids. An increased activity of the enzyme secretory phospholipase A2 (sPLA2) could be a reason for the reduction in phospholipid concentration in tears during lens wear.[104] In tears, the normal sPLA2 concentration is 54.5±33.9 µg/ml, but this is higher (79.6±29.6 µg/ml) among the young (20-29 years), and reduced (32.4±27.8 µg/ml) in older populations (>70 years). During contact lens wear (experienced soft contact lens wearers for a minimum of 2 years), the concentration of sPLA2 in tears was decreased (56.3±30.0 µg/ml) compared to its concentration in people who did not wear contact lenses (95.2±48.2 µg/ml).[105]

Tear film proteome changes with contact lens discomfort have not been studied extensively. No significant differences were found in the concentration of total protein, lysozyme, lactoferrin, or sIgA between tears of tolerant or intolerant contact lens wearers in the absence of lens wear compared to soft contact lens wear.[45,58] However, increased levels of lipocalin-1, sPLA2 and leukotriene B4 (LTB4) in tears were observed in intolerant individuals in the absence of contact lens wear compared to tolerant lens wearers.[106,107] A study that analysed diurnal

changes in tear protein concentrations with and without contact lens wear showed that absolute concentration of prolactin-induced protein was associated with end of the day discomfort,[108] but not related to changes in 15 different cytokines,[109] bradykinin, sPLA2, complement proteins C3 and C3a or secretory immunoglobulin A.[108] The role of resolvin-D1, which is one of the tear mediators that cease progression of acute inflammation, or cysteinyl leukotrienes and histamine, which are allergic meditors, in contact lens comfort were studied.[110] Although there was no association between absolute concentations of LTB4, sIGA, C3 and C3a with contact lens discomfort,[110] a drop in their levels was noted by the end of the day in both contact lens wearers and non-lens weares, with contact lens wearers presenting higher levels compared to non-lens wearers indicating an influence of contact lens on LTB4 concentration.[111]

Protein analyses also showed decreased levels of MUC5AC in the tears of subjects experiencing contact lens discomfort,[14] while another study could not confirm significant changes in the levels of transmembrane or secreted mucins, or in the content of glycosidic residues in non-goblet epithelial cell vesicles in intolerant contact lens wearers.[112]

Associations between microbiological characteristics of eyelids and contact lens comfort

As in other body sites, the ocular microbiota is expected to play a defensive role against colonization of pathogens.[113] Ocular bacterial communities have been studied using culture-dependent methods and more recently, with 16S r RNA gene sequencing in healthy subjects and in people with eye diseases. A recent study investigated the temporal stability of the ocular surface microbiome in a large cohort of healthy subjects.[114] This study showed a low diversity of microorganisms on the ocular surface, but most individuals shared several taxa.[114] Over 90% of operating taxonomic units were constituted of three phyla: Proteobacteria (64.4%) Firicutes (15.5%) and Actinobacteria (15.0%), and Species of Staphylococcus, Propionibacterium, Corynebacterium, Bacillus, Micrococcus, Rothia, Pseudomonas, Streptococcus, Methylobacterum, Acinectobacter, and member of the familie Oxalobacteracease and Enterobacteriaceae have been cultured from contact lenses.[115,116] Using non-culture methods, eyelid microbiota of lens wearers has been shown to be different from that of non-lens wearers, resembling closely the microbiota of the skin.[115] Little is known about the role of these ocular commensals in contact lens discomfort. The total colony forming units isolated from dry eye participants were significantly different from that of the non-dry eye group.[117] While another study showed that the relative proportions of bacteria did not change significantly in different severities of meibomian gland dysfunction and anterior blepharitis.[118] Given the discrepancies in these findings and the changes that occur to the lid microbiota during lens wear, it is possible that ocular microbiota might have some role in contact lens discomfort.

Blepharitis is known to provide a favourable environment for *Demodex* infestation,[119,120] and is associated with colonization of the eyelid margins by bacteria such as *Staphylococcus epidermidis*, *Propionibacterium acnes*, *Corynebacterium* and *Staphylococcus aureus*.[119,120] Some common ocular symptoms associated with *Demodex* infestation include itching, redness and tearing.[121] Clinically, the presence of *Demodex* in hair follicles can be confirmed using various techniques such as reflectance *in vivo* confocal microscopy,[122] cilia epilation and mite observation under a light microscope,[123] or by cilia manipulation and observing them in vivo under a high-magnification biomicroscope.[124] Infestation with *Demodex* mites has been shown to impact a number of ocular symptoms and clinical signs such as conjunctival inflammation and tear break-up time.[125,126] Additionally, a significant relationship between the number of *Demodex* and ocular discomfort measured with the ocular surface disease index (OSDI) has been reported,[126,127] but this could not be replicated in a recent study.[128] Hence, it is uncertain if *Demodex* influences contact lens comfort. Contact lens wearers may harbor more *Demodex* than non-contact lens wearers, with up to 90% of contact lens wearers harbouring mites.[128]

Associations between microbiological characteristics of eyelids and contact lens comfort

Investigating the influence of contact lens material, design and the lens care system is vital to understanding

contact lens discomfort. Differences between brands of contact lenses made from the same material (that may differ in geometric designs, edge configuration or production methods), differences in wearing modality (daily wear, overnight occasionally, or up to 30 nights continuous wear), duration of use prior to replacement, wearing time during the day (from just a few hours to most of the day) and finally the lens care products (which could range from no exposure in the case of daily disposable lenses to a preserved system) that has extensive uptake and release of product into the contact lens material may have an impact on comfort experienced by contact lens wearers.[129]

Most studies with robust experimental designs, including masking, randomization and concurrent controls have shown no difference in subjective comfort between silicone hydrogel and hydrogel lenses.[129] Daily disposable hydrogel lenses have been shown to be more comfortable than the same lenses worn daily on a frequent replacement basis and using disinfecting solutions to care for lenses.[130] High water content lenses,[85,131] and high coefficient of friction,[132-134] have been shown to be associated with contact lens related dryness symptoms. Ionicity,[85] and low-modulus of elasticity,[135-137] are not believed to influence comfort.

A thorough review of the literature shows that there are very few proven links between contact lens discomfort and factors related to the contact lens material, design, and care system.[138-142] However, clinical insight,[130,143] demonstrates that making changes to the lens material, design, care system, and replacement schedule can improve comfort in contact lens wearers who exhibit unacceptable comfort.

Summary

Contact lens discomfort is a substantial problem experienced by up to 50% of lens wearers globally and it is one of the factors associated with permanent discontinuation of lens wear.[144] With the available information, the lid margin, especially the lid-wiper region and tear biophysical properties, appear to strongly determine symptoms in contact lens wearers, while weak associations are noted with tear biochemistry, structural and functional alterations in the meibomian gland, bulbar and palpebral conjunctiva.

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