

The TFOS International Workshop on Contact Lens Discomfort: Report of the Contact Lens Interactions With the Ocular Surface and Adnexa Subcommittee

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See the tables in the Introduction for the members of the TFOS International Workshop on Contact Lens Discomfort.

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The report of this subcommittee concerns the impact of contact lenses (CLs) on the ocular surface, with a particular emphasis on CL discomfort (CLD). We define the ocular surface, its regional anatomy, and the physiological responses of each region to CL wear.

DEFINITION OF THE OCULAR SURFACE

The ocular surface consists of the continuous mucosal surface that begins with the cornea centrally and extends, via the limbus, to the bulbar and fornical conjunctiva to end with the tarsal conjunctiva.^{1,2} Classically, the tarsal conjunctiva is further subdivided into proximal and distal parts by the presence of a subtarsal fold,³ which runs parallel to the lid margin at approximately 2 mm from its posterior border. The distal part, termed the marginal conjunctiva, is of particular importance to lid function during blinking and extends from the fold to the mucocutaneous junction on the occlusal surface of the lid margin. That part that is apposed to the globe is the site of the so-called "lid wiper" zone of the lid, which has an important role in distributing the tear film across the ocular surface. Many aspects of the ocular surface are covered in several excellent reviews, including the functional anatomy and immunology,⁴⁻⁶ ocular allergy,^{7,8} and ocular surface reconstruction.⁹⁻¹⁵

THE TEARS AND TEAR FILM

The exposed ocular surface is at all times covered by the tear film. When the eyes are closed, the tear-filled space so formed is termed the conjunctival sac. Aqueous tears, secreted by the main and accessory lacrimal glands, enter the upper and outer parts of the sac, replenishing the tears. As the eyes open, in the upstroke of the blink, the tears exposed by the widening palpebral fissure form the preocular tear film and the tear menisci.¹⁶⁻¹⁸ The precorneal tear film is estimated to be approximately 3 μm in thickness.¹⁹

The menisci, lying at the interface between the lid margins and the surface of the globe, provide the route by which the tears reach the lacrimal puncta and canaliculi and thence enter the nasolacrimal system. In the steady state, tears lost from the exposed ocular surface by evaporation during the blink interval and those lost by tear drainage, balance that produced by tear secretion. Meibomian lipid (meibum), derived from the tarsal meibomian glands, is delivered to the lid margin skin just anterior to the mucocutaneous junction and is spread onto the surface of the tear film in the upstroke of the blink.^{20,21} The tear film lipid layer retards evaporative water loss from the eye, playing a critical role in protecting the ocular surface from desiccating stress.

Integrated Lacrimal Functional Unit

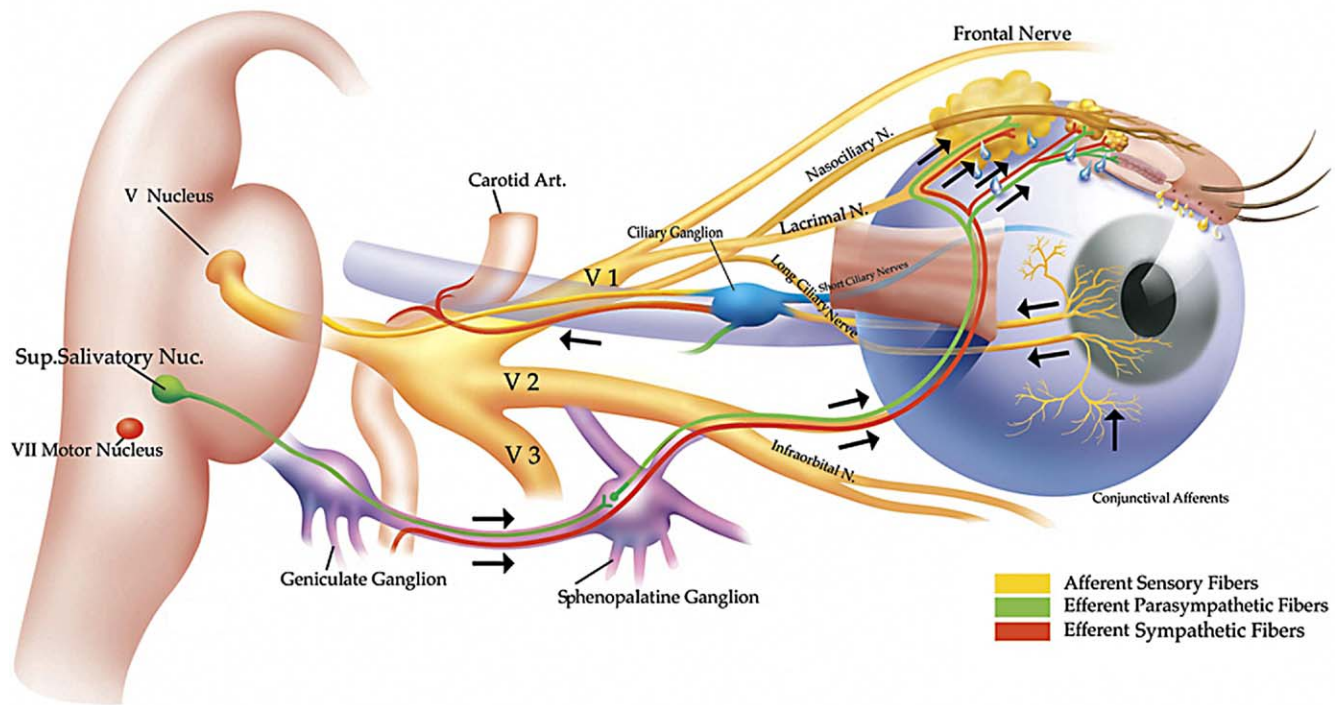


FIGURE 1. The Lacrimal Functional Unit is an integrated system comprising the lacrimal glands, ocular surface (cornea, conjunctiva, meibomian glands, goblet cells, and lids), and the sensory and motor nerves that connect them. Trigeminal sensory fibers arising from the ocular surface, particularly the cornea, run to the superior salivatory nucleus in the pons, from where efferent fibers pass, in the nervus intermedius, to the sphenopalatine ganglion. Here, postganglionic fibers arise that terminate in the lacrimal gland, nasopharynx, and vessels of the orbit. Another neural pathway controls the blink reflex, via trigeminal afferents and the somatic efferent fibers of the seventh cranial nerve. Higher centers feed into the brainstem nuclei and there is a rich sympathetic supply to the epithelia and vasculature of the glands and ocular surface.²³ Figure courtesy of Michael Stern.

OCULAR SURFACE AND THE LACRIMAL-FUNCTIONAL UNIT

The ocular surface may be thought of as an integrated functional unit,^{5,22,23} protected from environmental stress by homeostatic processes that control tear flow and tear film formation.²⁴ In addition to the cornea and conjunctiva,⁴ its component parts include the main²⁵⁻²⁷ and accessory lacrimal glands,²⁸ the meibomian glands²⁹ and mucin-producing epithelial cells and goblet cells,³⁰ the blink mechanism,³¹ and events accompanying the closed eye condition.³² Homeostasis involves, in particular, a reflex arc between the ocular surface and the brain stem,^{33,34} and in addition, immunologic,³⁵ inflammatory,³⁵ and endocrine regulation.³⁶

The ocular surface is richly innervated by trigeminal afferents and the lacrimal and meibomian glands each receive a parasympathetic and a sympathetic nerve supply. Inputs and outputs from these nerves form the basis of a reflex arc between the ocular surface, brainstem, and lacrimal glands, which adjusts tear secretion to meet daily demands. This is referred to as the *lacrimal functional unit*.^{33,34,37} The sensory innervation of the cornea is particularly rich,³⁸ while that of the lid margin mucosa is similar to that of the central cornea.³⁹ These afferents cooperate to stimulate reflex tear production and spontaneous blinking, in addition to mediating sensation. Additional inputs to the lacrimal gland from higher centers of the brain are involved in emotional tears. Sensory inputs from the nasolacrimal system may suppress tear production.⁴⁰ Figure 1 graphically portrays this integrated system.

A loss of sensory drive to the brain stem salivary or blink centers can inhibit tear secretion⁴¹⁻⁴⁴ and reduce the rate of spontaneous blinking,^{45,46} compounding the effect of desiccating stresses to the eye. Impairment of feedback by either injury or inflammatory cytokines acting on the ocular surface may be an important contributor to ocular surface inflammation in dry eye disease.^{4,33,34,47-54}

CL INTERACTIONS WITH THE OCULAR SURFACE

Contact lens discomfort must relate to the interactions between the CL and the ocular surface and alterations to its tissues during lens wear. These changes are described below on a regional basis.

IMPACT OF CLS ON THE CORNEA

Corneal Structure and Function

The cornea is the transparent, anterior, avascular part of the corneoscleral envelope, separated from the sclera by the limbus. It has a rich sensory nerve supply from the trigeminal nerve,^{55,56} details of which are discussed in the subcommittee report on the neurobiology of discomfort and pain.

The cornea is covered by a stratified squamous, nonkeratinized epithelium whose surface cells are connected by tight junctions that seal the intercellular space. These cells exhibit microvillae, which increase the surface area and facilitate interactions with the tear film. The apical membranes of these

cells express a glycocalyx composed chiefly of transmembrane mucins,³⁰ which confers wettability to the corneal surface.⁵⁷ A similar arrangement occurs in the conjunctiva. The glycocalyx, together with the tight junctions, creates a relatively impervious barrier to the passage of small, water-soluble molecules, such as the dyes used in clinical practice to stain the cornea (e.g., fluorescein and lissamine green).^{58,59} This is the basis for the very limited degree of punctate staining of the cornea and conjunctiva seen in the normal eye.

Deeper cells are highly interdigitated and connected by desmosomes. The deepest layer consists of columnar, basal cells, which are approximately 10 μm in diameter. The intercellular space, narrow in the normal epithelium, is expanded in the presence of epithelial edema and the separation of these regularly arranged cells, acting as a diffraction grating, is responsible for the “rainbows around lights” reported in the presence of early epithelial edema.⁶⁰ Specialized adhesion complexes, consisting of hemidesmosomes, anchoring fibrils, and anchoring plaques attach these cells firmly to the underlying anterior limiting layer, which is composed of fine, tightly woven collagen fibrils.⁶¹ These form a smooth, rigid base for the epithelium.

The transparent stroma is one of the most highly organized tissues of the body, composed of collagen fibrils arranged as flat lamellae, lying within a matrix of proteoglycans. The lamellae show greater interweave anteriorly, where a proportion are inserted into Bowman’s layer.^{62,63} The narrow and highly uniform width and spacing of the fibrils within the lamellae is the basis of stromal transparency.⁶⁴ Peripherally, as the lamellae pass through the limbus to combine with the sclera, this order is lost and the marked variation in fibril diameter and spacing results in the opacity of the sclera. Sandwiched between the lamellae are the keratocytes, which form an interconnecting network coupled by gap junctions.^{65,66} These cells are responsible for production and maintenance of the stromal collagen and the proteoglycans, which maintain spacing between the collagen fibrils. Keratocytes, transforming to myofibroblasts, are also the source of the fibrotic response to corneal stromal injury,^{67,68} which can lead to permanent scarring.

Descemet’s membrane is the basal lamina of the endothelium and forms a scaffold over which endothelial cells may spread to maintain continuity following cell loss or injury. Contiguous cells are joined by macula occludens junctions, which form a more leaky barrier than that found in the epithelium. They permit the movement of water and nutrients from the aqueous humor into the cornea. The energy-dependent activity of the corneal endothelium, driving Na^+ / K^+ -activated ion pumps, and the movement of sodium (Na^+) and bicarbonate (HCO_3^-) ions out of the cornea, leads to a steady, osmotically driven, outward movement of water into the anterior chamber.⁶⁹ This generates a negative hydrostatic pressure within the stroma, reduces its water content (corneal deturgescence), and preserves the regular order of the collagen fibrils necessary for its transparency. This negative pressure, transmitted to the intercellular spaces of the epithelium, ensures that it is normally edema-free.

When endothelial function fails and the hydrostatic pressure in the stroma becomes less negative, the stroma swells, fibril order is lost, and the cornea thickens and becomes progressively less transparent. Stromal swelling is more limited anteriorly where the lamellar interweave is greatest.^{70,71} In the presence of a normal ocular pressure, when the hydrostatic pressure becomes positive, epithelial corneal edema also occurs^{72,73} and there is a further and more marked loss of transparency, due to irregular, surface astigmatism. Epithelial, and to some extent stromal edema, may also result from breaches in the corneal epithelium.

In humans, mature corneal endothelial cells do not divide significantly and their density decreases with age,⁷⁴ and cells spread and enlarge to maintain a functional monolayer. Excessive cell loss due to injury can disturb the functional integrity of the endothelium, leading to corneal decompensation, stromal swelling, and loss of transparency.⁷⁵

The nutrition of the cornea relies almost entirely on materials supplied by the aqueous humor. The oxygen supply is provided by the tear film for the anterior cornea and from the anterior chamber for the posterior cornea. Carbon dioxide, the product of cellular metabolism, is readily lost to the atmosphere.

Epithelium

Many different effects of CL wear on the corneal epithelium have been reported. The epithelial cells of the cornea secrete a range of active soluble molecules into the tear film. This is discussed more fully in the subcommittee report on the CL interactions with the tear film.

Morphological Changes. CL wear has a number of effects on corneal morphology and ultrastructure, including epithelial thinning and increased cell size.⁷⁶⁻⁷⁸ Using specular microscopy, Mathers and colleagues⁷⁹ reported that extended wear (EW) soft contact lenses (SCL) and daily wear (DW) rigid lenses resulted in larger epithelial cells than controls, whereas the epithelial cells of DW SCL subjects were not different from controls. Similarly, other studies show that while mean cell area is not affected by DW, lenses worn on an EW modality induce a gradual increase in cell area.⁸⁰⁻⁸⁴

Epithelial cells harvested by corneal impression cytology from SCL wearers were also found to be larger than those from non-lens wearers.^{85,86} Overall, for hydrogel and silicone hydrogel (SiHy) DW lenses, effects on cell size are minor but become more obvious with EW.⁷⁷ For rigid lenses, cells increase in size by 10% to 30% during DW.⁸⁷ One hypothesis for this increase in cell size is that it is associated with slowing of epithelial renewal, such that cells are retained on the surface for a longer period of time, allowing more time for them to flatten and enlarge,⁸⁴ but other factors, such as mechanical compression, particularly with rigid lenses, may be involved.⁷⁷ Holden and colleagues⁸⁸ reported that long-term EW of SCL caused a 5.6% decrease in epithelial thickness. Several other studies have used in vivo laser scanning confocal microscopy (LSCM) to study lens effects on the epithelium. Ladage and colleagues⁸⁷ did not see an effect on epithelial thickness after 4 weeks of DW SCL, whereas an almost 10% decrease in thickness was observed with rigid lens wear. They also noted that epithelial cell surface area increased 3% to 10%, depending on lens type. Patel and colleagues⁸⁹ showed that temporal but not central epithelial thickness was reduced in corneas of long-term (>10 years) CL wearers. Corneal epithelial basal cells were found to be less regular in low oxygen transmissibility (Dk/t) lens wearers than high Dk/t and non-lens wearers, and both types of lens wear were associated with epithelial thinning, compared with non-lens wearers.⁹⁰ Yagmur and colleagues⁹¹ studied the eyes of hydrogel CL wearers (average wear duration of approximately 3.5 years) and controls. They observed that corneal epithelial cells were enlarged in eyes wearing lenses with a mean Dk/t ratio of approximately 27. They attributed this and other corneal changes, such as reduced keratocyte density, to both mechanical and hypoxic effects. A recent review by Robertson⁷⁶ summarizes epithelial thickness and size changes with various materials as a function of wear modality and the author suggests partial dependence on oxygen transmission for thinning associated with overnight hydrogel wear, but a mechanical cause for that seen with first-generation SiHy lenses.

Alonso-Caneiro and colleagues⁹² recently reported on the use of optical coherence tomography to assess the effects of 6 hours of SCL wear on morphology. Subtle, but significant, changes were observed and these were most apparent at the limbus, presumably due to greater pressure in this area. Epithelial thinning of $2.84 \pm 0.84 \mu\text{m}$ was observed for the cornea versus $5.47 \pm 1.71 \mu\text{m}$ for the limbus, with the SiHy lens causing the least surface changes.

A scanning electron microscopic study on samples of epithelium harvested prior to photorefractive keratectomy showed that there was no difference in the number of surface microvilli among CL wearers and non-lens wearers, but that epithelial mucin was reduced in the lens-wearing group.⁹³ Morphological studies in orthokeratology models have revealed an expected central epithelial thinning and peripheral thickening for myopic correction, and the reverse for hyperopic corrections.⁹⁴⁻⁹⁷ Nieto-Bona and colleagues⁹⁷ used LSCM to study epithelial morphological changes induced by 1 month use of orthokeratology lenses. Basal epithelial cell density was reduced and wing and superficial cells showed enhanced visibility. Superficial cells also were increased in height and width.

To date, no direct correlation between any of these morphological changes with CLD has been reported.

Epithelial Homeostasis. Studies have shown that the normal process of sloughing of corneal epithelial cells is impeded by CL wear. This occurs with all lens types and wear modalities and tends to recover over time, suggesting that an adaptation to lens wear occurs.^{87,98,99} Normal exfoliation is an apoptotic process driven by factors such as eyelid shear forces and centripetal pressure and involves loss of superficial cell expression of the antiapoptotic protein Bcl-2 prior to sloughing. Yamamoto and colleagues¹⁰⁰ observed a reduction in the total number of Bcl-2-negative and TUNEL- (marker for apoptosis) staining cells, suggesting that rigid lens wear blocks necessary changes in Bcl-2 expression that must occur before exfoliation is possible. Lens-induced effects on desquamation do not appear to be related to lens Dk/t.^{77,101}

More than a decade of studies indicate that lens wear inhibits basal epithelial cell proliferation in the central cornea, causes delay in vertical migration as cells move toward the surface, and reduces apoptotic desquamation of superficial cells. As normal corneal epithelial homeostasis helps maintain a smooth surface for refraction of light and barrier function, compromise to this process could contribute to ocular surface changes that lead to CLD. However, to date, no direct correlation has been demonstrated.

Barrier Function. The corneal epithelium forms a formidable barrier to the external environment and disruption of the barrier may result in edema and permit entry of microbes. Thus, compromise of the barrier by CL wear is an important issue. Although an early study by Boets and colleagues¹⁰² did not show any difference in corneal epithelial permeability in CL wear using a peroxide or biguanide care solution, hypoxia associated with lens wear has been implicated in reducing corneal barrier function.

Clinical studies using fluorometry to quantify fluorescein penetration from the tear film to the stroma, indicate that hypoxia and also tear stagnation play a significant role in reducing epithelial barrier function with various modalities of lens wear.¹⁰³⁻¹⁰⁷ However, other factors are also involved. Two studies using SiHy lenses, which eliminate concerns associated with hypoxia, confirm this. Lin and colleagues¹⁰⁸ demonstrated changes in epithelial permeability under a 30-day continuous wear modality. Notably, Asian eyes appeared to be more susceptible to permeability changes than non-Asian eyes. Duench and colleagues¹⁰⁹ demonstrated an increase in epithelial permeability with DW of a SiHy lens, which they

proposed was due to mechanical effects from the stiffer SiHy material. They were also able to show increases associated with the use of solutions. No direct link between CLD and epithelial permeability has been shown.

Corneal Erosions. CL wear has been associated with corneal erosions, in which a full-thickness detachment of epithelium in a localized, well-circumscribed area of the cornea occurs.¹¹⁰⁻¹¹² As reviewed by Markoulli and colleagues,¹¹¹ several mechanisms may be involved, including lens adhesion, mechanical damage from exacerbated thinning due to lens dehydration, bacterial proteases, and reduced epithelial density leading to reduced hemidesmosomes. Hypoxia-related decreased carbon dioxide efflux and epithelial cell acidification may contribute to altered cell appearance and metabolism during wearing of lenses with low Dk/t.^{113,114} This complication is typically symptomatic, especially following lens removal.

Corneal Staining. "Corneal staining" is a general term that refers usually, to the punctate uptake of a dye, such as fluorescein, rose Bengal, or lissamine green, into the corneal epithelium.¹¹⁵

Corneal staining is an ubiquitous feature of CL wear; however, it is important to note that it is also frequently observed in non-lens wearers.^{116,117} The frequency of corneal staining of any severity in a population of CL wearers may be as high as 60%,¹¹⁶ but often staining is of a low level and generally clinically insignificant. Brautaset and colleagues¹¹⁸ reported an incidence of 19.5% corneal staining among 338 adapted hydrogel lens wearers, with no subjects displaying staining greater than grade 2 (on a 0-4 scale).

Corneal staining can be caused by a number of factors, which can be grouped into various categories, including mechanical, inflammatory, exposure, metabolic, toxic, allergic, and infectious. Sources of mechanical staining include lens defects, poor lens quality (e.g., rough edge),¹¹⁹ lens binding (which may occur with overnight EW rigid lenses),¹²⁰ excessive lens bearing due to poor fit, foreign bodies beneath the lens, or abrasion occurring during lens insertion or removal.

In SCL wearers, exposure keratitis manifests typically as a band of inferior arcuate staining.^{121,122} This is due to epithelial disruption as a result of drying of the corneal surface¹²¹⁻¹²³ and is often associated with incomplete blinking. Desiccation staining with SCL can be categorized as a form of exposure keratitis.^{124,125} This condition appears as a central punctate stain and most often occurs when high water content lenses are made too thin, causing water to be drawn out of the cornea when the lens dehydrates.¹²⁶ The classic pattern of 3 and 9 o'clock staining in rigid lens wearers is also primarily thought to represent a form of exposure keratitis, whereby the eyelids are bridged away from the corneal surface at the lens edge at the 3 and 9 o'clock corneal locations.¹²⁷

All CLs are known to induce various levels of epithelial hypoxia and hypercapnia,¹²⁸ resulting in the production of various metabolites (e.g., lactic and carbonic acid). Evidence that such changes can adversely affect comfort is lacking.

In a case-control study of 413 CL wearers, Nichols and Sinnott¹²⁹ examined a variety of lens- and subject-related factors, to determine their potential association with sodium fluorescein corneal staining. Several factors were shown to be related to increased corneal staining, including increased daily wearing times ($P = 0.0006$), lower income ($P = 0.0008$), lissamine green conjunctival staining ($P = 0.002$), CL deposition ($P = 0.007$), increased tear meniscus height ($P = 0.007$), and decreased hydrogel nominal water content ($P = 0.02$). The wearing of SiHy lenses (as opposed to hydrogel lenses) was protective against corneal staining ($P = 0.0004$). Notably, these

authors reported that neither CL care solutions nor disinfectants were associated with increased corneal staining.

Relatively little information is available relating corneal staining to discomfort. A paradox of the corneal staining response is that there appears to be no clear relationship between the severity of staining and the degree of ocular discomfort. For example, an exposure keratitis in the form of an extensive inferior arcuate diffuse staining pattern can be virtually asymptomatic, whereas a small tracking stain caused by a foreign body trapped beneath a rigid lens can be excruciatingly painful.

Studies examining various corneal staining associated with the combination of various CL materials and solutions have produced equivocal results, with some studies showing no correlation between CLD and staining¹³⁰⁻¹³² and others indicating that increased staining is associated with a reduction in lens comfort.¹³³⁻¹³⁵ A recent study, comparing dryness and corneal staining in a group of Asian and non-Asian wearers,¹³⁶ demonstrated that the Asian subjects exhibited a greater amount of staining and reported a higher level of CLD. Among Asians, CLD and staining were not related, whereas they were among non-Asians.

Despite many publications examining corneal staining associated with CL wear, overall, there appears to be, at best, a weak link between CLD and corneal staining and it is not a major factor for most CL wearers.

Stroma

Keratocyte Density. Using LSCM, various authors have reported the normal keratocyte density in the anterior stroma to be approximately 993 cells/mm², or 29,917 cells/mm³, decreasing toward the posterior stroma to approximately 621 cells/mm², or 18,733 cells/mm³, an approximate 60% decrease in cells per area or volume.¹³⁷ Also, keratocytes in the posterior stroma are less densely packed and overall their nuclei appear to be slightly larger and flatter than those in the anterior stroma.¹³⁷ Keratocyte density does not differ between males and females or between right and left eyes of a subject.¹³⁸ There is a decline in the density of keratocytes throughout the stroma with age,^{138,139} as well as an increase in the spacing of collagen fibers throughout life (by approximately 14% by age 90 years).¹⁴⁰ The stroma also contains nerve fibers and microdots, which are small highly reflective dots found throughout this tissue layer. The composition of these microdots is unknown, but it has been hypothesized that they represent dysgenic or apoptotic cellular remnants lying dormant in the stroma.¹³⁷

CL wear has an effect on keratocytes. Several studies have demonstrated an apparent loss of keratocyte density of approximately 18% to 30% in the anterior stroma and 7% to 18% in the posterior stroma, when wearing various lens types on either DW or EW schedules.^{91,141-143} The decrease in density was maintained when accounting for possible edema.¹⁴¹ However, not all studies have found this decrease.^{89,144} When a reduction has been noted, the density change was not affected by the Dk/t of the lens material.^{141,145} In a study examining the differences between no lens wear, SiHy lens wear, and high Dk/t rigid lens wear, Kallinikos and colleagues¹⁴⁶ found some reduction in keratocyte density in the anterior stroma with rigid lens wear, and in the posterior stroma with SiHy lenses compared with no lens wear.¹⁴⁶ These authors suggested that this was due to the physical presence of the lens and perhaps mechanical stimulation of the release of epidermal growth factor and IL-8 from corneal epithelial cells. Loss of keratocytes may be more profound for SCL wearers compared with rigid gas permeable wearers.¹⁴⁵ No reports

have studied whether any change in keratocyte density is related to CLD.

Stromal Opacities. Apparently benign posterior stromal opacities or white dots have been reported in the corneas of CL wearers.^{137,147-150} These stromal opacities seen using slit lamp biomicroscopy may be related to the stromal microdots seen using LSCM. The microdots have a size of 1 to 4 μm .^{151,152} The initial contention that the appearance of the microdots was associated only with CL wear has been tempered by the finding that these can also be seen in the corneas of non-lens wearers, albeit to a lesser extent.¹³⁷ The pathology and etiology of these formations is unknown. Although Brooks and colleagues¹⁴⁸ and Hsu and colleagues¹⁵³ noted that the development of deep stromal opacities was associated with ocular discomfort and photophobia, none of the other reports of deep stromal opacification or stromal microdots have reported any associated discomfort.

Stromal Infiltrates. CL wear may result in recruitment of cells into the cornea. These cells or “infiltrates” are presumed to be polymorphonuclear leukocytes (neutrophils) from the limbal vasculature, and this has been confirmed from corneal biopsies of CL wearers, with the adverse event named CL peripheral ulcer.¹⁵⁴ While a review of adverse events with CL wear is beyond the scope of this article, infiltrates of the cornea can occur without symptoms and may occur even in the absence of lens wear.¹⁵⁵ The rate of asymptomatic infiltrates in the cornea of CL wearers appears to be influenced by wearing different combinations of SiHy lenses and multipurpose disinfecting solutions,¹⁵⁶ although these results are equivocal.¹⁵⁷

While infiltration of the cornea during overt adverse responses is associated with ocular symptoms, they may also be present in asymptomatic patients, indicating that there is not a straightforward relationship between low levels of corneal infiltration and comfort during CL wear.

Stromal Neovascularization. Wear of low Dk/t CLs may be associated with the ingrowth of blood vessels into the normally transparent cornea.¹⁵⁸ This process of neovascularization is generally categorized as superficial or deep stromal. CL-induced neovascularization is asymptomatic and thus not related to CLD.

Endothelium

Endothelial Blebs. A phenomenon referred to as “endothelial blebs” can be observed in the endothelium of CL wearers.¹⁵⁹ The appearance is of black, nonreflecting areas in the endothelial mosaic that correspond with the position of individual cells or groups of cells. Inagaki and colleagues¹⁶⁰ compared the time course of endothelial bleb formation and disappearance between lenses of varying Dk/t in 20 subjects. Lenses of higher Dk/t induced the lowest bleb response and no difference was observed between rigid and soft lenses of similar Dk/t values.

Histological studies of this response were conducted by Vannas and colleagues.¹⁶¹ The “blebbed” endothelium displayed edema of the nuclear area of cells, intracellular fluid vacuoles, and fluid spaces between cells. Thus, endothelial blebs appear to be the result of a local edema phenomenon, whereby the posterior surface of the endothelial cell bulges toward the aqueous. The endothelial cell bulges in this direction because this represents the path of least resistance, as Descemet’s membrane provides much greater resistance to cell swelling than the aqueous humor. Light from the blebbed cell is reflected away from the observer, which explains why they appear dark or absent.

The etiology of endothelial blebs has been explained by Holden and colleagues.¹⁶² These authors attempted to induce

blebs using a variety of stimulus conditions, and concluded that one physiological factor common to all successful attempts to form blebs was a local acidic pH change at the endothelium. Two separate factors induce an acidic shift in the cornea during CL wear¹²⁸: an increase in carbonic acid due to retardation of carbon dioxide efflux and increased levels of lactic acid as a result of lens-induced hypoxia and the consequent increase in anaerobic metabolism. When silicone elastomer lenses are worn, such metabolic changes do not take place because of their extremely high Dk/t. The time course of the appearance of blebs following lens insertion, and resolution following lens removal, is consistent with the time course of corneal pH change.¹⁶³

Endothelial Cell Density. Numerous studies have demonstrated a decrease in corneal endothelial cell density in the central corneas of rigid¹⁶⁴⁻¹⁶⁷ and soft^{166,168-170} lens wearers. One possible explanation for the apparent CL-induced endothelial cell loss has been provided by Wiffen and colleagues,¹⁷¹ who compared central and peripheral corneal endothelial cell densities in non-lens wearing subjects and long-term CL wearers. Central cell density (2723 ± 366 cells/mm²) was found to be significantly higher than peripheral cell density (2646 ± 394 cells/mm²) for the non-lens wearing group, but not for the CL-wearing group (2855 ± 428 cells/mm² central; 2844 ± 494 cells/mm² peripheral). Based on their results, Wiffen and colleagues¹⁷¹ suggested that CL wear causes a mild redistribution of endothelial cells from the central to the peripheral cornea. Thus, while there is no actual endothelial cell loss, there is a reduction in endothelial cell density in the central region of the cornea, which is counterbalanced by a commensurate increase in cell density in the corneal mid-periphery. The overall endothelial cell population of the cornea is therefore likely to be unaffected by CL wear and no reports exist of a correlation in cell density with CLD.

Endothelial Polymegethism. Polymegethism describes changes in endothelial cell size that occur such that the endothelial cells have a greater variation in cell size than normal, and is closely related to chronic hypoxia.^{172,173} Increases in corneal endothelial polymegethism are associated with the wear of polymethyl methacrylate (PMMA),^{144,164-167,174-178} rigid gas permeable,^{144,171,179,180} and conventional hydrogel^{188,166,169,171,177,178,181-185} lenses. However, SiHy^{168,186} and silicone elastomer¹⁸⁷ lenses do not induce significant levels of polymegethism. It is likely that the etiology of endothelial polymegethism is the same as that for endothelial blebs, in which lens-induced hypoxia and hypercapnia causes an acidic shift at the endothelium,¹⁶² resulting in altered cell morphology. Thus, endothelial polymegethism represents a chronic response and endothelial blebs represent an acute response to the same stimuli.

The morphological changes that constitute polymegethism have been explained by Bergmanson,¹⁸⁸ who conducted an ultrastructural study of the corneas of six long-term CL wearers. In normal circumstances, the lateral cell walls are extremely interdigitated. Bergmanson¹⁸⁸ noted that CL wear causes the cell walls to reorient so that, rather than remaining normal to the endothelial surface, they straighten out and align obliquely. The interpretation of this observation in terms of the three-dimensional structure of the endothelium is that endothelial cells have changed shape but the volume of each cell remains constant. By observing only the apical surface of the endothelium on specular reflection, it appears that a disparity in cell size has developed, whereas, in reality, the cells have merely become reoriented in three-dimensional space.

A further observation of Bergmanson¹⁸⁸ is that, although the endothelium of CL wearers showed some inter- and intracellular edema, the cells were otherwise of a healthy

appearance, containing normal organelles. This raises the possibility that, rather than representing an adverse effect, endothelial polymegethism is a nonproblematic adaptation to chronic metabolic stress induced by CLs.

Sweeney¹⁷⁷ has drawn an anecdotal association between endothelial polymegethism and a condition that she termed "corneal exhaustion syndrome." This is a condition in which patients who have worn hydrogel CLs for many years suddenly develop a severe intolerance to lens wear, characterized by CLD, reduced vision, photophobia, and an excessive edema response. These patients also displayed a distorted endothelial mosaic and moderate to severe polymegethism. Although the link between endothelial polymegethism and corneal exhaustion syndrome is not proven, it does appear that certain wearers can develop an intolerance of lenses over time as a response to chronic and severe lens-induced hypoxia. However, this is unlikely with modern CL materials and the link between hypoxia and CLD remains tenuous.

Endothelial Permeability. There is disagreement in the literature as to whether CL wear alters endothelial permeability. Dutt and colleagues¹⁸⁹ reported a significant increase in mean endothelial permeability, measured using corneal fluorophotometry, among CL wearers, indicating a defect in their endothelial barrier function. A significant increase in the mean endothelial pump rate was also noted among CL wearers. Using similar techniques, Chang and colleagues¹⁸⁴ reported decreased endothelial permeability among CL wearers. In contrast, Bourne¹⁹⁰ reported that the relative endothelial pump rate of 20 long-term CL wearers did not differ significantly from that of control subjects.

Despite these many alterations to the endothelium, to date there have been no reports of CLD associated with nonsevere endothelial cell changes.

Limbus

Limbal Structure. The limbus is a ring of tissue approximately 1.5 mm wide that marks the transition between the clear cornea and the sclera.¹⁹¹ The epithelium thickens on passing from the cornea to limbus and the number of cell layers increases to approximately 10^{192,193} and become arranged into a parallel series of radially disposed bars, separated by a vascular connective tissue.¹⁹⁴ These are the palisades of Vogt.¹⁹⁵ Visibility of the palisades at the slit-lamp is greatly enhanced in pigmented eyes, where the epithelial bars are outlined by pigmented basal cells. The vessels of the palisades arise from an episcleral vascular "circle," which also gives rise to the anterior conjunctival arteries and to the subepithelial marginal arcades of the cornea.^{196,197} The latter vessels form a series of vascular loops that surround the corneal periphery, their central tips providing a useful surface landmark for the periphery of Bowman's layer. They can be the source of superficial new vessels, arising as a pathological response to CL wear or to corneal injury, inflammation, or infection.

Basal, niche-like regions of the epithelial palisades house the stem cells of the cornea, whose division maintains the corneal epithelium.^{198,199} These cells divide infrequently in the normal cornea but give rise to daughter, transient amplifying cells,²⁰⁰ which migrate centripetally from the limbus to the cornea. Their further progeny migrate to the surface and undergo apoptosis prior to shedding.

Limbal Redness. The limbus can respond to CL wear by engorging the limbal vasculature, which is usually referred to as "limbal redness." During wear of low Dk/t SCL, the number of vessels filled with blood and the extent of filling increases, but this does not happen during wear of PMMA lenses,²⁰¹ suggesting that the response is local and not affected by hypoxia occurring at the central cornea. Papas²⁰² demonstrat-

ed that when eyes were exposed to anoxic conditions (100% nitrogen in goggles), the limbal vasculature responded by increasing blood flow, resulting in increased redness. Sustained increases in limbal redness during wear of low Dk/t lenses may lead to growth of limbal vessels into the cornea, which is considered to be an adverse response to lens wear. Wear of low Dk/t soft lenses for 9 months on an EW schedule results in a significant increase in neovascularization.²⁰³

With the advent of SiHy lenses, the number of studies examining limbal redness increased, with studies demonstrating no difference in limbal redness during wear of high Dk/t SiHy lenses compared with no lens wear.²⁰⁴ Use of low Dk/t soft lenses on a daily disposable basis resulted in higher levels of limbal redness than that determined when wearing two types of high Dk/t silicone hydrogel lenses.²⁰⁵ During EW, low Dk/t hydrogel lens wearers showed significantly higher levels of limbal redness than high Dk/t SiHy lens wearers.²⁰³ Refitting subjects from low Dk/t hydrogel lenses to high Dk/t SiHy lenses in either DW or EW schedules results in a significant decrease in limbal redness after just a few weeks.²⁰⁶⁻²⁰⁹ Refitting subjects with high Dk/t lenses also results in reduced signs of corneal neovascularization.²¹⁰⁻²¹² High Dk/t lenses do not induce changes to limbal redness even after 3 years of EW.²¹³

There is little evidence that limbal redness is related to CLD. While one study showed an improvement in comfort during lens wear after refitting with high Dk/t SiHy lenses and a corresponding decrease in limbal redness,²¹² another study demonstrated a similar improvement in comfort (but not limbal redness) even after refitting high Dk/t lens wearers into low Dk/t daily disposable hydrogel lenses.²¹⁴ The type of SiHy lens worn makes a difference to comfort, even though there may be no difference in clinical scores of limbal redness,²¹⁵ and while wearing a low Dk/t lens on a daily disposable basis resulted in increased limbal redness compared with wearing high Dk/t lenses on the same schedule, there was no relationship to comfort,²⁰⁵ suggesting that factors other than oxygen permeability (and, thus, limbal redness) are more important in the factors that drive the comfort response.

Limbal Stem Cell Deficiency. Limbal stem cells serve as the source for corneal epithelial cells, thus stem cell deficiency leads to an abnormal corneal surface, which exhibits fluorescein staining and a dull irregular reflex, often accompanied by decreased vision.²¹⁶ Other complications include photophobia, inflammation, hyperemia, recurrent or persistent epithelial defects, conjunctivalization, scarring, and ulceration.²¹⁶ Several studies show that SCL wear may result in stem cell deficiency.²¹⁶⁻²²⁹ The condition may be focal, affecting a small area, or, more rarely, occur as a severe, almost total stem cell loss.^{216,229} It has been suggested that the more severe form is the result of additional pathology to a cell population already stressed by years of lens wear that finally “exhausts” the stem cells.²²⁹ The true cause of the stem cell deficiency remains unknown, but it has been proposed that it may result from hypoxia and/or mechanical friction on the limbal tissue.^{216,220,228}

In a retrospective study of almost 600 SCL wearers, 2.4% of subjects were found to have focal limbal stem cell deficiency,²²¹ with approximately one-third being symptomatic, suggesting that the condition is more common than one would expect and often goes undetected.²¹⁶ Notably, the preponderance of subjects were female.^{216,221,229} Prolonged wear (both hours per day and numbers of years of wear) may also be a contributing factor.^{216,229} At least two studies show that the epitheliopathy resulting from this deficiency was primarily present in the superior cornea.^{216,221} Rigid gas permeable and scleral lenses do not cause limbal stem cell deficiency; indeed, these lenses have been reported as having beneficial effects in the management of corneal conjunctivalization and in the

reversal of stem cell deficiency.^{230,231} As yet there is no evidence for changes in limbal stem cells being related to CLD, and it seems unlikely that this could account for the acute form of CLD that occurs toward the end of the day, after as little as 1 day of wear in a neophyte wearer.

Corneal Edema

All CLs induce some level of edema, including silicone elastomer lenses, which have extremely high Dk/t values.²³² CLs restrict corneal oxygen availability,^{128,233,234} creating a hypoxic environment at the anterior corneal surface. To conserve energy, the corneal epithelium begins to respire anaerobically. Lactate, a by-product of anaerobic metabolism, increases in concentration and moves posteriorly into the corneal stroma. This creates an osmotic load that is balanced by an increased movement of water into the stroma. The sudden influx of water cannot be matched by the removal of water from the stroma by the endothelial pump, resulting in corneal edema and corneal thickening.^{235,236} A number of other possible mechanisms have been suggested as playing a role in lens-induced corneal edema, including retardation of carbon dioxide efflux (leading to tissue acidosis),¹²⁸ mechanical effects,²³⁷ temperature changes,²³⁸ hypotonicity,²³⁹ and inflammation.²⁴⁰ Nguyen and colleagues²⁴¹ have shown that the variability in CL-induced corneal swelling is associated with both corneal metabolic activity and endothelial function. This suggests that individuals with larger levels of corneal metabolic activity produce more lactic acid and thus more swelling.

The amount of edema is related primarily to the extent of corneal hypoxia that is induced by the lens. With low Dk/t hydrogel and rigid lenses, daytime central corneal edema typically varies between 1% and 6%,²⁴² and the level of overnight central edema measured on awakening generally falls in the range 10% to 15%.²⁴³ SiHy lenses induce less than 3% overnight central corneal edema,²⁴⁴ which is similar to the level of overnight edema without lenses.

While corneal swelling represents both a chronic and acute response to hypoxia, epithelial microcysts are considered to be an important indicator of chronic metabolic stress in the corneal epithelium in response to wearing low Dk/t lenses. Bergmanson²⁴⁵ postulated that microcysts represent an extracellular accumulation of broken down cellular material trapped in the basal epithelial layers. In a process similar to that which occurs in Cogan's microcystic dystrophy,²⁴⁶ the epithelial basement membrane reduplicates and folds, forming intraepithelial sheets that eventually detach from the basement membrane and encapsulate the cellular debris. There is no proven association of epithelial microcysts with CLD.

Dillehay²⁴⁷ argued that increasing levels of available oxygen during CL wear lead to improved comfort. However, these arguments were based largely on anecdotal information. No concrete evidence exists linking oxygen availability or the level of corneal edema during CL wear with CLD, and a recent review supports this.²⁴⁸

Shape Changes

Videokeratographic corneal mapping techniques reveal that all forms of CL wear are capable of inducing small, but statistically significant, changes in corneal topography.²⁴⁹⁻²⁵² Ruiz-Montenegro and colleagues²⁴⁹ reported the prevalence of abnormalities in corneal shape to be 8% in a control group of non-CL wearers, versus 75% in PMMA lens wearers, 57% in DW rigid lens wearers, 31% in DW hydrogel lens wearers, and 23% in EW hydrogel lens wearers.

The results of studies investigating corneal shape changes with SiHy lenses are equivocal. Various authors failed to observe

corneal curvature changes in subjects wearing low-²⁵³⁻²⁵⁵ and high-modulus^{253,254} SiHy lenses, during observation periods ranging from 1 to 18 months. However, Dumbleton and colleagues²⁵⁶ observed a small degree of central corneal flattening in both major meridians of 0.35 diopters (D) in subjects wearing high-modulus SiHy lenses over a 9-month period. Gonzalez-Mejome and colleagues²⁵⁰ noted a similar phenomenon in SiHy lens wearers over a 12-month wearing period. Maldonado-Codina and colleagues²⁵⁷ noted that, over a 12-month period of continuous wear, corneal curvature of subjects wearing high-Dk/t rigid lenses became flatter by 0.13 mm, compared with 0.04 mm for subjects wearing high-Dk/t SiHy lenses ($P = 0.0003$). The refractive findings in subjects wearing these lenses mirrored the corneal curvature changes.

Shape changes may also be induced by lens “binding,” in which the lens becomes immobile, which may occur with DW and EW of rigid lenses. Based on subject reports, lens binding occurs in 29% of DW²⁵⁸ and 50% of EW²⁵⁹ rigid lens subjects. Most other forms of lens-induced corneal shape change are either rare or are known to be associated with specific types of poorly designed or ill-fitting lenses.²⁶⁰

Corneal curvature changes in orthokeratology are deliberately induced to obtain a refractive effect, and appear to result from a combination of short-term corneal molding and a longer-term redistribution of anterior corneal tissue.^{261,262} It has also been suggested that the tear reservoir generated by the steeper secondary curves leads to pressure changes that are responsible for the corneal tissue redistribution.^{262,263}

To date, there are no reports linking CL-induced corneal shape change to CLD.

Temperature Change

Purslow and colleagues²⁶⁴ used a noncontact infrared camera to record the ocular surface temperature (OST) in subjects wearing hydrogel and SiHy CLs on a DW and EW basis. They found that OST immediately following CL wear was significantly greater compared to non-lens wearers ($37.1 \pm 1.7^\circ\text{C}$ vs. $35.0 \pm 1.1^\circ\text{C}$; $P < 0.005$). Lens surface temperature was highly correlated to, but lower than, OST (by $-0.62 \pm 0.3^\circ\text{C}$). There was no difference with modality of wear, but significant differences were found between the hydrogel and SiHy lens materials ($35.3 \pm 1.1^\circ\text{C}$ vs. $37.5 \pm 1.5^\circ\text{C}$; $P < 0.0005$). The authors concluded that OST is greater with hydrogel and greater still with SiHy CLs in situ, regardless of modality of wear, and concluded that the effect is likely due to the thermal transmission properties of the CL material.

Whereas Purslow and colleagues²⁶⁴ assessed OST immediately following CL wear, Ooi and colleagues²⁶⁵ developed a two-dimensional simulation of heat propagation in the human eye using finite element analysis to estimate OST during CL wear. In contrast to Purslow and colleagues,²⁶⁴ they calculated that the corneal surface temperature during CL wear decreased by an average of $0.52 \pm 0.05^\circ\text{C}$ compared with a bare cornea, for all lens types. The authors suggested that an increase in evaporation rate when a CL is worn increases the cooling effect on the ocular surface, resulting in a lower corneal surface temperature during lens wear. Neither of the above groups who examined OST changes with CL wear examined any link to CLD.

IMPACT OF CLS ON THE CONJUNCTIVA

Bulbar Conjunctiva

Conjunctival Staining. Dyes that have been used to assess conjunctival staining include sodium fluorescein, rose Bengal, and lissamine green. In SCL wearers, conjunctival staining is

often observed approximately 2 mm from the limbus, coinciding with the SCL edge.²⁶⁶ This is thought to be due to CL movement or changes in tear film characteristics at the lens edge.²⁶⁷

Several studies have shown greater conjunctival staining with CL wear compared with no CL wear. Lakkis and colleagues²⁶⁸ showed a significantly higher level of conjunctival staining in hydrogel wear compared to non-lens wearers, and found this to correlate with dryness and itchiness. Maldonado-Codina and colleagues²⁶⁷ showed greater conjunctival staining with two SiHy lenses compared with no lens wear or hydrogel lens wear. In a retrospective analysis of 338 experienced lens wearers, Brautaset¹¹⁸ found conjunctival staining in one-third of subjects. Morgan and colleagues²⁶⁹ found significantly greater conjunctival staining in a group of 35 neophytes fitted with SiHy daily disposable lenses compared with non-lens wearers, and this was the only clinical parameter measured to change significantly with lens wear. Guillon and Maissa²⁷⁰ assessed conjunctival staining and comfort in CL wearers using lissamine green. They found greater conjunctival staining in symptomatic subjects both with and without lens wear. These authors suggest that the pattern of staining indicates that the CL causes changes to the conjunctiva in areas not only confined to the lens edge, which they attributed to evaporation due to destabilization of the tear film by the CL.²⁷⁰

Various hypotheses have been postulated regarding CL-induced conjunctival staining, including changes to lens parameters with lens wear (Meadows DL, et al. *IOVS* 2009;50:ARVO E-Abstract 5652), CL modulus (Meadows DL, et al. *IOVS* 2009;50:ARVO E-Abstract 5652), poor lens fit (Meadows DL, et al. *IOVS* 2009;50:ARVO E-Abstract 5652),²⁷¹ or poor edge design.²⁶⁶ Meadows and colleagues (Meadows DL, et al. *IOVS* 2009;50:ARVO E-Abstract 5652) found that changing the lens material and fit impacted the level of conjunctival staining, whereas changing solution did not make a difference. Ozkan and colleagues²⁷² correlated changes to lens parameters with conjunctival staining. They showed a decrease in diameter with lens wear and increasing temperature, both in vivo and ex vivo, which did not correlate with comfort or conjunctival staining.²⁷² They were able to show that lenses with a “knife” or “chisel” edge-form caused more staining than a lens with a relatively “round” edge design. However, no significant difference in comfort was found between edge types after 1 week of wear and there was no correlation between conjunctival staining and comfort, or conjunctival staining and bulbar or limbal redness.²⁷² This is in agreement with Maissa and colleagues,²⁶⁶ who showed that conjunctival staining is most severe nasally and least severe superiorly, a factor they attribute to the flatter conjunctival topography in the nasal quadrant.

In rigid CL wearers, 3 and 9 o'clock corneal staining is visualized with the instillation of fluorescein, and is often accompanied by bulbar and limbal hyperemia and conjunctival staining. Greater inferior conjunctival staining in rigid CL wearers has been reported in a retrospective study by Swarbrick and Holden.¹²⁰ Van der Worp and colleagues²⁷³ showed that eyes with conjunctival staining demonstrated more corneal staining, compared with those with no conjunctival staining. Symptoms were more frequently reported in those with conjunctival staining, compared with those without.²⁷³

Conjunctival Flaps. The incorporation of silicone components into SCL materials, which increases the lens Dk/t, results in materials with higher modulus values.²⁷⁴ As a result, mechanical complications with SiHy materials are greater than those encountered with lower modulus hydrogel materials.^{110,112,275} One of these complications has been termed “conjunctival flaps.”^{112,276-280} These have been described as

“irregular free ends of the conjunctival tissue which move with blinking or other digital manipulation.”²⁷⁸

Conjunctival flaps are typically found 1.5 mm from the limbus in CL wearers and have been reported to resolve with lens discontinuation (Markoulli M, et al. *IOVS* 2007;43:ARVO E-Abstract 5391). Graham and colleagues²⁷⁹ found a 39% occurrence of conjunctival flaps in EW with SiHy lenses, whereas Santodomingo and colleagues²⁸⁰ reported a higher incidence with lotrafilcon A compared with balafilcon A and more events when lenses were worn overnight. Bergmanson and colleagues²⁷⁷ performed conjunctival impression cytology (CIC) on three non-CL wearers, three CL wearers with conjunctival flaps, and three CL wearers without conjunctival flaps. All CL wearers were fitted with lotrafilcon A in the 8.4-mm base curve. These authors found the samples taken over the conjunctival flap to consist of multilayers of epithelial cells and goblet cells and to be devoid of inflammatory cells. In contrast, the nonflap groups had only a single layer of epithelial cells. The authors conclude that conjunctival flaps consist of essentially healthy tissue that has been displaced by the CL edge.²⁷⁷ A biopsy study of the conjunctival tissue in the region of the conjunctival flap, compared with nonflap tissue in the same eye, supports the findings of the CIC study, that indeed there is no sign of inflammation.²⁷⁸ While the exact etiology of conjunctival flaps remains unknown, one compelling hypothesis put forward by Bergmanson and colleagues²⁷⁷ is that the mechanical effect of the lens edge results in a “snow plough” effect, where the CL “shovels” piles of epithelial cells aside. These cells form new desmosomal junctions to each other, but lose their connection to the underlying tissue, except to the side that they remain adherent.

The clinical impact of conjunctival flaps is currently unclear and it is not known whether their detection requires lens wear discontinuation until resolution. From the literature available to date it would appear not, although flaps may be an indication of a poor-fitting CL,²⁷⁷ which could require a change of lens modulus, edge design, base curve, or wear schedule. There appears to be no correlation between CLD and conjunctival flaps.

Lid Parallel Conjunctival Folds. Lid parallel conjunctival folds (LPCOFs) are subclinical parallel folds of the lower bulbar conjunctiva, parallel to the lower lid margin and have been found to be present in dry eye, but are not age-related.²⁸¹ Pult and colleagues²⁸² showed that lid wiper epitheliopathy (LWE) and LPCOF correlated with dryness in CL wearers, but other clinical factors, such as corneal staining, bulbar redness, or tear break-up time, did not correlate. The authors suggest that this could be due to a similar etiology of friction. The correlation among LPCOF, reduced tear film stability, and LWE could be suggestive of a mechanical etiology.²⁸² LWE also correlated positively with bulbar redness, suggesting that irritation from lens fit or other factors may be related to their development.²⁸²

Conjunctivochalasis. Conjunctivochalasis has been defined as the redundant, loose, nonedematous conjunctival tissue found at the lower eyelid, typically in older people. Because of its location at the position of the tear prism, it is thought that the presence of conjunctivochalasis can disturb the distribution of the tear film. Increased matrix metalloproteinase expression has been reported in the fibroblasts of conjunctivochalasis, suggesting that this is a result of collagen degradation.²⁸³ In support of this hypothesis, Zhang and colleagues,²⁸⁴ using optical coherence tomography, found reduced conjunctival thickness in those with conjunctivochalasis and in older subjects. Mimura and colleagues²⁸⁵ reported an increase in conjunctivochalasis with increasing duration of CL wear. No reports linking CLD and conjunctivochalasis exist.

Hyperemia. Increased bulbar hyperemia has been reported in asymptomatic CL wear, in wearers of both rigid and

SCLs.²⁶⁷ Both subjective and objective assessment of bulbar conjunctival vasculature did not show a significant progressive change with SCL wear over a 10-month period.²⁸⁶ A significant difference was found in the rigid wearers in the temporal bulbar conjunctiva after 4 months of wear, a factor that was attributed to adaptation to rigid lens wear.²⁸⁶ Cheung and colleagues²⁸⁷ hypothesized that CL use causes damage to the conjunctival microvasculature by direct vaso-occlusion, due to damage to the conjunctival vessels or to the conjunctiva itself. These investigators compared the abnormalities in the conjunctival microvasculature of CL wearers with at least 2 years of experience with non-CL wearers. They found significantly higher abnormalities in CL users as opposed to non-CL wearers, and reported increased vessel diameter and changes to vessel contour in the region of the CL edge.²⁸⁷

Conjunctival Squamous Metaplasia. CL wear can induce distinct changes to the conjunctiva around the limbus, characterized by conjunctival squamous metaplasia (i.e., flattening of epithelial cell shape and enlarged cell diameter with loss of goblet cells)²⁸⁸ and alterations to the nuclei of cells that has been termed “snake-like chromatin”²⁸⁹ (Figs. 2, 3). This was observed in all CL wearers in the first systematic and prospective studies on conjunctival cytology in CL wearers by Knop and Brewitt.^{290,291} These changes are believed to occur as a result of mechanical friction on the epithelial cell surface, and may be reversed by cessation of lens wear.²⁸⁸

Studies by Adar and colleagues²⁹² and Sengor and colleagues²⁹³ confirmed that almost all CL wearers have varying degrees of squamous metaplasia. Simon and colleagues²⁹⁴ investigated the correlation between severity of cytological alterations and symptoms in wearers of SCLs and rigid gas permeable CLs. They found that 60% of symptomatic CL wearers had cytological alterations after 6 months of CL wear, which increased in severity with duration of CL wear and occurred at a higher prevalence and severity in symptomatic compared with asymptomatic CL wearers. This supports similar findings from Adar and colleagues,²⁹² who observed in a population of soft and rigid CL wearers that 60% of CL wearers had minor complaints and that the presence of complaints was related to a higher prevalence and severity of cytologic changes in such subjects.

These two studies support a potential causative link between cytological alterations in CL wear and CLD. In asymptomatic subjects, none of the rigid gas permeable wearers and one-third of the SCL wearers had abnormal CIC samples, possibly due to differences in fit between these lens types. In a prospective study,²⁸⁸ it was observed that conjunctival squamous metaplasia was evident after only 2 weeks of CL wear. The extent of alterations appeared to reach a plateau within 6 months of CL wear, as later confirmed by another study,²⁹⁴ although a longer study time would be necessary to verify this. After CL wear ceased, the cytological conjunctival changes proved to be reversible, although this took much longer (up to 2 years) than their induction in the first case.²⁸⁸ This finding obviously argues against a strong association with CLD, as CLD is rapidly relieved by removal of the lens from the eye.

Goblet Cell Density. Goblet cell density (GCD) is potentially an important morphological factor in CL wear because the mucin they secrete,^{30,295,296} along with lubricating proteins,²⁹⁷ is conceivably important for their ability to reduce friction on the ocular surface, which could be linked to CLD.

CL-induced changes in GCD, as identified by CIC, have been summarized by Doughty.²⁹⁸ This review indicated that most published studies concluded that CL wear results in a decrease in goblet cells in the conjunctiva, but the data are equivocal, with several studies showing no change or indeed an increase.

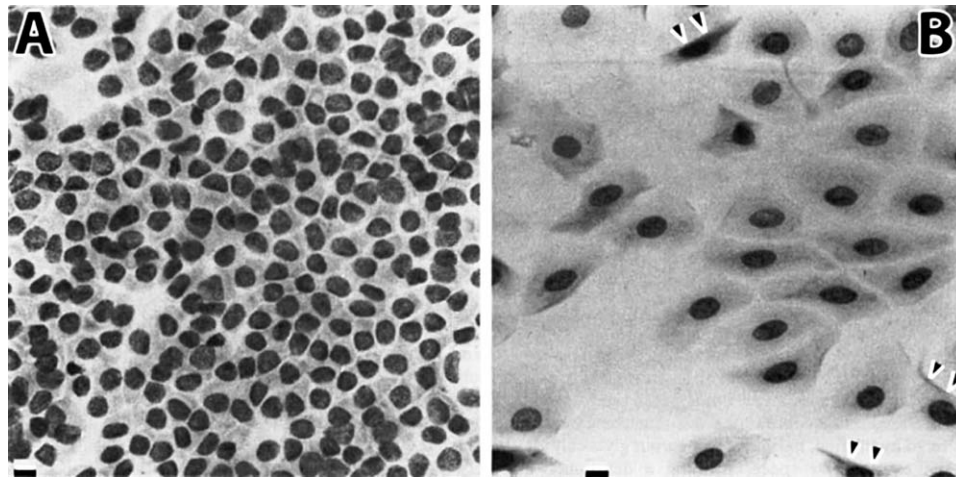


FIGURE 2. Conjunctival epithelial changes (squamous metaplasia) in CL wearers. After start of CL wear, a rapid change of the normal small cuboidal cell shape ([A] nucleo/cytoplasmic [n/c] ratio of approximately 1:1) into flat cells with enlarged diameter ([B] n/c ratio of approximately 1:5–1:8 or more) occurs in the bulbar conjunctiva, within the excursion zone of the lens. *Double arrowheads* in ([B]) indicate folding of flattened cell margins. Light microscopy; *scale bars*: 10 μ m. Reprinted with permission from Knop E, Brewitt H. Morphology of the conjunctival epithelium in spectacle and contact lens wearers—a light and electron microscopic study. *Contactologia*. 1992;14E:108–120. Copyright 1992 Georg Thieme Verlag.

This work highlighted the need for more objective and repeatable means by which to assess GCD by CIC.^{298–299}

Potential reasons for variations in GCD when assessed by CIC have been well described.^{288,301,302} Variations in results are related to a number of factors, including differences in sampling location, methodology to collect the sample, grading scale used to assess the collected tissue for squamous metaplasia, and field of view used to examine the tissue collected.^{288,299,300,302–304} One major issue when attempting to differentiate changes in GCD over time relates to the fact that in the perilimbal 12 o'clock position, which is the location used in many studies to conduct CIC, GCD changes

dramatically within just a few millimeters.^{288,305} Thus, even a small alteration in the location at which the CIC is conducted could produce very different results, without being related to true changes in GCD.

One other method that shows some promise for evaluating conjunctival changes is LSCM. Efron and colleagues³⁰⁶ performed *in vivo* LSCM on the bulbar conjunctiva of 11 healthy non-CL wearers and 11 asymptomatic CL wearers. The authors found greater conjunctival epithelial cell density in CL wearers in all cardinal positions compared with the non-lens wearing counterparts, but a reduced conjunctival epithelial thickness in lens wearers. The authors attribute this thinning to

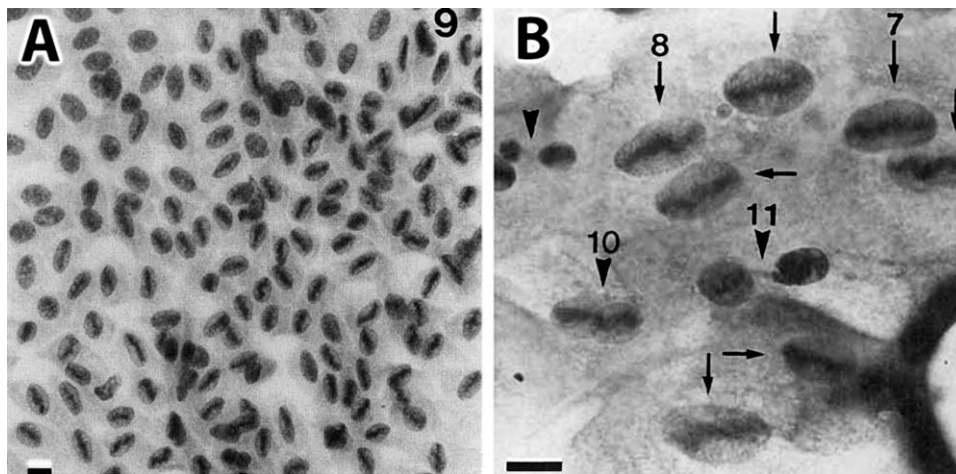


FIGURE 3. Conjunctival epithelial changes in CL wearers show a peculiar rearrangement of the nuclear chromatin (“snake-like chromatin”). Light microscopy overview (A) shows a group of such cells that are arranged similar to a fish “swarm,” here in a 7 to 1 o'clock direction. Increased magnification (B) shows individual flattened cells and nuclei with different stages of snake-like chromatin. Chromatin material, detached from the nuclear periphery, forms a central elongated structure that is first bar-shaped (nucleus “7” in [B]) and later undulated (nucleus “8” in [B]). Advanced stages develop a central segmentation (nuclei “10,” “11” in [B]). The accumulation of chromatin in the long axis of the nucleus together with later segmentation of the nucleus by cytoplasmic filaments that are rolled around it indicate the presence of chronic mechanical friction at the ocular surface of lens wearers that is conceivably related to CLD. Light microscopy; *scale bars*: 10 μ m. (A) Reprinted with permission from Knop E, Brewitt H. Morphology of the conjunctival epithelium in spectacle and contact lens wearers—a light and electron microscopic study. *Contactologia*. 1992;14E:108–120. (B) Reprinted from Knop E, Reale E. Fine structure and significance of snakelike chromatin in conjunctival epithelial cells. *Invest Ophthalmol Vis Sci*. 1994;35:711–719.³⁷⁵

a similar mechanism to that seen in corneal thinning in CL wear, as a result of mechanical and metabolic effects. The increased density was attributed to the delayed desquamation as a result of lens wear. GCD was not found to differ between the two groups.

To date, data linking GCD to CLD are lacking, but potentially worthy of future evaluation, particularly around the lid wiper region. Studies should examine the time course of GCD, and whether this links to CLD, or if the magnitude of GCD is linked to the severity of CLD.

Palpebral Conjunctiva

The palpebral conjunctiva plays an important role in controlling the interaction with the ocular surface and the CL. Slit-lamp examination of the upper tarsal conjunctiva reveals a pink mucous membrane with a satin-like, or a fine, uniform papillary appearance. Allansmith³⁰⁷ reported that 14% of non-CL wearers had a satin-smooth conjunctival appearance of the upper tarsal plate, 85% had small uniform papillae, and 1% had nonuniform papillae. Korb and colleagues³⁰⁸ reported that 0.6% of healthy subjects showed conjunctival papillae of more than 0.3 mm on the upper tarsal conjunctiva.

CL wear is known to induce CL papillary conjunctivitis (CLPC) in some wearers, which was first noted by Spring.³⁰⁹ It is a papillary reaction on the upper tarsal conjunctiva accompanied by discomfort and mucous production. The condition has been described in detail by Allansmith and colleagues,³¹⁰⁻³¹² and has been associated with both soft and rigid CL wear and can lead to CL intolerance and discontinuation of wear. The term “giant papillary conjunctivitis” is more general and indicates a noninfectious inflammatory disorder involving the superior tarsal conjunctiva with the presence of papillae measuring 0.3 mm or larger.

While subjects with overt CLPC will be symptomatic, there have been no direct reports linking CLD with general, nonpathological changes to the palpebral conjunctiva. However, the use of sensitive grading scales^{313,314} may be useful in detecting subtle changes to the palpebral conjunctiva, and may be useful in linking palpebral conjunctival changes with CLD. In one study that examined differences in comfort response and slit-lamp findings between two groups of CL wearers using different multipurpose disinfecting solutions, there was a possible effect of palpebral roughness on the symptoms of grittiness and scratchiness during CL wear.³¹⁵

IMPACT OF CLS ON MEIBOMIAN GLANDS

The meibomian glands are large sebaceous glands that are located in the tarsal plates of the eyelids^{316,317} and produce the lipids that serve, as the outermost layer of the precorneal tear film, to retard evaporation of the aqueous phase of the tears.³¹⁸ Meibomian gland dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.³¹⁹

There is a long-standing clinical impression that CL wear increases the risk of MGD. Korb and Henriquez^{320,321} investigated the meibomian glands of individuals with a primary complaint of CL intolerance. They described clinical and cytological evidence indicating that the syndrome is due to obstruction of the meibomian gland orifices by desquamated epithelial cells that tend to aggregate in keratotic

clusters, resulting in changes in the meibomian gland contribution to the precorneal tear film.

Several studies have reported the prevalence of MGD in CL and non-CL wearers.^{320,322-324} A meta-analysis of such studies³²⁵ revealed that the prevalence did not differ significantly between the two groups, thus suggesting that CL wear may not increase the risk for MGD. This could be because many of these studies employed small sample sizes and used a wide variety of methods to confirm MGD.

In contrast, Arita and colleagues³²⁶ provided direct evidence that CL wear may affect the morphology of meibomian glands. Morphological observation of the meibomian glands revealed that the frequency of meibomian gland loss was significantly higher in CL wearers compared with non-lens wearers. These results strongly suggest that CL wear is a potential cause of alteration in meibomian glands, and may result in MGD.

Meibomian Gland Orifice Changes

Foaming of the lower tear meniscus, especially toward the outer canthus, is sometimes observed in individuals with CL-associated MGD.^{320,322} Korb and Henriquez³²⁰ found that foaming on the lower lid margins was apparent in 66.2% of symptomatic CL wearers but in only 3.7% of asymptomatic CL wearers ($P < 0.0001$). Hypersecretory CL-associated MGD is characterized by the release of a large volume of meibomian lipid (meibum) at the lid margin (foaming) in response to pressure on the tarsus. It remains unclear, however, whether the increased amount of lipid is the result of true hypersecretion, or the damming back of mildly obstructed secretions.³¹⁹ Long-standing cases of CL-associated MGD may be linked to lid margin abnormalities, such as vascularization, morphological irregularity of the lid margin, blockage (plugging) of orifices, and damage to the mucocutaneous junction.³²⁷ In severe cases, in which the meibomian gland orifices are blocked, there is an absence of glandular secretion. Symptomatic CL wearers in whom lid margin abnormalities are not apparent may have a condition referred to as “nonobvious MGD.”³²⁸

Morphological Changes of Meibomian Glands

Some studies have found no relation between meibomian gland dropout and CL wear.^{329,330} However, these studies examined only the glands in the central area of the lower eyelid, which may not necessarily reflect meibomian gland changes across the full width of the lid margin. Arita and colleagues³³¹ use a noninvasive meibography system that allows observation of the meibomian glands in both upper and lower eyelids (Fig. 4). They found that CL wear likely affects the morphology of meibomian glands, with the effects being greater on meibomian glands throughout the upper eyelid than on those in the lower eyelid.³²⁶ Partial or complete loss of the meibomian glands in each eyelid was significantly higher for CL wearers than for control individuals. The length of the affected meibomian glands was less than half that observed for normal glands. These patterns of meibomian gland changes were rarely detected in non-lens wearers, and suggest that CL wear is a potential cause of MGD.

The results of Arita and colleagues³²⁶ also suggested that CL wear produces different effects on the upper and lower eyelids. Wearers of rigid lenses showed a tendency for meibomian gland dropout in the upper eyelid, whereas wearers of SCLs showed a tendency for shortening of the glands in the lower eyelid. Their data suggested that lens material does not play a key role in CL-associated MGD.

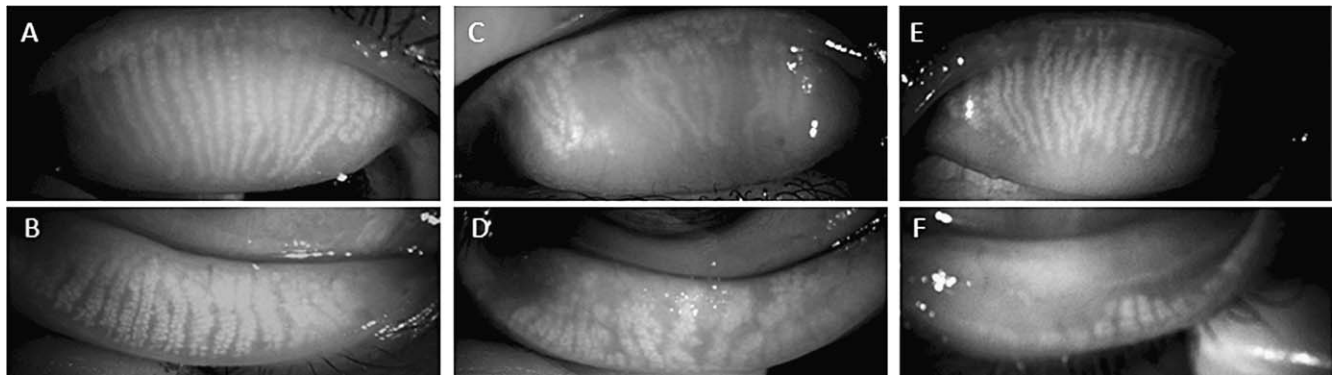


FIGURE 4. Representative noninvasive meibography images in a control subject (A, B) and in two CL wearers (C–F). Noninvasive meibography views of the meibomian glands from the conjunctival side, with the lids everted. The meibomian glands appear white. (A, B) A 31-year-old female, non-CL user. Meibomian glands in the upper (A) and lower (B) eye lids were observed. Shortening or dropout of meibomian glands was not observed. (C, D) A 37-year-old male who had used rigid CLs for 17 years. Those regions of the upper lid where meibomian glands were absent, appear black (dropout) (C). Shortening and distortion of meibomian glands were observed in the lower eye lid (D). (E, F) In a 32-year-old female who had used hydrogel CLs for 13 years, most meibomian glands in both the upper and lower eyelids were shortened. The shortening of the meibomian glands began not at the free border of the lid (in the region of the orifices), but proximally (in the fixed border of the tarsal plate).

Acinar Density and Size

Villani and colleagues³³² examined morphological changes in meibomian glands and the status of periglandular inflammation in CL wearers by LSCM (Fig. 5) and then investigated the relation between clinical and confocal findings. LSCM was applied to determine the cell density of the mucocutaneous junction epithelium, acinar unit density and diameter, glandular orifice diameter, meibum secretion reflectivity, and the appearance of the glandular interstice and acinar wall. The duration of CL wear was found to be correlated with acinar unit diameter ($P < 0.05$). Morphological changes in the meibomian glands revealed by LSCM were indicative of signs of meibomian gland dropout, duct obstruction, and periglandular inflammation. A comprehensive LSCM evaluation of the ocular surface in CL wearers should better clarify the role of

meibomian gland dropout and eyelid margin inflammation in the pathogenesis of CL-induced dry eye.

Meibum Composition

It remains unclear whether CL wear affects meibum composition or whether meibum composition affects the comfort of CL wear. Robin and colleagues³³³ found that all 15 subjects who wore EW SCLs and had lipid deposition on the lens showed abnormalities of meibomian gland morphology. Only 2 of the 13 subjects without lipid deposition on the lens had meibomian gland abnormalities. These results suggest that MGD may be associated with the development of SCL deposits, which can impact lens wettability and ultimately lead to CLD.

It is possible that CL wear affects not only the lipid layer of the tear film but also meibum composition itself. However, there is still a dearth of information regarding the exact nature of

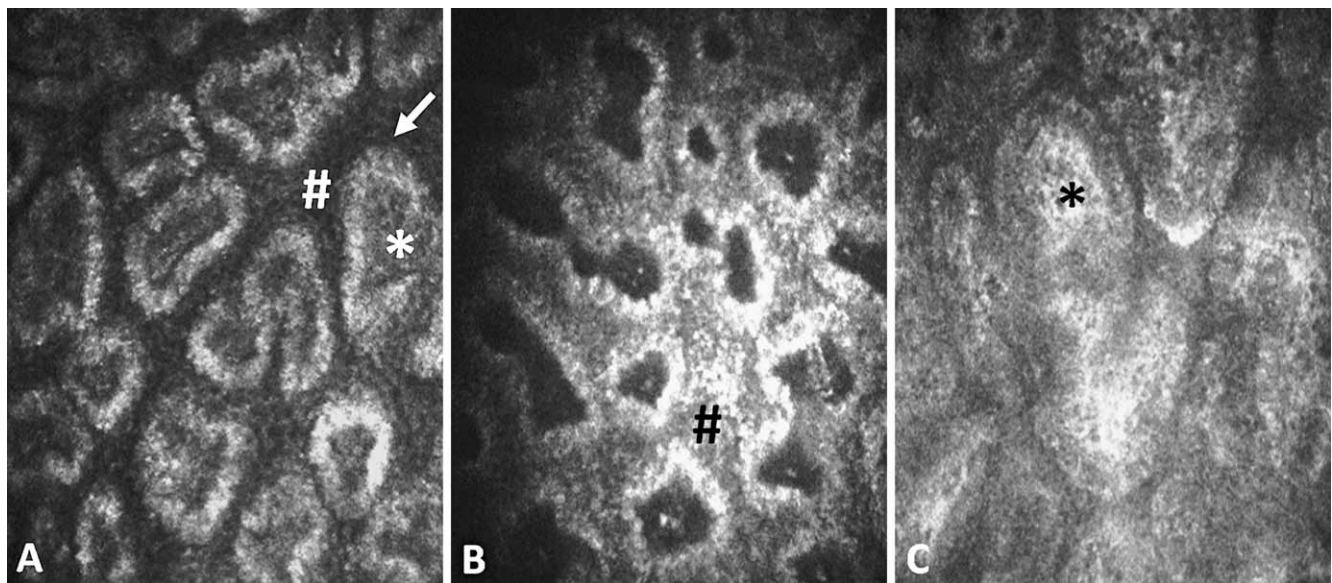


FIGURE 5. Meibomian gland changes in CL wearers, illustrated by in vivo confocal microscopy, performed at the lid margin. (A) Meibomian glands of a 35-year-old male, showing no obvious changes in acinar lumina (*), wall thickness (arrow), or interstitial space (#). (B) A 32-year-old male: The acinar unit density and size are slightly reduced and there is apparent periglandular infiltration (#), presumably by inflammatory cells. (C) A 39-year-old female: The acinar units appear greatly enlarged and hyper-reflective (*).

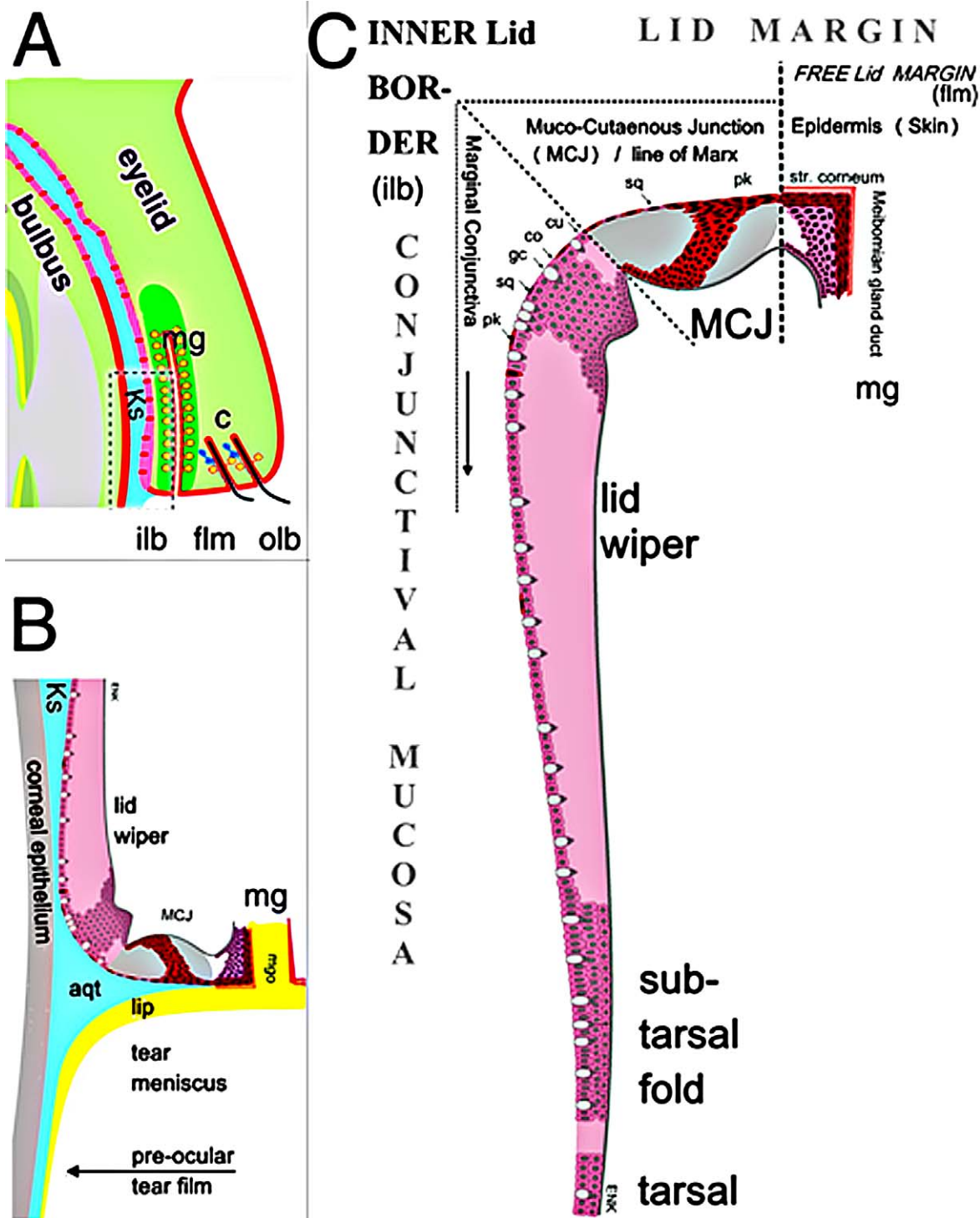


FIGURE 6. Tissue zones at the posterior eye lid margin. **(A)** Complete upper eye lid with meibomian gland (mg) and cilia (c); the area marked by a *dotted rectangle* represents the inner lid border. The rounded outer lid border (olb) can be differentiated from the sharp inner one (ilb) and the free lid margin (flm) extends from the cilia (c) to the meibom orifice. **(B)** The inner lid border is seen with the aqueous tear meniscus (aqt) overlying the line of Marx, and the tear film lipid layer (lip, not to size). The lid wiper is the only point of the lid margin that is apposed to and in touch with the globe; the upper tarsal conjunctiva is separated from the globe by Kessing's space (Ks in [A, B]). The marginal conjunctiva constitutes a thickened epithelial lip that represents the device for distribution of the tear film during a blink. **(C)** The lid wiper has goblet cells (*white dots* in [B, C]) for a rich mucin-water gel at the surface for lubrication and reduction of friction. Further zones of the posterior lid border are the mucocutaneous junction (mcj), the surface of which is the line of Marx) located between the crest of the inner lid border and the meibom orifice. The cornified epidermis extends from the free lid margin around the posterior rim of the meibom orifices where the meibomian oil is delivered onto the precorneal tearfilm. In most parts only the surface cells are shown. **(A)** Reprinted with permission from Knop N, Korb DR, Blackie CA, Knop E. The lid wiper contains goblet cells and goblet cell crypts for ocular surface lubrication during the blink. *Cornea*. 2012;31:668-679. **(B, C)** Modified from Knop E, Knop N, Zhivov A, et al. The lid wiper and mucocutaneous junction anatomy of the human eyelid margins: an in vivo confocal and histological study. *J Anat*. 2011;218:449-461.

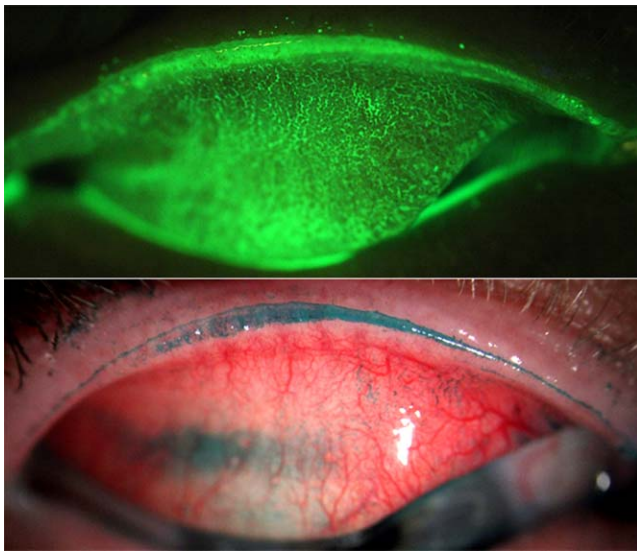


FIGURE 7. Lid wiper epitheliopathy. Horizontal band of lid margin staining extending horizontally from the medial canthus to the lateral canthus, and from the Marx line (*sharp green line* or border of superior staining) to the tarsal sulcus fold. Lid wiper epitheliopathy stained with fluorescein (*top*) and lissamine green (*bottom*). Photo courtesy of Sruthi Srinivasan.

meibum, as a result of the small sample quantities available. Recent advances in analytical techniques have provided some insight into meibum composition,^{334,335} but further work is necessary to determine the extent of interindividual variability in normal meibum, its effect on the comfort of CL wear, and the effect of lens wear on meibum composition.

IMPACT OF CLS ON THE LID MARGINS

Lid Margin Anatomy

The lid margin can be structurally and functionally differentiated into three distinct zones: the anterior and posterior lid border, and the free lid margin that is located between these.² The posterior border has at least three zones (Fig. 6)³³⁶; the posterior extension of the free lid margin skin epidermis (that encircles the meibomian orifices), the transition between the epidermis and conjunctival mucosa (mucocutaneous junction with its surface being the line of Marx), and the lid wiper zone (or the marginal conjunctiva).

The lid-wiper region is a thickened epithelial “lip” that has a conjunctival mucosal morphology that extends from the tarsal conjunctiva up to the crest of the posterior lid border, is apposed to the globe, and helps to distribute the precorneal tear film. The lid wiper contains goblet cells that produce mucin, which is likely used for lubrication and reduces the frictional force between the globe and lid margin during blinking.²⁹⁶ The lid wiper, because it is conceivably the only part of the lid margin that is in direct contact with the globe,³³⁷ will be in contact with the CL surface and is thus subjected to mechanical friction during the blink. The lid wiper zone has the highest neural sensitivity of all the conjunctival and lid regions, and is similar in this respect to the central cornea.^{39,338} Thus, it is of obvious importance during lens wear.

The line of Marx extends from the crest of the posterior lid border and is seen at the bottom of the tear meniscus.³³⁹ A thin band of stainable epithelial cells directly behind the mucocutaneous junction is the basis for Marx’s line. Previously, the line of Marx was assumed to be the zone in touch with the globe and to

represent the wiping surface of the lid border.^{340,341} However, this theory is not supported by its geometrical orientation to the globe, by the fact that it is visible in the upper eye lid without lid eversion,³⁴² and because it lacks specific lubrication.²⁹⁶

The conjunctiva extending proximally from the posterior lid margin to the subtarsal fold, corresponds to the lid-wiper region of the lid margin,^{343,344} which is directly apposed to the surface of the globe and is important in tear distribution during blinking and eye movements.³⁵⁶ Riolan’s muscle, the most central part of the orbicularis muscle at the lid margin, probably plays a role in this, as does the lubricative function of the goblet cells present in this region.²⁹⁶

Lid Wiper Epitheliopathy

A thickened epithelium at the posterior lid margin was observed as long ago as 1877 by Sattler³⁴⁵ and later by Virchow and Saemisch.³⁴⁶ However, its immediate functional implication was not recognized until the mid-1960s by Ehlers.³⁴⁷ He noticed that this “bead gliding over the cornea” must be assumed to be a perfect “windscreen wiper.” More recently, this region has received increased attention because of an observation by Korb and colleagues^{343,344,348} linking changes in this region of the lid in subjects who are symptomatic of dryness. The authors postulate that when the tear film is thinned or becomes unstable, or a lens surface is not stable and wettable, there is an increased mechanical/frictional effect on the lid-wiper region, as the lid travels across the ocular or lens surface during blinking. This process may lead to lid-wiper trauma and epitheliopathy, which can be viewed clinically by staining the marginal conjunctiva with commonly used ophthalmic dyes^{343,344,349} (Fig. 7).

LWE is found in 67% to 80% of symptomatic CL wearers, but in only 13% to 32% of asymptomatic subjects.^{343,350} This condition is also observed in the lower eyelid,³⁵¹ but significantly different LWE scores between symptomatic and asymptomatic subjects were found only in the upper eyelid.³⁵² By histology it has been verified in selected cases that cells with atypical keratinization (para-keratinization) increase in number and extend from the natural stainable line of Marx, where they physiologically occur, over the surface of the lid wiper epithelium.³³⁶

LWE may be one of the few clinical signs truly associated with dryness in lens wearers and nonwearers and much work is currently under way to determine its value in providing a better understanding of CLD.

Changes in Normal Microbiota

The lid margin is more frequently colonized with microbes than the conjunctiva and CLs,³⁵³ but the frequency of isolation varies. The number of colony-forming units that can be grown from swabs of the lid range from zero in some subjects up to 465.³⁵⁴⁻³⁵⁷

As shown in the Table, the most frequently isolated microbes are the coagulase-negative staphylococci, in both non-lens wear³⁵⁸⁻³⁶¹ and during lens wear.^{353,354,356,357,360,362,363} Other commonly isolated bacteria from both lens wearers and non-lens wearers include *Micrococcus* sp., viridans streptococci and other *Streptococcus* sp., *Corynebacterium* sp., *Propionibacterium* sp., and *Bacillus* sp. Gram-negative bacteria are not commonly isolated from the lid margins of CL or non-CL wearers. Stapleton and colleagues³⁵³ found that the frequency of isolation of microbes from lids increased significantly with time for experienced wearers of DW lenses, but for experienced wearers of EW lenses the frequency of isolation of microbes from lids reduced with time, but there was a greater frequency of isolation of potentially pathogenic microbes during EW. Other

TABLE. Frequency of Microbes Isolated From Lids of Non-Lens Wearers and Lens Wearers^{353,354,356-361,363}

Microbial Type	Non-CL Wearers, % Subjects	CL Wearers, % Subjects
Gram-positive bacteria: Firmicutes, Firmibacteria, Bacillales		
Coagulase-negative staphylococci	84-100	28-97
<i>capitis/warneri/cobnii/saprophyticus</i>	<1	2-43
<i>epidermidis/hominis</i>	28	25-62
<i>haemolyticus</i>		2-8
<i>lugdunensis</i>		<1-3
<i>hyicus</i>		5
<i>intermedius</i>		<1-2
<i>schleiferi</i>	<1	1-3
<i>Staphylococcus aureus</i>	3	<1-21
<i>Planococcus</i> sp.		<1-1
<i>Bacillus</i> sp.	22-26	<1-5
Gram-positive bacteria: Firmicutes, Firmibacteria, Lactobacillales		
<i>Streptococcus pneumoniae</i>		<1
<i>S. pneumoniae</i> and viridans streptococci	6	<1-3
Viridans streptococci	<1-41	1-15
<i>Streptococcus</i> sp.	4	1-6
<i>Lactobacillus</i> sp.		<1-1
Gram-positive bacteria: Actinobacteria, Actinobacteridae, Actinomycetales		
<i>Micrococcus</i> sp.	6-14	0-26
<i>Stomatococcus</i> sp.		1-2
<i>Corynebacterium</i> sp.	43	<1-32
<i>Propionibacterium</i> sp.	4-18	<1-61
Gram-negative bacteria: Proteobacteria, Gamma proteobacteria, Pseudomonadales		
<i>Acinetobacter baumannii</i>	4	
<i>Acinetobacter</i> sp.	<1	<1-9
<i>Moraxella</i> sp.	<1	1-3
<i>Moraxella catarrhalis</i>		<1
<i>Neisseria</i> sp.	5-6	<1-6
<i>Pseudomonas</i> sp.	<1	1-3
<i>Pseudomonas aeruginosa</i>		<1-1
Gram-negative bacteria: Proteobacteria, Gamma proteobacteria, Enterobacteriales		
<i>Escherichia coli</i>	<1-3	
<i>Escherichia vulneris</i>	<1	<1-1
<i>Enterobacter</i> sp.		<1-1
<i>Enterobacter cloacae</i>		<1
<i>Proteus</i> sp.	3	
<i>Serratia marcescens</i>	<1-6	<1-3
<i>Serratia ficaria</i>	6	<1-1
<i>Serratia liquefaciens</i>		3
Gram-negative bacteria: Proteobacteria, Gamma proteobacteria, Pasteurellales		
<i>Haemophilus influenzae</i>	<1	<1-5
<i>Haemophilus parainfluenzae</i>		<1
Gram-negative bacteria: Proteobacteria, Beta proteobacteria, Burkholderiales		
<i>Achromobacter</i> sp.		<1-1
<i>Achromobacter xylosoxidans</i>		<1
Gram-negative bacteria: Bacteroidetes, Flavobacteriaceae, Flavobacteriales		
<i>Chryseobacterium meningosepticum</i>		<1
Unidentified gram-negative rods	<1-2	2-5
Fungi (molds or yeasts)		2-4

microbes, such as fungi or protozoa, are not usually isolated. There are no reports of viral colonization of lids in healthy asymptomatic subjects.

There have been no studies to date examining the lid microbiota during CLD. One study³⁵⁹ examined the lid microbiota of dry-eye subjects (including those with MGD or

Sjögren's syndrome) and found that all dry-eye subjects had increased numbers of colonies of bacteria isolated compared with healthy non-dry eye subjects (106 ± 82 vs. 12 ± 18 colony-forming units per lid, respectively). There also tended to be more frequent lid colonization by *Corynebacterium* sp., *Staphylococcus aureus*, and coliform bacteria in the dry-eye

subjects compared with the non-dry eye control group. Given these findings, and the changes that occur to the lid microbiota during lens wear, there is the possibility that the ocular microbiota might have some role in CLD.

IMPACT OF CLS ON BLINKING

Blink patterns impact lens movement and the degree to which the lens and ocular surface may dry between blinks, both of which can affect the interaction of the lens with the ocular surface. In addition, a lens that is too mobile will interact with the lid during the blink and can influence lens comfort. Thus, consideration of blinking in CL wearers is warranted.

The manner in which a CL interacts with the ocular surface during eye movement and blinking is distinctly different for soft, rigid, or scleral lenses, due to differences in size, material, modulus, form, and fitting philosophy for these lens types. Rigid corneal lenses require a greater period of adaptation and often modify blink patterns during this adaptation phase. Although soft lenses are intrinsically tolerable,³⁶⁴ acceptance is greatly influenced by a variety of material properties, including water content, modulus, oxygen transmission, and wettability. Lens surface drying and feelings of discomfort will potentially impact blink frequency.

Blinking and Its Role in CLD

Blink rate is strongly influenced by the surrounding environment, attention, eye exposure, personal activity, and mental state and may vary with age and sex. Wide variations in normal blink rate are reported, likely due to the influence of different environmental conditions or measurement techniques. Blink rate is increased in dry eye disease and is further amplified by increasing airflow over the eye, in both healthy individuals and subjects with dry eye complaints.^{365,366} The increased blink rate appears to serve two functions, in that it refreshes the tear film more frequently and also increases the period of tear film coverage over the ocular surface, as both blink frequency and blink time are increased. In contrast, a reduction in blink rate increases the blink interval, thereby increasing evaporative loss from the eye for a given palpebral aperture size. This has obvious consequences for lens behavior, particularly related to tear film break-up and surface drying over the lens. Finally, blink completeness is reduced in CL wearers compared with healthy individuals.⁴⁶

CL Movement During Blinking

In the CL wearer, physical stresses are generated between the lens and the ocular surface, which vary according to lens type and fit, the nature and extent of the lid and eye movements, and how the lens sits on the surface of the eye.

The points of contact with the cornea and conjunctiva in the primary position of gaze differ significantly among the major lens subtypes. In the blink interval, rigid corneal lenses sit on the cornea, within the palpebral aperture, either making no contact with the lids, or, with a lid-attached fit, engaging with the upper tarsus. Occasionally, the lower lens edge may be supported on the lower lid margin.³⁶⁷ In comparison, soft and scleral lenses tuck beneath the upper and lower lid margins, straddling the cornea and perilimbal conjunctiva, and, with scleral lenses, extend onto the bulbar conjunctiva. Although soft lenses are flexible and modify their shape over the corneal and limbal area, scleral lenses are not, and conform very differently to either rigid corneal or soft lenses. There is only a very thin film of fluid between a soft lens and the cornea and minimal tear exchange occurs. The tear film is more

substantial in the case of corneal and scleral lenses, resulting in greater mobility for rigid corneal lenses. For the scleral lens, mobility and tear exchange is restricted by size and peripheral interactions with the bulbar conjunctiva. A key function of the blink is to replenish the tear film in front of and behind the lens. In some circumstances, lens fit may interfere with spreading of the tear film and this, along with the presence of the lens-edge-related meniscus, may encourage drying outside the edge of the lens (resulting in 3 and 9 o'clock staining), which can influence rigid lens comfort.^{368,369}

Blinking exerts both a backward, squeeze pressure on the lens and a shearing force, parallel to its anterior surface.³⁷⁰⁻³⁷² As the lens moves or fluid is exchanged behind the lens, these forces are transmitted to the cornea, limbus, and bulbar conjunctiva to varying degrees, according to lens type and fitting characteristics. Although there is limited tear exchange under a soft lens during the blink, the volume and distribution of fluid behind the lens is a major determinant of mobility.^{121,373} The post-lens tear fluid provides lubrication between the lens and the corneal surface and cushions the effects of blinking. It also facilitates tear exchange with the body of the tears and, thus, is important for the removal of cells and debris from behind the lens.³⁷⁴ For the relatively mobile, rigid corneal lens, the relationship between the lens and the ocular surface is dynamic. The lens moves with the eye during a large eye movement. By contrast, eye movement when wearing a well-fitted, relatively immobile soft lens will draw the lens surface across the upper and lower tarsal conjunctiva during horizontal versions, the locus of contact changing when the eye is elevated or depressed. These differences in physical interaction between lens subtypes and the ocular surface are relevant to the development of a variety of well-described complications that can result in CLD, including lid-wiper epitheliopathy.³⁴³ However, detailed studies of the relationship between the blink during wear of different CL types and CLD have yet to be undertaken.

CONCLUSIONS AND FUTURE DIRECTIONS

This report has reviewed CL-associated changes to the ocular surface and adnexa, and has considered which of these changes are associated with CLD. We have concentrated on physiological changes that may be associated with CL wear, but not necessarily identified or designated as an adverse response.

In this context, some evidence is available to suggest a link among LIPCOF, conjunctival metaplasia, GCD, MGD, and LWE with CLD, with the strongest evidence being that related to MGD and LWE. No convincing evidence of a link to CLD was unearthed with respect to any of the other forms of CL-associated tissue changes considered in this report.

When investigating the source of CLD, a full examination of all the anterior ocular structures that can be impacted by CL must be undertaken. This report draws particular attention to the importance of undertaking a careful assessment of the meibomian glands and lid margins, so as to establish the role that changes to these tissue structures may play in the cause of CLD.

Potential future areas of study could include closer inspection of the role of corneal staining in CLD, the development of more repeatable methods to ascertain GCD, and extensive work characterizing changes to the meibomian glands during CL wear and the role of LWE in CLD. Such studies would benefit from longitudinal designs that attempt to understand what pathophysiological changes occur in new wearers over time and whether changes to CL materials, design, fit, or other changes impact MGD and LWE. Studies

should also examine whether the magnitude or timing of changes can be linked to the magnitude and timing of CLD.

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