BCLA CLEAR - Effect of contact lens materials and designs on the anatomy and physiology of the eye

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\begin{abstract}
This paper outlines changes to the ocular surface caused by contact lenses and their degree of clinical significance. Substantial research and development to improve oxygen permeability of rigid and soft contact lenses has meant that in many countries the issues caused by hypoxia to the ocular surface have largely been negated. The ability of contact lenses to change the axial growth characteristics of the globe is being utilised to help reduce the myopia pandemic and several studies and meta-analyses have shown that wearing orthokeratology lenses or soft multifocal contact lenses can reduce axial length growth (and hence myopia).

However, effects on blinking, ptosis, the function of Meibomian glands, fluorescein and lissamine green staining of the conjunctiva and cornea, production of lid-parallel conjunctival folds and lid wiper epitheliopathy have received less research attention. Contact lens wear produces a subclinical inflammatory response manifested by increases in the number of dendritiform cells in the conjunctiva, cornea and limbus. Papillary conjunctivitis is also a complication of all types of contact lenses. Changes to wear schedule (daily disposable from overnight wear) or lens materials (hydrogel from SiHy) can reduce papillary conjunctivitis, but the effect of such changes on dendritic cell migration needs further study. These changes may be associated with decreased comfort but confirmatory studies are needed. Contact lenses can affect the sensitivity of the ocular surface to mechanical stimulation, but whether these changes affect comfort requires further investigation.

In conclusion, there have been changes to lens materials, design and wear schedules over the past 20+ years that have improved their safety and seen the development of lenses that can reduce the myopia development. However, several changes to the ocular surface still occur and warrant further research effort in order to optimise the lens wearing experience.
\end{abstract}

1. Introduction

Contact lenses are medical devices worn to offer refractive correction or a medical solution to a clinical problem at the ocular surface. In all circumstances, a key aim is for a contact lens to achieve its desired performance whilst either (a) leaving the anatomy and physiology of the eye unaffected or (b) altering ocular characteristics only as intended (e.g. the programmed, structural change of the eye during in myopia control with contact lenses). Given the complexity of the anatomical
structures and physiological processes with which a contact lens interacts, this has proven to be a high threshold and one not yet fully met by modern lenses despite significant improvements in designs and materials, especially over the past 50 years.

This paper outlines the various changes caused by contact lens wear, how these alter with different contact lens types and their degree of clinical significance. The information is provided on a structure-by-structure basis and broadly follows the order in which an eye care practitioner might examine the integrity of the eye during a contact lens examination. This paper aims to review information which is different to the CLEAR Complications Report [1] which features as a sister paper in the CLEAR initiative. In general terms, the CLEAR Complications Report [1] describes changes to the eye which require clinical intervention. The current paper covers physiological and anatomical alterations which do not require such intervention either because this is not considered to be helpful for patient care, or because the described ocular change has only recently been described and/or the appropriate clinical management is not yet established. Inevitably there is modest overlap in these papers but due to the deliberately different approaches taken (this paper takes an anatomy-based approach whereas the CLEAR Complications Report [1] adopts an aetiology-based structure), where this occurs it is relevant, helpful and additive.

2. The eyelids and adnexa

2.1. Blinking

Blinking is an important ocular surface physiological mechanism, maintaining physiology and providing good optics [2]. It involves both the upper and lower eyelids: the upper lid moves in the vertical and inward, whereas the lower lid moves in a temporal-to-nasal direction [3]. Blinking is either voluntary (a conscious and deliberate blink), reflex (elicited by external tactile, light, sound or electrical stimulation), or spontaneous (an unconscious blink in the absence of deliberate stimuli), with the latter the most common and most relevant to contact lens wear. The spontaneous blink-rate varies between 8 and 21 blinks per minute (in primary gaze) [4], has a duration of about 300 ms and an upper blink excursion of 7–10 mm [5,6].

These key blink variables can be influenced by various factors. For example, both dry eye disease (DED) and contact lens wear cause an increase in blink-rate [7–9]. Substantial variability in spontaneous blink rate has been reported in the literature, which may be attributed to a number of factors including methodology employed [10], task performed during blink assessment [7,11–14], gaze direction [12,15,16], cognitive and emotional factors [17] and inter-participant variability [18,19]. The exact nature of the stimulus responsible for the increase in blink-rate during contact lens wear is not clear, but tear film instability, visual disturbance and symptoms of ocular irritation may provide stimulation for blinking [7,20]. One report has noted an association between greater subjective dryness and increased blink-rate [21]. There appears to be little difference between the sexes [22,23] and although blink-rate increases with age, this may be due to age-related dry eye disease issues [9].

Increased blink-rate and unaltered blink completeness has been reported in the early stages of hard and rigid corneal lens wear [11,24,25], whereas no difference in overall blink-rate was found between long-term rigid corneal lens wearers and non-wearers [26]. However, long-term rigid corneal lens wearers showed fewer complete blinks and more blink attempts than non-wearers. In addition, rigid corneal lens wearers with 3- and 9-o’clock staining showed more incomplete blinks and more blink attempts than wearers with minimal staining and non-wearers [26]. A trend toward an increased blink-rate was also shown in neophytes fitted with soft lenses [27,28], as well as in adapted soft contact lens wearers [7,29,30]. There was no clear effect of soft contact lens wear on blink completeness [27–29], which appeared to be more influenced by the task performed during the assessment [7].

There is limited evidence of the effect of different soft lens materials and designs on blink characteristics. A shorter inter-blink interval (i.e. increased blink-rate) was reported after 10 min of soft contact lens wear, particularly for toric lenses (a periballast design and a double slab-off design), although none of the changes were statistically significant [25]. An increased blink-rate was found in subjects wearing a hydrogel contact lens (etafilcon A) after exposure to controlled adverse environmental conditions, whilst no change was observed in subjects wearing a SiHy lens (narafilcon A) [31]. The authors suggested that the higher blink frequency was ‘a compensation mechanism to alleviate the relatively higher dryness over the lens surface.’ A higher blink-rate for SiHy lens wear (comfilcon A), compared with hydrogel lens wear (omafilcon A), was seen during exposure to controlled standard and adverse environmental conditions [32]. According to the authors, the higher dehydration observed for the SiHy lens in the study could be the reason for the rise in blink-rate ‘in an attempt to refresh the tear film more frequently’, although other work has found dehydration to be greater with conventional hydrogels [33,34]. Contrary to these studies, other investigators found no significant difference in the increment of blink rate after two months of lens wear between hydrogel (hilafilcon B) and silicone hydrogel (lotrafilcon B) materials [28]. The effects of contact lens wear on other aspects of blink dynamics, such as velocity and duration, have not yet been studied.

The notion of incomplete blinking may be relevant to contact lens wear as incomplete blinking accounts for a two-fold increase in the risk of DED, meibomian gland atrophy and poor tear film stability [3]. Incomplete blinking might be more problematic for patients with low blink-rates, as this combination of effects will increase the exposure of the inferior ocular surface. This means that potential contact lens patients who are more predisposed to incomplete blinking, those who are using computers or ‘digital devices’ [9] or some ethnic groups (e.g. Asian patients [35]), may require closer clinical attention prior to fitting and during the aftercare process.

The measurement of blink characteristics has been challenging and complex using traditional methods [17,36]. However, the increased availability and accessibility of technologies such as high-speed digital cameras [10,37,38] and mobile phones [39] have facilitated the investigation of human blinking. Additionally, commercially available instruments designed for tear film analysis, such as the LipiView II interferometer or the IDRA ocular surface analyser, have the capability to measure some aspects of blink dynamics, allowing eye care practitioners (ECPs) to assess blink characteristics in the clinical setting.

2.2. Ptosis

Eyelid ptosis is the prolapse of the upper eyelid below its normal position [40]. Blepharoptosis is the more specific term for this ophthalmic condition and it can be either congenital or acquired [41]. Ptosis related to contact lens use is described.

Typically, the distance between the upper lid margin and the eyelid
fold is minimal, but in contact lens induced ptosis this is enlarged, which may be of cosmetic concern [3]. Since the vast majority of patients wear contact lenses bilaterally, this condition may not be noticeable and so its prevalence may be higher than that reported in clinical practice. A systematic review has suggested that there is an increased risk of ptosis in rigid corneal (OR 17.4x) and soft contact (OR 8.1x) lens wearers compared to non-wearers [42]. Previous studies have highlighted the association of prolonged rigid corneal lens wear with acquired ptosis [43–50]. Although the exact mechanism remains unknown, most authors agree that excessive physical manipulation of the eyelids during insertion and removal of rigid corneal lenses may be responsible for inducing damage to the levator aponeurosis [43,46,48,51]. Other proposed mechanisms include eyelid oedema or inflammation [44] and contact lens-induced irritation [46,49]. There are fewer reports of contact lens induced ptosis in soft contact lens wearers [49,52]. Contact lens application and removal and contact lens induced irritation may play a role in the pathogenesis of ptosis in soft contact lens wearers [47,49,52].

The vertical palpebral aperture size of rigid corneal lens wearers is significantly smaller than non-wearers, but this phenomenon does not occur with soft lens use [51]. This observation has been confirmed in long-term adapted rigid corneal and soft lens wearers, when compared to non-lens wearers. The palpebral aperture size of the rigid corneal lens, soft lens and non-lens wearer groups were: 9.76 ± 0.99 mm, 10.25 ± 0.94 mm and 10.10 ± 1.11 mm, respectively [53]. Ptosis is a feature of the upper eyelid and rigid corneal lenses cause a reduction in palpebral aperture size of about 0.5 mm [51,53].

Subjects fitted on an overnight wear basis with a rigid corneal lens in one eye and a soft lens in the other eye for 13 weeks had a maximal reduction in palpebral aperture size of 12 % with the rigid corneal lens at one eye and a soft lens in the other eye for 13 weeks had a maximal 0.94 mm and 10.10
to non-lens wearers. The palpebral aperture size of the rigid corneal lens, furthermore, the structural changes worsen with years of wear [65]. Other researchers have also reported apparent changes to Meibomian glands related to contact lens wear [66,67]. However, the methodology used (Meibomian gland acini reflectivity and acinar unit diameter measured by in vivo laser scanning confocal microscopy) is now considered to not image the Meibomian glands but rete ridges present at the dermal-epidermal junction [68]. Furthermore, there is no association between rete ridges parameters measured by laser scanning confocal microscopy and actual Meibomian glands seen in meibography images [69].

The relationship between contact lens-related allergic conjunctivitis and morphological changes in the Meibomian glands has been investigated. It has been shown that allergic reaction, rather than contact lens wear, causes Meibomian gland distortion in patients with contact lens-related allergic conjunctivitis. However, contact lens wearers both with and without contact lens-related allergic conjunctivitis showed higher Meibomian gland dropout in contrast to non-wearers even though it was (marginally) not significant (p = 0.051). There was no significant difference between the mean Meibomian gland distortion between rigid corneal and hydrogel lens wearers [58].

Other workers have found no association between changes in the Meibomian gland morphology (both in Meibomian gland distortion and dropout level) and contact lens use. Here, contact lens wearers had significantly worse meibum quality and orifice plugging and furthermore, abnormal meibum quality was strongly correlated to the duration of contact lens wear [59]. This group challenged previous findings [58] suggesting that contact lens replacement schedule and wearing time should be considered when assessing the effect of contact lens wear on Meibomian gland morphology [59]. Other studies have also failed to show that contact lens use affects Meibomian gland structure and function [60,70].

The aforementioned findings suggesting that the duration of contact lens wear correlates with characteristics of the Meibomian glands stand in contrast to another study that did not find that correlation [71]. According to these authors, functional and structural Meibomian gland changes in soft contact lens wearers occur within the first two years of wear and do not worsen thereafter; however, the changes seem to be permanent as contact lens dropouts did not show signs of improvement [71]. These results are consistent with other findings that found Meibomian gland characteristics in SiHy contact lens wearers worsen significantly after three years of contact lens wear but remain stable after seven years of wear [72]. The earliest change that can be observed in Meibomian gland appearance caused by contact lens wear is thickening of the upper eyelid glands [72].

A detailed analysis of various characteristics of Meibomian glands,
such as area of dropout, number of glands, Meibomian gland length, Meibomian gland width and Meibomian gland irregularity has been provided [73]. This showed that experienced contact lens wearers had larger areas of dropout and shorter glands when compared to non-contact lens wearers, but those changes were not correlated to years of wear. However, neophytes fitted with daily disposable soft contact lenses did not show any structural changes in Meibomian glands within the first 12 months of wear suggesting that changes happen later in time. Differences between contact lens materials were also examined. Here, hydrogel contact lens wearers showed some significant variations in the total number of glands and the area of gland atrophy in contrast to SiHy wearers. Non-invasive tear film breakup time also appeared to be dependent on the lens material. Furthermore, the changes in the percentage area of gland atrophy correlated with the fluorescein tear film breakup time in SiHy contact lens wearers. Moreover, the preferred habitual lens modality (monthly/fortnightly) seems to have an impact habituation lens modality (monthly/fortnightly) seems to have an impact habituation influence of overnight orthokeratology (ortho-k) on Meibomian glands. The influence of overnight orthokeratology (ortho-k) on Meibomian glands has also received some attention in the literature. No significant differences in Meibomian gland appearance and fluorescein tear film breakup time after 3 years of ortho-k wear in children and adolescents have been reported [67]. These findings are supported by another study that did not find significant changes in non-invasive tear film breakup time and evaporation rate) were associated with symptoms of discomfort among the symptomatic contact lens wearers [81]. In addition, there was no difference in pre-lens tear breakup time between symptomatic and asymptomatic contact lens wearers [82]. Many other studies have shown that subjective symptoms are related to contact lens wear [57, 61, 65, 66, 72] but on the other hand, there are also some that did not observe this relation [59, 60, 71, 83, 84].

The relation between subjective symptoms in contact lens wear and Meibomian glands is also ambiguous. One study found that disturbed Meibomian gland function characteristics (foam at Meibomian gland orifices, expressibility, meibum quality, lipid layer thickness, fluorescein tear film breakup time and evaporation rate) were associated with symptoms of discomfort among the symptomatic contact lens wearers [67] whereas another did not find a difference in lipid layer patterns between asymptomatic and symptomatic contact lens wearers [81]. In addition, there was no difference in pre-lens tear breakup time between symptomatic or asymptomatic groups [82]. Many other studies have shown that subjective symptoms are related to contact lens wear [57, 61, 65, 66, 72] but on the other hand, there are also some that did not observe this relation [59, 60, 71, 83, 84].

The influence of overnight orthokeratology (ortho-k) on Meibomian glands has also received some attention in the literature. No significant differences in Meibomian gland appearance and fluorescein tear film breakup time after 3 years of ortho-k wear in children and adolescents have been reported [67]. These findings are supported by another study that did not find significant changes in non-invasive tear film breakup time, orifice plugging, meibum quality, difficulty of meibum excretion and Meibomian gland dropout level when comparing time points prior to and 2 years after the ortho-k wear in teenagers [83]. These outcomes are contrary to that one study that found that Meibomian gland appearance in the upper eyelid got gradually worse and non-invasive tear film breakup time significantly decreased within 12 months of ortho-k wear [84].

Overall, then, the mechanism for Meibomian gland loss in contact lens wear is not fully understood. Possible explanations involve mechanical trauma, chronic irritation and aggregation of desquamated epithelial cells at the orifices of the glands [62, 63, 85].
3. Conjunctiva

3.1. Bulbar and limbal conjunctiva

3.1.1. Hyperaemia

Hyperaemia is a visible response to the wearing of a contact lens (or to some other irritating or inflammatory factor) that is expressed as dilation of the conjunctival blood vessels [87]. This dilation changes the appearance of the exposed sclera and overlying bulbar and limbal conjunctiva within the palpebral aperture from a quiescent ‘white’ to a provoked ‘red’. The shift in hyperaemia is a sign that some underlying factor has altered the homeostatic conjunctival blood flow balance. No eye is ever perfectly ‘white’ as the conjunctiva contains visible blood vessels. There is a normal range in the hyperaemia appearance for the general population, reflecting physiological variation between individuals and non-irritative influences on the homeostatic balance [88–90]. It is therefore important, when assessing change in hyperaemia with contact lens wear, to establish the non-lens wear baseline for each patient and to compare future change to that baseline.

The hyperaemia is produced by increased dilation of the arterioles in the limbal corneal arcades and/or the bulbar conjunctival arteries [91]. The arteriolar walls are encircled by smooth muscle cells that control the diameter of the arteriole and thus blood flow through the arteriole. When stimulated, the smooth muscle relaxes leading to an increase in the arteriole diameter [91]. This changes the ratio between the hyperaemia of the blood vessels to the whiteness of the scleral background and the eye appears redder. The smooth muscle cells are innervated by sympathetic nerves [92], which provide central autonomic control over the arteriole diameter. The muscle cells are also affected by local factors. These locally-derived factors are moderated by chemical agents, such as prostaglandins or cytokines, that form part of the inflammatory response [90,93,94].

Increased dilation of the arterioles can be caused by mechanical irritation, hypoxia, hypercapnia, acidic shift (increase in lactic and carbonic acids), increased osmolarity, increased potassium, toxic reactions to a noxious agent, (e.g. preservatives, hydrogen peroxide), or as part of the inflammatory response to allergens or infection [95–97]. Many of these factors can be present in contact lens wear and can be acute or chronic in their expression.

Hyperaemia is such a common response to contact lens wear [93, 98–101] that it is easy to forget that hyperaemia can be a sign the eye is experiencing stress [90,102,103]. It is therefore important to include questions about any reported or observed ocular hyperaemia as part of the patient’s lens wear history during a clinical examination [104]. The clinician should identify the potential causes for the hyperaemia and make suitable changes to the lens specifications, wear schedule, or lenses care solution to prevent the condition becoming chronic. The clinician can use visual scales to grade hyperaemia severity and to monitor lens wearer adaptations.

● Pre-lens surface deposits are a feature of all contact lens wear modalities, including daily disposable, although with this modality the clinical consequences of deposits are negligible. Deposit formation occurs as a result of chemical interactions between the lens material and the tear film [119]. The deposits produce an allergic-type inflammatory reaction [120,121]. Treatment is by initiating or increasing the frequency of the surface cleaning regime, or by changing lens wear modality.

● Post-lens hypoxia is produced by insufficient gas-exchange through the lens, principally due to low lens Dk [122]. Hypoxia was a particular feature of early low Dk soft lens materials [93]. Silicone hydrogel (SiHy) lens materials have effectively removed hypoxia (and thus hypercapnia) as a source for limbal and bulbar hyperaemia [123,124]. Post-lens hypoxia is treated by choosing a lens material with a higher Dk [125,126]. Hypoxia is still an issue for scleral/overnight medical wear due to the effect of the post-lens fluid reservoir [127,128].

● A less stable tear film can be produced in contact lens wear, which induces increased tear evaporation [129–131], leading to partial dehydration of the lens material [132,133]. This may produce mechanical effects from a tighter lens fit or increased friction from the lens surface [131,134]. Treatment is by choosing a lens material, lens wear modality, environmental conditions (if possible) and other lens wearer adaptations.

● Lens care solutions can produce bulbar and limbal hyperaemia [135–138]. This may be a direct effect from a biologically incompatible reaction between solution component and ocular surface, or indirectly through a failure of the product to work effectively, e.g. an ineffective protein cleaner. Treatment is by changing lens care solution modality or by lens wear modality.

● Lid-related infections, such as blepharitis or meibomian gland dysfunction, can be related to poor lid hygiene [139]. For these cases, improved lid hygiene can produce a significant improvement in ocular hyperaemia.

3.1.2. Sodium fluorescein, lissamine green and rose bengal staining

Two types of dye, sodium fluorescein and lissamine green, are currently used to examine the conjunctiva as part of contact lens pre-fitting and aftercare examinations [140]. Experimentally, fluorescein is actively taken up by healthy cells in cell culture [141,142]. Clinically, it is thought to permeate the cytoplasm of living but damaged cells, whereas lissamine green stains the cell membrane of dead or damaged cells. The presence of lissamine green staining is thus highly specific for dry eye disease [143]. Both stains are enhanced by the use of filters: a yellow filter with blue light in the case of fluorescein and a red filter with white light for lissamine green. Lissamine green has largely replaced rose bengal, which is toxic, even in relatively low concentrations and uncomfortable, if not painful, for the patient [144].

Two main types of conjunctival staining are noted in soft contact lens wearers: i) dryness-related staining, primarily located on the nasal and temporal bulbar conjunctiva and ii) circumlimbal mechanical staining from contact lens edges.

Conjunctival fluorescein staining is commonly seen in non-contact lens wearers, but typically at lower levels than in contact lens wearers. Some conjunctival staining was seen in 98 % of a mixed group of contact lens wearers and non-wearers; however the proportion of subjects showing greater than Grade 1 staining (0–4 scale) was much higher in the contact lens group: 62 % versus 12 % [145]. Another study found conjunctival fluorescein staining in approximately half (53 %) of non-wearers versus 63 % of lens wearers [146]. With both groups, the incidence of staining was significantly higher for those classified as symptomatic.

Lissamine green conjunctival staining is less common than fluorescein staining in both contact lens wearers and non-wearers. However, lissamine green staining (outside of the limbal area normally covered by the lens edge) is more discriminating in identifying symptomatic
patients, particularly contact lens wearers [146]. The authors hypothesised that reduced blinking in soft lens wearers results in greater evaporation and poorer conjunctival lubrication which, in turn, leads to increased friction during the blink and tissue damage.

There has been little research on the effect of soft lens wear on conjunctival staining. However, two studies have shown useful light on the significance of edge design [117,147]. Soft lens edge profiles broadly fit into three categories: rounded, knife and chisel edge designs. Edge design was the primary factor in controlling circumlimbal fluorocoeurine staining for SiHy lenses [117]. A rounded edge produced the least circumlimbal staining, while a thin knife edge design produced the most, with an inverse association between staining and comfort. Comfort was poorest with the rounded design and highest with the knife edge (72 vs. 87 out of 100) [117]. The study also noted lens rigidity as a secondary factor, finding that a lens of higher modulus generated more circumlimbal staining than a similar design of low modulus. Another study found broadly similar results with a wider range of lens types [147]. With both chisel and knife edge designs, the higher modulus SiHy designs showed significantly more conjunctival staining than their hydrogel counterparts.

Conjunctival staining induced by the lens edge is rarely symptomatic or accompanied by hyperaemia and, therefore, does not necessarily require a change of lens. An exception might be instances of significant conjunctival indentation which has been imaged by optical coherence tomography in soft lens wearers [148-151]. Clinically, this is revealed by pooling of fluorocoeurine in circumlimbal indentations corresponding to the positionning of the lens edge. In one study of nine different soft lens types, conjunctival indentation was associated with poorer comfort [152]. This can be alleviated by switching to a lens of thinner edge design and/or lower modulus.

3.1.3. Lid-parallel conjunctival folds

Lid-parallel conjunctival folds (LIPCOF) are observed as small folds on the bulbar conjunctival surface, close to the lower lid margin and near to the limbus. They occur in both the lower temporal and nasal bulbar conjunctival areas (at around 4 and 8 o’clock of the corneal location), while the patient is looking in the primary gaze [118,153]. The term lid-parallel conjunctival fold was first introduced in 1995 [154] and the feature has been the subject of research by others subsequently [82,153,155,156].

LIPCOF are thought to be caused by increased shearing forces during blinking, as a result of increased friction between the ocular surface and the lids, which, in turn, has been caused by reduced lubrication due to a deficient tear film [157]. These causal factors are particularly found in dry eye disease and studies have shown that LIPCOF is highly correlated with dry eye disease and associated symptoms [153,156-159]. The movement of the eyelids on the conjunctiva causes it to wrinkle into the folds. The model proposes that the greater the friction, the greater the size or extent of the LIPCOF. The folds are not permanent, but are maintained by the position of the eyelid. If the lower lid is retracted, the LIPCOF will disappear, but will reappear after normal blinking [157]. LIPCOF can also occur in subjects showing no other signs or symptoms of dry eye disease [160].

LIPCOF are classified in two ways: by assessing the height of the folds [154] or by counting the number of folds [161-163]. The number of folds approach has been adopted for both slit-lamp biomicroscopy and optical coherence tomography assessment [153,155,164]. LIPCOF is interrelated with tear meniscus assessment, either of the tear meniscus radius [165], height [165,166] volume [167,168], curvature, depth or cross-sectional area [162]. LIPCOF may affect tear film mixing, spreading and thus ocular surface lubrication, although the precise mechanism for this is unclear [169].

‘Contact lens discomfort’ is an adverse clinical response to contact lens wear, characterised by the wearer reporting symptoms of discomfort and possible reduced lens wear time. Symptoms are not always associated with clinical signs. LIPCOF has been proposed as a feature of contact lens discomfort [82,161,170-172].

The aetiology of LIPCOF in contact lens wear is thought to be similar to that in dry eye disease - increased friction between the moving eyelid and the ocular surface. The presence of the contact lens in the eye alters the normal spreading and stability of the tear film over the ocular surface and the normal apposition of the eyelid against the bulbar conjunctival surface. These changes lead to an increase in friction at the ocular surface between the eyelid and conjunctiva during blinking, particularly in the 4 and 8 o’clock area where the shear forces are thought to be greatest [170,173]. Within this model, improving the wettability of the lens surface and thus the distribution of the tear film over the lens and exposed conjunctiva, should also reduce friction and the incidence of LIPCOF. However, it should be noted that a clear relationship between the coefficient of friction and LIPCOF is yet to be proven [118].

There is a limited literature on the effects of different contact lens types, materials and designs on LIPCOF. Most studies report a positive correlation between the presence of LIPCOF and discomfort symptoms or with the extent of lens wear experience. In a series of studies on subjects experiencing discomfort when using low to medium water content (24-62 %) monthly disposable hydrogel contact lenses, LIPCOF was strongly positively correlated to discomfort symptoms, older age, lid wiper epitheliopathy (LWE) and to a lower mucin production [82,171,174].

The effect is also seen with neophyte lens wearers. One study reported that the main discriminators for contact lens-induced dry eye in neophyte contact lens wearers wearing vifillon A hydrogel contact lens and senofilcon A SiHy contact lenses was LIPCOF [160]. Similarly, neophytes who wore SiHy lenses full time for six months showed an increase in LIPCOF [80]. The extent of lens wear experience is also a factor in the development of LIPCOF. Using the term ‘conjunctivochalasis’, but using the Hoh LIPCOF scale to describe conjunctival changes (suggesting LIPCOF might have actually been reported), an increase in LIPCOF with lens wear experience and with lens wearer age has been reported [175]. Also, a positive correlation between LIPCOF and duration of contact lens wear (with LIPCOF findings higher after at least a year of SiHy usage) has been found [176].

There is one contrasting report that found no relationship between LIPCOF and contact lens materials (hydrogel contact lens and SiHy contact lenses) or lens wear modality (yearly disposable contact lens and monthly disposable contact lens) [155], although this could be due to the small number of study subjects in this work.

It has been proposed that LIPCOF should be incorporated into the clinical assessment of lens wearers to identify those wearers at greater risk of developing contact lens discomfort symptoms. This is based on the finding that ocular dryness symptoms are strongly linked to a combination of LIPCOF and non-invasive tear film breakup time [156]. However, even though the specificity and sensitivity of LIPCOF ‘sum’ scores (a combination of nasal and temporal score) has proved to be excellent [160], the repeatability of LIPCOF is limited, although probably better than other measures that may be associated with contact lens discomfort such as tear break-up time, Schirmer test, meniscus height or phenol red thread test [177].

It is important to note that, clinically, LIPCOF should not be mistaken for conjunctivochalasis or conjunctival flaps. LIPCOF refers to small conjunctival folds of about 0.08 mm height, visible under white light (slit-lamp magnification ×18) [179,180] and caused by friction forces during blinking [181]. Conjunctivochalasis may partly share the same aetiology as LIPCOF, but it is also age-related and can be located anywhere on the bulbar surface [157,181-184]. ‘Conjunctival flaps’ are epithelial sheets, containing goblet cells, which are detached from the conjunctiva, are sized of 0.01 mm height, can be located anywhere on the bulbar surface in irregular directions and are mainly reported after SiHy contact lens wear [157,184-187].

The management of LIPCOF in contact lens wearers has been aimed at reducing the amount of friction between the lids and the contact lens,
either by recommending the use of artificial tears or by changing to a contact lens with improved lens surface wettability (see CLEAR Maintenance and Biochemistry Report [188] for discussion on contact lens wettability). A recent study demonstrated that moving experienced monthly replacement daily contact lens wearers to senofilcon A two-weekly replacement lenses, or to spectacle wear, significantly improved LIPCOP after three months [173]. However, a clear framework for such intervention is yet to be formulated [180].

3.1.4. Sub-clinical inflammatory response

The inflammatory response to contact lens wear, which occurs in response to a myriad of factors including mechanical interactions between the lens and ocular surface, hypoxia, tear film alterations, deposits on the lens surface, lens care solutions and hygiene, is observed clinically as hyperaemia at the conjunctiva as discussed above. Sub-clinical biomarkers, such as dendritiform cells which may initiate and modulate the immune response by stimulation of T and B cells (see also review [189]), can be imaged using in vivo confocal microscopy [190] (Fig. 1). Although the effects of contact lens wear and ocular surface conditions on dendritiform cells in the corneal epithelium have been studied (see Section 4.1.5) [190,191], less is known about any impact on dendritic cells within the conjunctiva and limbus.

The density of dendritiform cells in the temporal bulbar conjunctiva was increased following one week daily wear of SiHy and hydrogel reusable hydrogel lenses (disinfected with hydrogen peroxide), but not of the same hydrogel lenses replaced daily [192]. This increase was of similar magnitude to that observed at the lid margin (Section 3.2.3) and central cornea (Section 4.1.5) in the same study. Increased numbers of immune cells in the bulbar conjunctiva were confirmed using impression cytology and flow cytometry [192]. In contrast, another report demonstrated that one week wear of daily disposable hydrogel lenses resulted in a rise in the number of dendritiform cells in the nasal conjunctiva [193]. This difference may be attributed to lens type or to methodological differences as dendritic cell numbers are shown to differ across bulbar conjunctival regions; here, cell numbers were reduced after four weeks and returned to similar numbers to pre-lens wear levels at six months of lens wear [194]. There was no difference in the number of conjunctival dendritiform cells between experienced wearers of reusable hydrogel lenses (with a mean of 10 years wear experience) and non-contact lens wearers [194].

Upregulation of the immune response may be more likely to occur when contact lenses are re-worn and proteins and lipids on the lens surface [195] or microbial contamination of the lens storage case may play a role in initiating such a response. Lens material or lens design cannot be excluded and the role of these factors in upregulation of conjunctival inflammation requires further investigation; as does the impact of rigid corneal lenses. Nevertheless, the return towards pre-lens levels [194] suggests the immune response is transient and adaptation occurs.

In the normal cornea, the highest density of dendritiform cells at the ocular surface is found at the limbus [191]. In this region, dendritiform cells are activated to mature and migrate via the lymphatic vessels between the cornea and lymph node [196]. They are also nearby the limbal blood vessels, enabling travel in the circulation to further facilitate the immune responses. They also have a role in intravascular surveillance within the limbal vessels [197]. The impact of contact lenses and specifically materials and edge design on limbal dendritic cells has not yet been studied, but this area is worthy of research given the essential role these cells play in ocular surface defence.

3.1.5. Sensitivity changes

Before considering conjunctival sensitivity, it is helpful to differentiate the neural architecture in the conjunctiva, which consists of epithelial free nerve endings and specialised receptor bodies [92], from the cornea, which consists of epithelial free nerve endings [198-201]. The density of sensory nerve fibres in the cornea is the highest in the body. These nerve fibres are arranged in large overlapping receptive fields, providing an extremely high level of sensitivity [202,203]. The conjunctival neural density is much less than the cornea and provides a reduced sensitivity as a result [204]. It is also helpful to define the limits of bulbar and limbal conjunctiva. For this review, bulbar is considered to begin 2 mm from the visible limbal/cornea junction and the limbal conjunctiva to be contained within a 2 mm annular zone around the visible junction [205]. A soft contact lens can be expected to cover and move over the limbal area during wear [114].

3.1.5.1. Bulbar sensitivity changes. There is a limited literature on bulbar and limbal conjunctiva sensitivity changes with contact lens wear and the results are mixed. Early studies showed a reduction in bulbar sensitivity with PMMA corneal, rigid gas permeable corneal and low Dk soft hydrogel lens wear [206,207]. In contrast, both an increase [208] and no change [209] in sensitivity with contact lenses have also been reported. An increase in sensitivity in lens wearers who discontinued wear due to discomfort has been reported [206]. No studies have reported on bulbar sensitivity changes with scleral lens wear.

A convincing mechanism to explain the process that produces an
altered bulbar sensitivity is lacking for both rigid and soft lens wear. This may be due to the large overlapping receptive fields of the ocular surface receptors and the imprecision of current sensitivity measurement techniques. The conjunctival blood supply facilitates gas exchange and ensures a normal metabolism for the bulbar conjunctiva and since the lens is not physically present, a mechanical interaction does not occur. A possible effect from conjunctival drying, associated with 3 and 9 o’clock staining or with insufficient blinking during lens wear [210] affecting conjunctival epithelial nerve fibre endings is possible, but this has not been tested. The lack of an obvious mechanism for sensitivity loss in the bulbar conjunctiva, in combination with the current results, suggests that sensitivity is not significantly changed in bulbar conjunctiva for any modern lens wear type.

3.1.5.2. Limbal conjunctiva sensitivity changes. The general evidence for the limbal conjunctiva is that short-term and long-term wear of soft hydrogel and SiHy lenses produces an increased limbal conjunctival sensitivity [116,211]. An increase in sensitivity was also found in previous lens wearers who discontinued wear due to discomfort [211]. In contrast, other studies have found no change in inferior limbal conjunctival sensitivity for both low Dk soft hydrogel and SiHy lens wearers [212,213].

The presence and movement of the soft lens edge over the limbal conjunctival zone during lens wear suggests a mechanical interaction between the lens and the limbal conjunctival sensory nerves [214]. Evidence for this mechanical interaction on the limbal zone has been observed as circumlimbal staining following SiHy lens wear [117]. However, in contrast to the reduced sensitivity produced by adaptation to a mechanical stimulus as reported for the corneal nerves (Section 4.1.6), the mechanical interaction with the limbal zone increases sensitivity. This suggests that the mechanical interaction has a different form which promotes an increased neural response or that the neuroreceptors respond differently [201,215]. Moreover, the neural architecture is different in this area, possessing specialised pressure sensors [201,216,217].

It is unclear whether this difference has a role in the altered neural response.

Increased limbal sensitivity may lead to symptoms of discomfort by the lens wearer and so form part of the contact lens discomfort model [218]. The form that this symptomatic limbal zone/lens interaction takes is unclear, but lens edge design, lens modulus and lens thickness might all influence the strength of the mechanical interaction [117]. Significantly, these factors have also been linked to lens wear discomfort [118,137,219].

The alternative mechanism for how the lens could affect limbal conjunctival sensitivity (hypoxia) can be rejected since this would lead to a depression in neural activity [220] rather than the observed increase. An alteration in corneal or conjunctival metabolism is, in any case, unlikely with the presence of the extensive blood supply through the limbal arcades [205].

3.2. Palpebral and marginal conjunctiva

3.2.1. Papillary hyperaemia and roughness

The palpebral conjunctiva forms the back surface of both eyelids [221]. It is a key part of the ocular lubricating system, in conjunction with the tear film, that assists with eyeball and eyelid movement [222]. It is formed into an epithelial layer, containing mucin secreting cells (goblet cells) and a stromal layer that contains the blood supply, derived from the episcleral arteries and some inflammatory cells. The normal appearance of the palpebral conjunctiva is satiny or smooth in 14 % of people, containing small uniformly sized ‘micropapillae’ (<0.3 mm diameter) in 85 % of people, or containing non-uniform papillae (up to 0.5 mm diameter) in <1 % of people [120]. Palpebral hyperaemia and roughness can be graded using visual grading scales [105]. Similarly to bulbar and limbal hyperaemia, there is considerable inter-participant variation [223] and a normal baseline should be obtained for each patient before lens wear to allow comparison with subsequent lens wear. Assessment should only be made across the central area of the everted lid as other areas of the conjunctiva can be affected by non-contact lens-related effects or by the lid eversion process, which can distort the lid along the lid margin [224].

Changes to the papillary conjunctiva are a significant complication of all types of contact lens wear and are caused by the interaction between the front surface of the contact lens and the back surface of the eyelid [101,120]. The interactions can be mechanical or allergic in nature, producing an inflammatory response that alters the homeostatic balance in the conjunctival blood vessel diameter (hypoxemia) [91] and an inflammatory cell response that produces localised swelling in the conjunctival epithelium and stroma (roughness) [94,224]. The mechanical interaction is produced by increased friction between the palpebral conjunctiva and lens surface, due to lens dehydration or lens surface deposition [170,225]. A papillary reaction can also be caused by surface deposits or by chronic leakage of lens care solution ingredients (e.g. PHMB) from the lens during wear [136]. These clinical signs and their cause are characteristic of contact lens-induced papillary conjunctivitis [226]. Differential diagnosis should also be made for allergic, atopic and vernal conjunctivitis, which can show similar clinical appearance and symptomatology [227].

The appearance of contact lens-induced papillary conjunctivitis can vary with time from onset, lens wear type or modality and inflammation severity [228]. Onset can be within a few weeks (from initial lens wear) for soft contact lenses, or up to 14 months in rigid corneal lens wear [224]. Studies indicate that 6–12 % of soft hydrogel lens wearers will present with contact lens-induced papillary conjunctivitis at some stage in their lens wear lifetime [229–233], that overnight lens wear increases the incidence rate (up to 18 %) [234,235] and that daily disposable lens wear reduces the rate (as low as 2 %) [236]. Silicone hydrogel lens wear produces a slightly higher incidence rate than soft lens wear [100,235]. A contact lens-induced papillary conjunctivitis incidence rate of 2 % has been reported in overnight rigid corneal lens wear [229].

Contact lens-induced papillary conjunctivitis presents as both increased hyperaemia, which appears first, and increased lid roughness. In soft hydrogel lens wear, papillae are more populous than in rigid corneal lens wear, are located towards the upper tarsal plate and the apex of the papillae has a rounded, flatter form [120,224]. In rigid corneal lens wear, the papillae are crater-like and are located towards the eyelid margin [120,224]. In severe cases, papillae can develop up to 1 mm in diameter and extend over a wide area of the conjunctiva. Here, patients can complain of discomfort/itching (which may be sufficient to cause the patient to stop lens wear) and blurred vision from increased mucin production. Treatment may involve stopping lens wear for a period of time, along with the use of anti-inflammatory therapy, a change in lens wear type/modality and/or lens care solution [224,228].

3.2.2. Lid wiper epitheliopathy

The lid wiper is the portion of the eyelid marginal conjunctiva that is in contact with the globe and wipes the ocular or contact lens surface during blinking. Lid wiper epitheliopathy (LWE) is a clinical condition observed through the staining of the lid wiper region with fluorescein, lissamine green or rose bengal [237], which extends beyond the physiological staining of Marx’s line [238]. Lid wiper epitheliopathy is observed in both upper and lower eyelid and has been shown to occur in contact lens wearers as well as in non-wearers [209,237,239–247]. The severity of lid wiper staining is most commonly graded subjectively based on the horizontal and vertical extent of lid margin staining [248], although objective/automated techniques have also been used [249,250].

Although the exact aetiology of LWE remains unclear, the primary hypothesis is that LWE results from increased friction between the lid wiper and the ocular or contact lens surface during blinking in the absence of adequate lubrication [237]. LWE is likely to be a
multifactorial condition with different underlying causes [134], including deficient tear film [251], altered mucin production [171], increased tear osmolarity [252–254], inflammation [134], incomplete blinking [255] and eyelid pressure [256,257]. A recent study supports the primary hypothesis that inadequate lubrication causes friction factors and results in LWE [258]. Upper LWE may have a different aetiology to lower LWE [239,253]. During contact lens wear, the frictional properties of contact lenses may contribute to the aetiology of LWE [170].

Lid wiper staining was observed in 25% of patients presenting to an eye clinic, including contact lens wearers and non-wearers [259]. Some reports suggest a greater prevalence and grade of LWE staining in contact lens wearers (52%–84%) compared with non-wearers (13%–40%) [239,241,244], whilst others have found no difference [242,243,245,246]. Studies investigating longitudinal changes in LWE have shown increased upper lid wiper staining with lens wear [50,160,254,260]. Upper LWE staining significantly increased in neophytes after four weeks of hydrogel contact lens wear [160]. Similarly, increased upper LWE grades were found in neophytes following six months of SiHy contact lens wear [80]. Increased upper lid wiper staining was reported after 10 days of SiHy lens wear, compared to spectacle wear at baseline, whilst no change was found for the lower lid [254]. Regarding diurnal variation, upper lid wiper staining significantly increased throughout the day in contact lens wearers, whilst no change was observed in non-wearers [261]. An increased area of lower lid wiper staining has been reported after 12 h of soft contact lens wear, whilst no change was found in non-wearers [209].

There is limited evidence of the effect of different contact lens materials and designs on LWE. Greater LWE prevalence and grade in rigid corneal lens wearers compared with soft contact lens wearers was reported for the upper lid, whilst lower LWE was similar between groups [239]. Similarly, rigid corneal lens wear was associated with greater LWE grades compared with soft contact lens wear, particularly at the upper lid margin [262]. These findings would suggest a mechanical effect possibly related to lens-related factors such as modulus, edge design, movement. Conversely, a study on daily wearers of hydrogel, SiHy or rigid corneal contact lenses failed to demonstrate an effect of lens type on upper lid wiper staining [263]. In addition, a number of studies showed no significant differences in LWE grades or patterns between SiHy lens types [254,260,264]. In contrast, in a study of a large sample of soft contact lens wearers, habitual senofilcon A wearers were found to have the lowest LWE grades. However, according to the authors, the clinical significance of the differences observed was unclear [265]. To date, no studies have demonstrated a link between contact lens coefficient of friction and LWE.

A limited number of studies have investigated the impact of contact lens wear on the lid wiper at a cellular level using impression cytology techniques. No differences were found in the appearance of epithelial cells and density of goblet cells of the upper marginal epithelium between contact lens wearers and non-wearers [245]. Expression of keratinization-related proteins (filaggrin, traneglutaminase-1 and cytokeratin 1/10) was demonstrated in the lid margin epithelium, which may indicate that a pathological process occurs at the lid wiper. In contrast, soft contact lens wearers with short and moderate experience had altered cytoplasmic and nuclear characteristics, as well as reduced goblet cell density in the upper lid wiper compared with non-wearers [246]. Interestingly, the lid wiper epithelium of previous contact lens wearers was similar to lid of non-wearers suggesting that changes during contact lens wear might be reversible to some extent. Rigid corneal contact lens wear has been associated with a wider, more keratinised, lid wiper conjunctiva compared with soft contact lens wearers and non-wearers, both at the upper and the lower lid margin [262]. These findings lend support to the proposed mechanical or frictional nature of LWE.

The relationship between vital staining of the lid wiper and the specific underlying morphological changes remains unclear. Although, in some instances, histological widths of the lid wiper conjunctiva were significantly correlated with lissamine green staining grades [262], no correlation was found between lissamine green staining and morphological changes in the lid wiper epithelium [246].

Only two studies have investigated the vascular response of the lid wiper to contact lens wear. Redness of the upper and lower lid wiper (as an analogue of vascular response) in soft contact lens wearers and non-wearers did not significantly change through the day or following ≥6 h of lens wear [244]. In contrast, increased microvascular network density has been reported in the upper lid wiper after 6 h of SiHy lens wear in neophytes, whilst no change was observed through a day of no lens wear [266].

While LWE has been established as a diagnostic marker for dry eye disease [162], the relationship between LWE and contact lens discomfort is not clear. Several studies have reported greater LWE prevalence and grade in symptomatic contact lens wearers (67% and 90%, respectively) compared with asymptomatic lens wearers (13%–32%), primarily for the upper lid wiper [67,82,171,237,240–243]. In contrast, an approximately similar number of studies have been unable to show a relationship between LWE grading and contact lens associated dryness/discomfort [80,134,209,244,247,254,262]. This could be partly due to differences in methodology, population characteristics and classification criteria for contact lens discomfort. Histological widths of the lid wiper conjunctiva have not been associated with contact lens comfort [262]. No association was also observed between lid wiper hypertaemia and subjective comfort [244]. On the other hand, increased microvascular density in the lid wiper was significantly correlated with decreased contact lens comfort [266]. Recently, a study investigating the use of fluorescein-labelled wheat germ agglutinin as a marker for ocular surface mucins found that symptomatic lens wearers showed reduced wheat germ agglutinin fluorescence in the lid wiper, which may suggest altered density and/or structure of mucins [267].

Contradictory results in the literature may be partly due to discrepancies in staining protocol and grading technique. Lid wiper staining has been shown to be influenced by dye concentration [250,268], instilled volume [250], frequency of lid evasion [268,269], sequential instillation and timing of assessment [270], which highlights the need for a standardised methodology. The limited repeatability of subjective grading of LWE staining [177,271] and variations between brands [272] may have also contributed to inconsistencies in the literature.

Whether LWE really represents a pathological process and its clinical significance are still under debate. Nonetheless, subjects showing severe lid wiper staining may benefit from treatments aimed at increasing lubrication during contact lens wear [241]. Management strategies could include altering lens type and wearing modalities, improving blinking behaviour [255] and the use of lubricant eye drops [263,273,274].

3.2.3. Sub-clinical inflammatory response

Given the nature of the interaction between the tissues of the palpebral conjunctiva and lid margin with the contact lens edge and surface, it would be reasonable to speculate that recruitment of immune cells would be seen in these tissues. The density of dendritic cells at the lid margin was increased following one week of daily SiHy and hydrogel reusable lens wear, but not in daily disposable wear of the same hydrogel lenses [192]. This increase was of similar magnitude to that observed on the bulbar conjunctiva and central cornea in the same study. The rise in number of dendritic cells was supported by a rise in leukocytes shown with impression cytology and flow cytometry and suggests an upregulation in inflammation occurs at the lid margin with the wear of reusable lenses, but not when these lenses are replaced daily. It is hypothesised that degraded proteins and lipids on the lens surface or microbial contamination of the lens storage case and then transfer of microbial product to the lens may play a role in initiating such an inflammatory response [195].
Interestingly, another study of daily disposable hydrogel lens wear reported elevated density of dendritic cells at the lid margin after 6 months of wear in patients with symptoms of contact lens discomfort, but not in asymptomatic wearers [275]. Pre-lens wear dendritic cell density was not measured, so it is impossible to surmise whether the recruitment of immune cells into the lid margin was a response to the presence of the lens itself or a subclinical inflammation due to contact lens dry eye. No relationship was found between lid margin dendritic cells and lens comfort [192]. Nevertheless, the demonstrated relationship between contact lens-induced discomfort and higher numbers of dendritic cells at the lid margin is worthy of further study.

Immune cells on the palpebral conjunctiva have not been observed in the context of contact lens wear. Examination of the palpebral conjunctiva conducted in normal patients and in those with severe allergy (vernal keratoconjunctivitis) has suggested that dendritic cells can be observed on the palpebral conjunctiva using in vivo confocal microscopy [276,277]. It is not clear whether the reported cells were observed in the thin 2-3 layer epithelium of the palpebral conjunctiva or in deeper tissue [277]. A study which examined the palpebral conjunctiva in normal eyes and in trachoma showed no association between the number of dendritiform cells viewed in vivo in the palpebral conjunctiva and the number of cells labelled as dendritic cells in an immunohistochemical examination of biopsy specimens from the same patients [278] suggesting that the dendritiform cells may not all be true dendritic cells.

3.2.4. Sensitivity changes

There is a very limited literature on changes in the palpebral and lid margin conjunctival sensitivity in contact lens wear. In part, this may be due to difficulties in measurement of this area - for example, lid manipulation and exposure of the tissue under measurement may impact on the values obtained. In general, studies indicate that soft contact lens wear produces a reduction in upper lid palpebral conjunctival sensitivity, but a possible increase in sensitivity in symptomatic lens wearers. A reduction in palpebral conjunctival sensitivity in rigid corneal lens wearers and in low Dk soft lens wearers has been reported [279]. A decrease in palpebral sensitivity with soft contact lens wear, but an increase in sensitivity in symptomatic soft lens wearers has also been reported [280]. There was an increase in palpebral sensitivity for soft lens wearers compared to non-lens wearers [281]. One study reported reduction in upper lid palpebral sensitivity in soft lens wearers, but an increase in lower lid palpebral sensitivity in the morning [209]. The mechanism for these effects appears to be the mechanical interaction between the anterior lens surface and the overlying palpebral conjunctiva during eyelid blinking producing an adaptation in the neural response to the repeated stimulation. The increase in sensitivity in symptomatic lens wearers suggests a possible effect on lens wear discomfort from this route [280].

Lid margin sensitivity is the highest of all the conjunctival areas [282–284]. It is generally considered to be reduced in both rigid corneal and soft lens wear [209,279,281,282,285,286]. The mechanism for this effect is thought to be linked to a neural adaptation from the mechanical interaction between the eyelid margin and the edge of the contact lens during blinking.

4. Cornea

4.1. Epithelium

4.1.1. Fluorescein staining

Fluorescein is versatile enough to reveal most disruptions to the ocular surface and is helpful in detecting a wide range of contact lens-related stress factors, including: desiccation, trauma, infection, allergic and toxic effects. As well as differentiating various corneal disorders through the pattern of staining (Fig. 2), it indicates the severity through the depth and extent of staining and, therefore, is an invaluable pointer towards management.

Despite its long history of use in ophthalmology, the mechanisms of corneal staining are not fully understood [287,288], although recent research has expanded this. Sodium fluorescein is water soluble and is more accurately described as a dye rather than a stain. Early theories suggested that punctate staining represented an accumulation of fluorescein in intercellular spaces or pooling in sites of missing cells. However, these have been largely discredited. Several observations point towards the fact that fluorescein enters the epithelial cells themselves: i) rinsing with saline fails to eliminate punctate staining [289], ii) punctate staining matches the size and shape of epithelial cells [290], iii) cells shed by apoptosis show fluorescein staining and iv) even healthy epithelial cells fluoresce, albeit at a much lower level than damaged cells [291]. In the case of deeper corneal damage, fluorescein can diffuse in the stroma and show a background glow [292].

An extensive study of contact lens wearers (91.5 % soft, 8.5 % rigid corneal) noted corneal staining in 54 % of patients [293]. Factors related to increased corneal staining included: increased daily wearing times, lissamine green conjunctival staining, contact lens deposition, increased tear meniscus height, decreased hydrogel nominal water content and lower financial income. The wearing of SiHy (as opposed to hydrogels) gave lower levels of corneal staining.

4.1.1.1. Desiccation. With both rigid corneal and soft contact lenses, desiccation induced staining is the most commonly encountered type of corneal staining. Desiccation staining occurs in locations where the tear film is thinnest and/or least stable. Soft lens smile-shaped staining occurs parallel and adjacent to the lower lid. Not surprisingly, desiccation staining is more common with partial blinking and often marks the lowest extent of the upper lid during the blink. Desiccation staining can also coincide with the edge of the lower tear meniscus due to a thin band in the tear film from surface tension [29].

Low levels of desiccation staining can be tolerated since this can often be present in the normal non-lens wearing eye [294]. Low to moderate levels of corneal desiccation staining can be mitigated by improved blinking, the use of wetting drops, reduced wearing time, or the use of dehydration-resistant lens materials [295].

Rigid lens 3 & 9 o’clock staining is also a type of desiccation staining but occurring through instability of the pre-corneal rather than pre-lens tear film. The characteristic triangular shape of 3 & 9 o’clock staining can be explained in terms of poor corneal wetting during the blink due to vaulting of the lid between the lens edge and ocular surface. The largest gap occurs when the lid crosses the widest part of the lens. Less widespread 3 & 9 o’clock staining, closer to the lens edge can be explained by localised tear film thinning adjacent to the tear meniscus surrounding the lens. Both types of staining are best mitigated by modifying the lens design to improve corneal wetting, i.e. decreasing edge clearance, decreasing edge thickness, decreasing diameter, or increasing diameter [296].

4.1.1.2. Trauma. The simplest example of corneal trauma is foreign body abrasion caused by dust or an eyelash being trapped beneath the lens. Epithelial abrasions can heal at more than one square millimetre per hour, depending on the initial wound size; larger wounds healing faster [297]. Based on the results of animal studies [292], a temporary discontinuation of lens wear has been proposed based on the depth and extent of corneal staining: 24 h if slight stromal diffusion, two to three days if moderate stromal diffusion.

Superior arcuate corneal staining (also termed Superior Arcuate Epithelial Lesion) was relatively common with early hydrogel designs and perplexed ECPs for some time, partly due to its similarity to superior limbal keratitis. However, it became clear that Superior Arcuate Epithelial Lesions are due to trauma from relatively stiff soft lenses [298]. Superior Arcuate Epithelial Lesions are typically located on the cornea under the upper lid approximately a millimetre from the limbus. Lenses of high modulus or thick lenses of any modulus that fail to align
with the corneal shape can result in pressure points. Additional pressure from the upper lid and lens motion during the blink produce an abrasion which is invariably severe enough to warrant a change of lens design.

The edges of both rigid corneal and soft lenses, when in contact with the corneal surface, can cause corneal staining of varying degrees. Rigid lenses with inadequate edge clearance can produce arcuate staining close to the limbus. This can be confused with 3 & 9 o’clock staining but is differentiated by examining the peripheral lens fit. When the lens is moved close to the limbus, the fluorescein fit should show some peripheral clearance, even if only minimal. Soft lenses whose edges encroach onto the peripheral cornea can also result in mild staining. In aligning with the ocular surface, soft lenses show the greatest deformation at the edge, which typically stretches about 4% causing a band of pressure [299]. In both cases, the remedy is to modify the lens fit to avoid corneal contact with the lens edge.

4.1.1.3. Toxicity. Solution-induced corneal staining (SICS) is a common side effect of soft lens multipurpose disinfection systems. Unlike other types of staining, SICS is usually evident in three or more peripheral corneal sectors. Often the punctate staining follows a circular pattern which is invariably severe enough to warrant a change of lens design. Group 2 hydrogel lenses in conjunction with polyhexamethylene biguanide (PHMB) solutions induce the greatest level of staining. This can be explained in terms of the preservative uptake-release characteristics; being highly temperature sensitive, Group 2 materials discharge a relatively high proportion of solution into the post-lens tear film, thus increasing the dosage. Second, the staining usually reaches a maximum two hours after insertion but then disappears after a further two hours [305]. This is at least partly explained by an associated increase in shedding of corneal cells with SICS, suggesting a temporary increase in epithelial apoptosis [306]. SICS may be related to an increase of dynamin-mediated uptake of fluorescein into cells which in turn is due to the presence of Tetronic 1107, a block co-polymer included in a number of multi-purpose solutions [142].

4.1.2. Hypoxia-related responses: microcysts and epithelial oedema

Contact lens-induced hypoxia has inspired a large body of research and led to many insights into corneal physiology [122,207,208]. In relation to the corneal epithelium, hypoxia leads to: decreased epithelial metabolic rate [309,310], reduced basal cell mitosis [311,312], epithelial cell enlargement and increased cell life [313], epithelial thinning [309,314,315], lactate accumulation, acidification and increased bacterial binding [316,317]. The main clinical manifestations of this include: epithelial microcysts, compromise in junctional integrity, neovascularisation and decreased corneal sensation (Section 4.1.6).

Soft contact lens wear has been reported to suppress corneal basal epithelial cell mitosis in rabbits [312]. Subsequent work showed a correlation between reduced oxygen supply and reduced exfoliation of epithelial cells with both rigid corneal and soft lens wear [318–320]. A correlation with the ability of Pseudomonas aeruginosa to bind to exfoliated epithelial cells was reported that was hypothesised, but not proven, to be a factor in increased risk of corneal infection [321]. Binding of P. aeruginosa to corneal cells was greater with hydrogel lenses than SiHy lenses [319] but, by contrast, hyper-oxygen permeable rigid corneal lenses did not increase P. aeruginosa binding. However, a subsequent study has shown a reversal of this effect over a longer period (6–12 months) of wear [322].

There is no evidence for corneal epithelial swelling due to anoxia [323,324] or hypoxia [325,326]. Corneal epithelial oedema is a rare manifestation of contact lens wear, usually arising from significant trauma or being exposed to a hypotonic environment. Fluid accumulates in the intercellular spaces rather than within cells. Increased lactate production during hypoxia may accumulate between basal cells and draws water out of the cells by osmosis [327]. Light scattering from these vacuoles of lower refractive index can result in cloudy vision and coloured haloes. Visual phenomena with epithelial oedema are similar to those experienced with stromal oedema but occur much earlier, i.e. with relatively low levels of oedema. With high levels of epithelial oedema, vacuoles may be visible on slit lamp examination and are distinguished from epithelial microcysts by marginal retro illumination; vacuoles show unreversed illumination [328].

Epithelial microcysts are an indicator of disordered epithelial metabolism and in contact lens wearers, occurs as a delayed response to high levels of chronic hypoxia [229]. Since they are associated with overnight wear or contact lenses of low oxygen transmissibility, they are rarely seen with daily wear of current SiHy lenses.

Epithelial microcysts are translucent, typically 15–50 μm in diameter and show reversed illumination, indicating a higher refractive index than surrounding tissue [328]. They form in the basal layers, gradually moving to the corneal surface, at which point they may stain with fluorescein. Non-contact lens wearers can show small numbers (<10) of microcyst but, in lens wearers, larger numbers, even hundreds, may be present. They are usually asymptomatic and, except in severe cases, severe cases may be associated with reduced comfort [300–302] and an increased incidence of infiltrative events [303]. The phenomenon of SICS shows a number of interesting features. First, the severity varies greatly according to the lens-solution combination [304].
have no effect on vision. There is an inverse relation between lens oxygen transmissibility and the number of microcysts [329]. Hydrogel lenses are associated with a greater number of microcysts compared to rigid corneal lenses with similar Dk/t [329].

Their aetiology and morphology is not fully understood but microcysts are believed to represent degenerated (apoptotic) cells [330] due to altered mitosis of the basal epithelial cells [329]. A curious feature of microcysts is their time-course; their onset is slow, reaching a peak after several months and, when lens wear is ceased, first increase in number before disappearing over a period of 2–3 months. The return of basal cell mitosis to normal levels may accelerate the process of bringing cellular debris to the surface [309].

4.1.5. Sub-clinical inflammatory response

A review of early case reports (1965–1988) noted that, out of 473 cases, 343 (72.5 %) were associated with rigid corneal lenses and 130 (27.5 %) with hydrogel lenses [335]. Another report found corneal warpage was associated with the fit of rigid corneal lenses [336]. Several reports discussed corneal warpage with early examples of opaque tinted lenses [337,338]. In a more recent study of prospective refractive surgery patients [339], contact lens wearers were required to cease lens wear for 5 days to 3 weeks depending on lens type; 6.7 % (11/165) patients showed significant corneal warpage. The recovery rates varied with lens type, soft overnight wearing eyes taking the longest (11.6 ± 8.5 weeks) and rigid corneal lenses the shortest (8.8 ± 6.8 weeks).

Corneal warpage is a rare occurrence with contemporary high Dk contact lenses, but remains a possibility with low Dk lenses. Notably, there is one report of keratocous being wrongly diagnosed in the case of corneal warpage due to soft lens wear [340] and the correct discrimination of these two conditions is still a subject of study [341].

4.1.6. Sensitivity and nerve changes

Since the earliest introduction of contact lenses, changes in corneal sensation have been a feature of contact lens wear. Although an optical benefit is produced by lens wear, the mechanical interaction of the contact lens with the cornea and eyelids can produce a strong foreign body sensation, particularly in rigid corneal lens wear. Thus adaptation to the presence of the lens is a desired side-effect for successful rigid corneal lens wear [21,282,286,352-354]. Adaptation to soft lens wear is not needed to the same extent, but discomfort from soft lens wear raises a different question about how the corneal nerves respond to lens wear and whether a lack of adaptation may be contributing to discomfort [21].

Wearing PMMA or rigid corneal lenses will produce a marked reduction in corneal sensitivity in the wearer, with the magnitude of the effect depending on the length of lens wear, both in the short-term (over a period of a day) and in the long-term (over a prolonged period of daily lens wear), up to a maximum effect for that wearer [355-362]. There is also reduced sensitivity in wearers of reverse geometry ortho-k lenses [363]. A total loss of sensitivity does not occur, although sensitivity may be sufficiently reduced to increase the risk of an undetected foreign body [357,359]. Peripheral corneal sensitivity, not covered by the lens, is unaltered [364]. Recovery of sensation after lens wear follows a similar effect - a shorter period of lens wear allows for an earlier recovery, with full recovery appearing to occur [355,365]. No significant morphological changes in corneal nerve structure have been noted with high Dk rigid corneal lens wear [366].

Ortho-k lenses, by virtue of being rigid, and also of being worn overnight, produce a reduction in sensitivity, with similar changes related to duration of wear as those seen in standard rigid corneal lenses. Central sensitivity is reduced by approximately 50 % and recovers to pre-lens wear levels after cessation of lens wear [367-369]. Corneal nerve morphology is affected by ortho-k, with a reduction in nerve fibre
density and re-organisation of the nerve fibre orientation [368–372]. The nerve fibre changes also resolve with cessation of ortho-k lens wear, in sync with the recovery in sensitivity [369,372]. These features strongly indicate a direct link between sensitivity loss and the mechanical effect of the ortho-k lens on the corneal epithelium during overnight lens wear [367]. A metabolic effect from hypoxia under the lens is not considered to be a factor, since very high Dk lens materials are used and no corneal oedema is observed.

No studies have reported on corneal sensitivity change in scleral lens wear, but the vaulting of the lens over the cornea, combined with good Dk lens materials and an appropriate post-lens fluid reservoir thickness, suggests that no change in sensitivity is likely. This is supported by evidence that corneal neural structures are unchanged with scleral lens wear [366,373]. However, scleral lens materials with an insufficient Dk [374], or with an excessive post-lens tear reservoir [127,128] will produce oedema, suggesting that either scenario may produce a reduced sensitivity.

For low Dk soft hydrogel lenses, both a mild reduction in sensitivity [116,362,375,376] and no change in sensitivity has been reported [211,377,378]. For studies that reported a reduction, a full recovery to pre-lens wear levels occurs when lens wear is stopped [375,376]. The duration of wear does not appear to produce an increase in effect beyond

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Corneal epithelial dendritic cell density (cells/mm²)</th>
<th>Centre</th>
<th>Periphery</th>
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<tbody>
<tr>
<td>Zhivov et al 2007 [344]</td>
<td>Contact lens wearers (n=54)</td>
<td>HCL: 36 ± 22</td>
<td>HCL: 189 ± 34</td>
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<td></td>
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<td>SCL: 114 ± 41</td>
<td>SCL: 228 ± 35</td>
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<td></td>
<td>Non-wearers (n=70)</td>
<td>34 ± 3</td>
<td>98 ± 8</td>
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<td>Sindt et al 2012 [345]</td>
<td>Contact lens wearers (n=53)</td>
<td>All: 64 ± 71</td>
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<td>significantly higher than non-wearers</td>
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<td>Hy: 47 ± 44</td>
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<td>SiHy DD: 69 ± 77</td>
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<td>no significant difference between lens types</td>
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<td></td>
<td>Non-wearers (n=10)</td>
<td>29 ± 23</td>
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<td>López-De La Rosa et al 2018 [346]</td>
<td>Contact lens wearers (n=40)</td>
<td>Hy: 132 ± 83</td>
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<td>significantly higher than SiHy &amp; no wear</td>
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<td>SiHy: 68 ± 77</td>
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<td>not significantly different to no wear</td>
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<td></td>
<td>Non-wearers (n=20)</td>
<td>58 ± 20</td>
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<tr>
<td>Alzahrani et al 2017 [193]</td>
<td>Contact lens wearers (n=60)</td>
<td>1w Hy DD: 47 ± 25</td>
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<td>significantly higher than no wear</td>
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<td>24w Hy DD: 32 ± 29</td>
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<td>not significantly different to no wear</td>
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<td></td>
<td>Non-wearers (n=23)</td>
<td>27 ± 19</td>
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<tr>
<td>Golebiowski et al 2020 [196]</td>
<td>Contact lens wearers (n=20)</td>
<td>20.1 ± 26.3</td>
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<td>not significantly different to no wear</td>
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<td>Non-wearers (n=20)</td>
<td>18.6 ± 23.9</td>
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<td>Saliman et al 2020 [192]</td>
<td>Contact lens wearers (n=20)</td>
<td>1w Hy DD: 15.2 ± 7.1</td>
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<td>1w Hy: 24.1 ± 11.1</td>
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<td>1w SiHy: 22.7 ± 7.8</td>
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<td>significantly higher than BL</td>
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<td></td>
<td>Baseline (n=20) (experienced wearers)</td>
<td>14 ± 7.5</td>
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<tr>
<td>Liu et al 2020 [347]</td>
<td>Contact lens wearers (n=20)</td>
<td>1w Hy: 32.29 ± 5.47</td>
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<td></td>
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<td>4w Hy: 60.52 ± 12.29</td>
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<td>12w Hy: 62.71 ± 13.25</td>
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<td>24w Hy: 55.94 ± 10.63</td>
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<td></td>
<td>4-24w significantly higher than no wear</td>
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<tr>
<td></td>
<td>Non-wearers (n=20)</td>
<td>16.25 ± 2.58</td>
<td>19.06 ± 2.53</td>
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</table>
the maximum effect for the wearer [362]. Depending on the water content of the lens and the duration of wearing, some loss in sensitivity is likely.

For high Dk soft hydrogel, daily disposable and SiHy lenses, no significant loss in sensitivity has been noted using any type of instrument [211–213,379], although differences in sensory processing have been noted [379,380]. The consequences for this latter finding are unclear, but may have a role in contact lens discomfort. No significant changes in corneal neural architecture have been noted with soft contact lens wear in the central or mid-peripheral cornea, although the changes may be more subtle than those visible with confocal microscopy [213,366,381–383].

The different patterns of effect with each lens type illustrate the two main mechanisms proposed to explain sensitivity loss: sub-lens corneal hypoxia and mechanical pressure or rubbing [201,214,384,385]. The importance of gas exchange through the lens material is demonstrated by the reduction in sensitivity loss with increasing lens Dk and/or tear exchange [214]. This matches with experimental studies that demonstrate a reduced corneal sensitivity with a reduced pre-corneal oxygen concentration (compared to normal) [386,387]. The exact mechanism for this reduction has not been established, but has been linked to an altered corneal metabolism, i.e. the change in gas exchange rate leads to an altered metabolic level within the cornea that produces a new sensitivity baseline. This change may be moderated by hypoxia and/or hypercapnia [220], as well as altered stromal pH [220], neurotransmitter [213,388,389] and acetylcholine transferase activity [386,390,391]. Evidence for a hypoxia-related mechanism is shown by the recovery in corneal sensitivity in PMMA lens wearers refitted into rigid corneal lenses [392] and in low-Dk soft lens wearers refitted into SiHy lenses [208,212].

The mechanical effect is revealed by the different findings between the rigid and soft lens material, each of which delivers significantly different stimulation to the corneal nerves. The mechanical interaction of the lens with the corneal surface produces a sustained response from the corneal nerves (and thus symptoms of discomfort in the lens wearer), which gradually reduces with neural adaptation [393]. This adaptation may be at the receptor level or at a higher level [393].

4.2. Stroma

4.2.1. Neovascularisation

The limbal vasculature does not provide the required nutrition and oxygen for corneal metabolism [394]. The cornea receives the required oxygen for its respiration from the anterior surface through diffusion of atmospheric oxygen that is dissolved in the tear film. The required nutrition (e.g. glucose and amino acids) for the avascular cornea diffuse from the aqueous humour across the leaky corneal endothelium [395,396].

Peripheral corneal oxygen deprivation by contact lens wear may lead to limbal hyperaemia that is inversely related to peripheral lens oxygen transmissibility (Dk/t) [123,397]. The increased limbal hyperaemia by contact lens wear could be a precursor to corneal neovascularisation. However, a direct link between limbal hyperaemia and the neovascular ingrowth has not been established [307]. The absence of vessels in the cornea is a major factor in maintaining its transparency. The loss of corneal transparency by progressive growth of invading new vessels in the cornea could be sight threatening [398]. A suggested mechanism for maintaining corneal avascularity is through an active balance between corneal angiogenic and antiangiogenic factors [399]. Peripheral corneal swelling can facilitate limbal vessel penetration into the cornea but the presence of stromal swelling by itself is not a sufficient trigger to the growth of new vessels. Contact lens-induced corneal neovascularisation may be triggered by corneal hypoxia through down-regulating antiangiogenic factors and up-regulating angiogenic factors [399,400]. However, corneal hypoxia may affect the balance between corneal angiogenic and antiangiogenic factors through two different mechanisms [401]:

- Hypoxic route: the hypoxia itself may trigger the release of vascular endothelial growth factor in an attempt to rescue the oxygen-thriving epithelial and endothelial cells.
- Hypoxia mediated inflammatory route: hypoxia-induced corneal inflammation may signal the release of inflammatory vaso-stimulating factors in the stroma.

Corneal limbal vasculature has an insignificant role in corneal oxygenation. The vascular arcade does not penetrate the normal clear cornea due to barrier function of limbal stem cells among other things. However, as a result of the imbalance from hypoxia the limbal vessels may penetrate and continue to encroach the stroma towards the corneal apex. The depth of corneal vascularisation may depend on the location of the angiogenic site in the cornea hence deeper stromal vascularisation could be expected with higher degrees of corneal hypoxia. The posterior oxygen supply to the peripheral endothelial cells from the aqueous could, at least in part, explain the uncommonness of contact lens-induced deep stromal vascularisation. Deeper stromal vascularisation could pose a higher risk of corneal opacification from leaking lipid into the stroma [399], plus the additional risk of intracorneal haemorrhage [402].

Clinically, the state of corneal oxygenation can be gauged from its inverse relation with contact lens-induced corneal swelling. Hypoxia-induced corneal vascularisation may rarely occur with rigid corneal overnight wear lenses, or with PMMA daily wear. This is attributed to the smaller diameter of hard lenses hence greater exposure of peripheral cornea to oxygen. The risk of corneal vascularisation is increased with overnight wear, compared to daily wear, of conventional hydrogel lenses [99,403]. The same is true with SiHy lenses. Although, on average, the risk of corneal vascularisation has been minimised with greater oxygen availability in SiHy lenses [125,404,405], a cautious approach to identify and monitor high-swellers is still suggested [406–408]. This is to prevent potentially sight-threatening outcomes from silent vessel ingrowth, as well as to lower the risk of possible inflammatory events associated with vascularisation in these patients [409]. This is particularly important in lenses with higher minus power, thicker lens edge profile and especially in SiHy overnight wear [407,408,410].

4.2.2. Hypoxia-related responses: swelling, striae, folds, haze

Hypoxia-induced corneal swelling mainly occurs in the stroma which accounts for around 90% of corneal thickness [411]. The stroma plays an important role in maintaining corneal transparency because of its uniquely organised lamella structure of collagen fibrils [412] with anterior stromal keratocytes contain a crystalline protein to minimise backscattering of the light [413]. Collagen fibrils in the anterior stroma are more tightly packed than the posterior stroma to provide adequate rigidity and strength for maintaining the anterior corneal curvature and shape against the stress from stromal swelling [414].

In open-eye conditions at sea level the bare cornea is exposed to the atmospheric partial oxygen pressure (PO2) of 155 mmHg [415]. The PO2 is reduced to one third or ~55 mmHg that is largely supplied by the palpebral conjunctival blood vessels in closed eye conditions [415]. A contact lens barrier will reduce the available PO2 leading to increased anaerobic metabolism of glucose [416,417] in corneal epithelial cells. Lactic acid, the product of the anaerobic metabolism, diffuses posteriorly into the stroma. The increased osmotic pressure caused by elevated levels of lactic acid production from anaerobic corneal metabolism leads to stromal swelling [418–420]. This is because the hydrophilic components of the stromal ground substance will expand by diffusion of additional water from the anterior chamber, across the leaky corneal endothelium by osmosis [421]. This phenomenon can physiologically occur when eyelids are closed during sleep (overnight corneal swelling) and is in the range of 3–4% of corneal thickening [422–424]. Typically,
the cornea is at its maximum thickness upon waking in the morning and it gradually recovers to its daytime thickness within a few hours after eye opening [422,423,425–429]. A contact lens barrier can also induce corneal swelling. There is a direct linear relationship between corneal hydration and thickness [430, 431]. Therefore, corneal swelling is often used to determine the level of oxygen supply through a contact lens [407, 432].

Assuming an average of 4 % overnight central corneal swelling without lens wear in their original study, a minimum Dk/t criterion of 87 Dk/t units was established to avoid lens-induced overnight corneal swelling in overnight wear [433]. Although a higher lens transmissibility requirement of at least 125 Dk/t units was reported after updating the assumption of no-lens overnight swelling to 3 % [434]. However, based on clinical studies with SiHy lenses, even at higher lens Dk/t levels of 175 [428] and 211 [410] Dk/t units, closed-eye lens-induced corneal swelling could not be eliminated.

It was also suggested that 24 Dk/t units was needed to prevent average central corneal swelling in daily wear [435]. This criterion was re-estimated in a more recent study and determined to be 19.8 and 32.6 Dk/t units, respectively, to avoid average central and peripheral corneal swelling in soft lens daily wear [435]. The results of current short-term studies suggest expecting an average minimal ocular physiological impact in open-eye wear with a minimum central Dk/t ~25 units and peripheral Dk/t of ~11 units [436,437]. It is noteworthy that the suggested minimum Dk/t values for closed or open-eye lens wear can only predict the population average corneal swelling values and are inherently incapable of reflecting individual Dk/t requirements in practice [408].

There is a greater degree of swelling in the posterior cornea [438] compared to its anterior region [439]. Differential corneal swelling is supported by the relevant physiological [440,441], physical [439,442, 443] and ultrastructural [414,444–446] differences between stromal anterior and posterior properties. This is in line with the reported [438] higher water content of the mammalian posterior than anterior stroma [447] attributed to higher ratio [448] of keratan sulphate, a more hydrophilic glycosaminoglycan [449], in the posterior stroma compared to higher ratio of dermatan sulphate, a less hydrophilic glycosaminoglycan in the anterior stroma. In this process, stromal collagen fibrils do not have the capability to absorb water. They are only being more separated because of the expansion of their surrounding ground substance in direct relation to the hypoxia. This can lead to increased light scattering that may affect corneal transparency.

Corneal transparency depends on the precise ultrastructure of the corneal stroma, which remains steady under aerobic conditions [446,450]. In the presence of sufficient oxygen, the corneal stroma can stay at a constant level of 78 % hydration (desaturance), ensuring transparency [451,452]. Stromal light scatter occurs because of increased distances and decreased uniformity of the collagen fibrils in the oedematous stroma [412]. Intense light scattering was reported with slight swelling of the anterior stroma, but relatively slight light scattering has been observed with a higher degree of posterior stromal swelling [442]. The stromal haze may occur as a result of an increased amount of back scattered light from the anterior stroma [453]. Therefore, the haze is more likely to occur with higher levels of corneal swelling (>15 %), for example after closed-eye wear of a low Dk/t lens and/or in high-swellers. However, haze is more commonly seen in corneal pathological conditions (e.g. Fuchs’ dystrophy). Corneal haze can clinically be measured with customised slit-lamp biomicroscopy, confocal microscopy or using a Scheimpflug device [453].

Stromal striae and folds are two important short-term clinical indices of corneal swelling that are more commonly seen with low Dk/t hydrogel lenses and especially after closed-eye lens wear [454,455]. Striae and folds are reported at swelling levels as low as ~4 and ~7 %, respectively [456]. A useful clinical tool for estimating the magnitude of corneal swelling was devised using the correlation between the number of striae or folds to the level of the observed corneal swelling in the study [457]. Striae and folds gradually disappear as a result of stromal deswelling after removal of hypoxic stress. Striae are clinically seen as vertical lines in the posterior stroma because of increased fluid separation of the posterior stromal fibrils due to posterior stromal swelling. Folds are seen in the posterior corneal surface as a result of buckling/flattening of the posterior limiting lamina from further increase in the posterior stromal swelling as the stroma cannot expand laterally. Striae and folds of the swollen posterior stroma are reported to be visible in different angular directions, including horizontally, using confocal microscopy [458]. Results from a clinical study suggested significantly less flattening of the posterior corneal surface with a SiHy lens (lotrafilcon A) compared to a hydrogel lens (etafilcon A) after one week of overnight wear [459]. There was less posterior corneal flattening with the hydrogel lens in their study compared to an initial report from another group who examined 3 h closed-eye wear of a thick hydrogel and a PMMA contact lens, respectively [460]. This is in line with lower levels of corneal swelling in their study because they used lenses of higher Dk/t in overnight wear and examined corneal swelling and posterior curvature later in the day (instead of immediately after eye opening in the initial 3 h closed-eye study). Although a more recent open-eye study [461] measured posterior corneal steepening with a hydrogel toric lens in daily wear this was attributed to the regional pattern of corneal swelling in this study showing higher swelling in the corneal periphery than the centre because of lower oxygen transmissibility in the thicker peripheral stabilization zones of the lens. Stromal striae and folds are less frequently expected with daily wear of hydrogel or with overnight wear of SiHy lenses. However, they can still occur in those with high levels of swelling [408]. Stromal striae were 4 times less frequent with overnight wear of a SiHy lens (balafilcon A) compared to overnight wear of a hydrogel lens (etafilcon A) in a 12-month study [462].

4.2.3. Thinning

Early studies revealed an asymptomatic progressive corneal thinning phenomenon with overnight wear of hydrogel lenses [463,464]. A landmark 5-year study [309] of unilateral soft lens overnight wear showed that, 7 days after the discontinuation of lens wear (recovery period of the chronic swelling), the average stroma was ~11 microns or 2.3 % thinner than the baseline (~2 microns thinning/year). This finding was attributed to the possible effects of the chronic stromal swelling on morphology and/or the function of stromal keratocytes thereby reducing their ability for synthesis of the stromal components and/or to the possible effects of hypoxia-induced acidosis on breaking down the components of the stromal grand substance [309]. However, similar progressive thinning effects were also reported in daily wear of hydrogel and rigid corneal lenses, as well as in overnight wear of SiHy lenses [465,466].

A novel study [467] using confocal microscopy investigated the effect of 6-month overnight wear on the stromal keratocyte density in neophytes where subjects wore a hydrogel lens (etafilcon A) in one eye and a SiHy lens (balafilcon A) in the other eye. They found that the posterior stromal keratocyte density was reduced in both eyes equally, independent of lens oxygen transmissibility [467]. Therefore, they concluded that the reduction of the keratocyte density in overnight wear was not dependent on lens-induced hypoxia and/or swelling [467]. Based on these results they suggested a mechanical aetiology for the loss of keratocytes from the physical presence of the lens on the cornea [467].

Further investigation in this regard, a study [468] found that, in a group of neophyte subjects, keratocyte densities were lower in the SiHy and rigid corneal lens-wearing eyes compared to their contralateral controls, despite similar levels of anoxia-induced corneal swelling for 2 h in the lens-wearing and control eyes. They also found higher levels of tear inflammatory markers after rubbing the no-lens eyes compared to their contralateral controls in the final part of their experiment. These findings led them to hypothesise that “the mechanical stimulation of the corneal surface, due to the physical presence of a contact lens, induces
the release of inflammatory mediators that cause keratocyte dysgenesis or apoptosis” [468].

A 12-month study of 30 days of overnight wear [469] found no significant differences in corneal thickness and in overall stromal keratocyte density among the SiHy group, the rigid corneal group and non-wearers. However, some inflammatory markers in the tear film of the lens-wearing groups were higher than in the control group; specifically, higher concentrations of epidermal growth factor were found in wearers of both SiHy and rigid corneal lens wearers compared to non-wearing controls whereas interleukin-8 was shown to be increased in rigid corneal lens wearers only.

A more recent 6-month daily wear study found a greater decrease in the overall keratocyte density in hydrogel than in rigid corneal lens wearers [470]. Also, the decrease found in each group was higher than their neophyte counterparts. They attributed the higher loss of keratocytes in the hydrogel group to a contribution from higher stromal hypoxic stress in hydrogel compared to rigid corneal lens wear. However, they found no changes in the corneal thickness of the neophyte lens-wearing groups during the 6-month study period.

Current knowledge on the aetiology and mechanisms of the stromal thinning is still inconclusive and requires further research. Contact lens-induced stromal thinning may affect the integrity of the cornea in extreme cases. Also, progressive loss of corneal thickness in long-term contact lens wearers could be a point of concern for suitability for future refractive surgery.

4.3. Endothelium

4.3.1. Polymegethism and pleomorphism

The endothelium is the most posterior layer of the cornea and is formed by a monolayer of differentiated epithelial cells. The primary role of the endothelium is as part of the homeostatic mechanism of maintaining a balanced water content in the corneal stroma, which ensures corneal transparency [205]. Metabolic ion pumps within the cells promote a shift in solute concentration between the corneal stroma and the anterior chamber and water moves along the concentration gradient in response and out of the stroma [471].

At birth, the cells are evenly distributed across the posterior corneal surface and take a polygonal shape that is most efficient in achieving full coverage [205]. This produces a typical hexagonal cell shape, which is found in 70–80 % of cells. Endothelial cell density averages 3100 (2700–3500) cells/mm² in children and reduces with age to approximately 2200 (1000–3000) cells/mm² by the age of 80 years (a reduction rate of c.0.25 % per year) [472–475]. A minimum endothelial cell density of 400–700 cells/mm² is thought to be necessary to maintain adequate endothelial function and corneal transparency, but an endothelial cell density between 1000–2000 cells/mm² is susceptible to corneal decompensation [476]. The gradual reduction in endothelial cell density is due to physiological attrition in the cell numbers and to the absence of cell replication, an effect thought to be due to contact inhibition between the cells [477,478]. This contact inhibition also encourages cells to spread to maintain contact with neighbouring cells, especially following death of a neighbouring cell. It is important to compare any changes observed from contact lens wear with these physiological changes that occur with age.

As the cells decrease in number, the remaining cells spread out to cover the gaps. Polymegethism describes the appearance of the corneal endothelium where the usual consistency of cell size is lost. At the same time, the cells lose their hexagonal regularity. This is called pleomorphism, which describes the increase in cell shape variation [479]. Both phenomena have been shown to increase with age [480].

As a metabolically active cell layer, the endothelium is affected by any reduction in available oxygen supplied through the cornea from the atmosphere [415,481]. This happens physiologically with eye closure during sleep, resulting in a small amount of overnight corneal swelling (oedema) due to the impaired oxygen supply to the endothelium [429]. The swelling rapidly decreases upon eye opening. In contact lens wear, this physiological effect can be artificially-induced with both rigid corneal and soft contact lenses of low Dk/t, producing central corneal oedema [482–485]. The low Dk/t also creates hypoxic stress to the endothelial cells, promoting increased cell death as a result of the chronic reduction in oxygen supply to the endothelium, in combination with the effect of contact lens-induced pH changes [486]. The cell death leads to a reduced endothelial cell density and increased polymegethism and pleomorphism [487,488]. An increased effect is observed with increasing lens wear experience [489]; a short lens wear experience does not produce a significant effect.

With modern lens materials of higher Dk/t, these effects are no longer a common feature of contact lens wear [490–493]. However, when low Dk/t lenses must be used, careful monitoring of the corneal endothelium should be made.

4.3.2. Bedewing

Clusters of oedematous droplets or leucocytes deposited on the surface of the corneal endothelium were first reported in chronically intolerant PMMA contact lens wearers in 1979 [494]. They proposed that the droplets were composed of inflammatory cells whose release was stimulated by hypoxic stress caused by over-wear of low Dk/t lenses. The ‘precipitates’ were observed on the endothelium in the area of the inferior pupil margin at high magnification and the phenomenon was termed ‘endothelial bedewing’. The authors noted that management with low Dk/t soft lenses had mixed results. However, endothelial bedewing has been reported in 20 % of 70 non-contact lens wearers, which supports much earlier work that bedewing is a physiological feature [495]. The authors argued that the need to use slit-lamp marginal retro-illumination to view the bedewing (indicating that the droplets had a higher refractive index than the surrounding aqueous humour) supported the theory that the droplets contained inflammatory cells.

Bedewing is certainly a physiological phenomenon in a non-lens wearing eye and may be associated with hypoxic stress in low Dk/t lens wear. The main associated symptom is fogging of vision, which may be sufficient to reduce lens wear time or cease lens wear. Best treatment when observed in low Dk/t lens wearers is to re-fit with a high Dk/t contact lens material to avoid hypoxic stress, should that be the causative factor. However, even so, symptoms and endothelial bedewing may continue.

The presence of inflammatory cells in the anterior chamber is always a sign of possible inflammation, which may be of much more severe aetiology and consequence. Contact lens ECPs should take care to investigate and exclude other causes for the presence of inflammatory cells [496].

4.3.3. Blebs

The term endothelial blebs is used to describe apparent holes observed in the regular mosaic of the corneal endothelium. They were first described in 1977 [497] and further explained by the confocal microscopy work of Efron. The authors proposed that the apparent absence of endothelial cells was due to oedematous swelling of the cell causing light, reflected from the ‘bulging’ posterior surface of the affected endothelial cell, to be directed along a divergent path and away from the axis of observation [498]. They can occur on any area of the cornea covered by the contact lens [499].

Blebs are visible within minutes of contact lens application, with their numbers peaking after 30 min and diminishing over the following hours [487,497,500,501]. The phenomenon has been linked to localised areas of endothelial swelling from acidosis caused by hypercapnia (increased carbon dioxide) and hypoxia (reduced oxygen supply), resulting from altered gas diffusion through the cornea [502]. This impaired diffusion is particularly a feature of low Dk/t contact lens wear [500,501] and can be provoked by exposing the corneal surface to a reduced O₂ partial pressure to simulate hypercapnia or anoxia [502].
Scleral lens wearers fitted with a large post-lens tear reservoir (400 μm vs 200 μm) also develop blebs, due to hypoxia at the corneal surface [503]. Even with moderate to high Dk/t SiHy lenses, endothelial blebs can form after one hour of eye closure [504]. In a closed eye situation, the bleb response has been reported as being greater in Asian vs. non-Asian eyes when wearing a low Dk/t soft contact lens [505].

Endothelial blebs should not be confused with endothelial guttae, which are generally larger, are found at the central cornea and can be associated with corneal disease, such as Fuchs’ dystrophy [478,506, 507]. Nor should they be confused with Hassall-Henle Bodies, which, although benign, are found in the corneal periphery and are associated with aging [205,507].

Endothelial bleb formation may be occurring more frequently than expected, particularly in new contact lens wearers. Experienced lens wearers do not show the same incidence level, but with additional interference in oxygen supply, perhaps with prolonged eyelid closure, bleb formation may be promoted. However, there is no known clinical significance and no lasting negative consequence to corneal health [508]. The best clinical treatment is to use higher Dk/t materials and to encourage lens wearers to avoid sleeping in their lenses.

4.4. Intentional changes to corneal thickness with orthokeratology

In modern ortho-k, rigid contact lenses are fitted to deliberately alter corneal curvature by a targeted amount during sleep to correct ametropia on lens removal. The anterior corneal surface flattens in response to wear of ortho-k lenses designed to correct hyperopia [512,513]. While small change to posterior corneal curvature [514] and asphericity [515] have been reported over the short term in response to ortho-k for correcting myopia, over the longer term posterior corneal curvature has been shown to remain unchanged [516,517]. Instead the corneal thickness profile alters to compensate the change to anterior corneal curvature, with the central cornea thinning and paracentral cornea thickening in myopic ortho-k and the opposite profile of central thickening and paracentral thinning in hyperopic ortho-k [518].

The changes to corneal thickness profile from myopic ortho-k, when applied to Munnerlyn’s formula [519] used to calculate ablation depth in laser refractive surgery, accounts for the degree of refractive change that is achieved [510,520] and closely to that reported for hyperopic ortho-k [518]. This affirms evidence that ortho-k lens wear only influences anterior corneal curvature rather than bending the overall cornea.

Using the optical pachometer, one study [521] reported an increase to central stromal thickness immediately after lens removal following overnight wear of both standard rigid corneal lenses and ortho-k, consistent with that expected from closed eye wear contact lens induced hypoxia [433]. Less central thickening was reported in the ortho-k lens compared to standard rigid corneal lenses wearing eyes, however, leading the authors to suggest that myopic ortho-k suppresses the central corneal oedema response from overnight rigid corneal lens wear. Once overnight oedema has subsided there is general agreement that the central corneal thinning response from myopic ortho-k is predominantly due to thinning of the central corneal epithelium [520,522, 523], however there is disagreement on which structure influences the reported paracentral thickening from myopic ortho-k lens wear, possibly due to limitations of the instrument being used. Whilst one study [520] reported paracentral stromal thickening alone using an optical pachometer, another report [522] instead paracentral epithelial thickening using time-domain optical coherence tomography. Another study [523] reported thickening of both the paracentral stroma and epithelium using spectral-domain optical coherence tomography. Central and paracentral corneal thickness returns to baseline values within 3 days of discontinuing myopic ortho-k lens wear [522].

Only short-term changes to corneal thickness have been reported for hyperopic ortho-k. One study [524] reported increased thickening measured by time-domain optical coherence tomography of both the central and paracentral epithelium after a single night of hyperopic ortho-k lens wear, with greater central thickening with higher targeted refractive change (+3.50D vs +1.50D). Instead, another study [518] used optical pachymetry after 1 and 4 nights of ortho-k lens wear to reveal central and paracentral stromal thickening consistent with the expected overnight wear oedema response. However, when measures were repeated 8 h later to allow overnight oedema to subside, only paracentral epithelial thickening was observed, leading the authors to conclude that the anterior corneal steepening profile induced by hyperopic ortho-k was limited to change to the paracentral corneal epithelium thickness alone. While it is not known whether changes to corneal thickness induced by longer term wear of hyperopic ortho-k will return to baseline after cessation of lens wear, it is reasonable to expect that this would occur as in myopic ortho-k [522], given that it is only alterations in posterior ortho-k lens curvature that differentiate the two approaches and that corneal topography changes induced by 7 nights of overnight hyperopic ortho-k lens wear in presbyopic lenses return to baseline within 1 week of cessation [525].

5. Ocular growth modification with contact lenses

5.1. Changes to axial length

Contact lens wear can have a marked impact on the axial growth of the eye and there is increasing interest in slowing ocular growth in children with contact lenses [526]. This is because there is mounting evidence for the increasing frequency of myopia in many populations around the world and across ethnicities. By 2050, it is predicted that almost half of the world’s population - five billion people - will be myopic, with nearly one billion high myopes at serious risk of myopia-related ocular pathology [527]. While high myopia is strongly linked to higher risk of cataract, retinal detachment and myopic maculopathy, even lower levels of myopia are associated with increased life-long risk of pathology compared to emmetropia [528]. Already, increasing rates of vision impairment and blindness in the working age population, due to myopic maculopathy, are evident in Asian countries [529,530].

With recent understanding that even reducing final myopia by 1D over a lifetime reduces risk of myopic maculopathy by 40 % [531], there is much scientific interest in slowing the progression of myopia in children. Recently analyses have indicated that axial length bears a strong relationship to risk of life-long vision impairment, with an axial length of greater than 26 mm associated with a likely risk of vision impairment across a lifetime of at least 25 % and over 90 % for eyes longer than 30 mm [532]. Axial length is consistently correlated with myopic refraction, although the refraction-to-axial-length ratio isn’t consistent across age groups or with increasing axial length [533]. Despite this, due to the repeatability and incremental measurement possible with axial length compared to myopic refraction, the former has become the gold standard in assessing treatment efficacy for myopia control in scientific studies [534]. Contact lens influence on axial length is therefore the focus in this review.

Myopia control is the terminology for any intervention which reduces the axial and refractive progression of childhood myopia, by whatever mechanism and level of efficacy compared to a control [534]. Optical interventions for myopia control include both rigid corneal and soft contact lens modalities. The appeal of an optical intervention is its ability to both correct myopic ametropia as well as potentially slow its progression as a monotherapy and thus far contact lens interventions have performed with more consistent and statistically significant efficacy than spectacle lens interventions [535].

5.2. Single-vision contact lenses and myopia control

Studies investigating the effects of single-vision, full correction rigid
corneal lenses and soft contact lenses on the progression of myopia have demonstrated no statistically significant efficacy [536-539]. In determining this lack of effect, rigid corneal lenses and soft contact lenses have been compared to each other and to single-vision spectacle corrections.

Standard-design rigid corneal lenses were first purported to slow myopia progression in the mid-1970’s [540] with subsequent studies in the last 20 years both supporting [541] and refuting [537] this presumption. These studies suffered methodological limitations, most notably very high drop-out rates of almost 50 %. Managing this with a run-in adaptation period to rigid corneal lenses, the axial and refractive myopia progression in 116 single-vision distance-corrected children, aged 8–11 years, randomised to wear either rigid corneal lenses or soft contact lenses was compared. Over the three year study, the rigid corneal lens wearers’ myopia progressed by around 0.50D less, but the soft contact lens wearers showed steepening of the steep corneal meridian by 0.88 ± 0.57D compared to 0.62 ± 0.60D in the rigid corneal lens wearers. With this different corneal steepening accounting for about half of the refractive effect and no statistically significant difference in axial elongation, both single-vision contact lens correction types were indicated as similar from a myopia control perspective [538].

A comparison of single vision distance soft contact lenses with spectacles for their differential myopia control effect, in 484 children aged 8–11 years, debunked the concern of ‘myopic creep’ (increasing myopia) in soft contact lens wearers. Three years of full-time childhood wear revealed no difference in either axial or refractive myopia progression between the groups. There was no measured change in steep corneal meridian over time or difference between groups [539].

Subsequent contact lens myopia control studies have typically employed single-vision distance soft contact lenses or spectacles as the control group. Only one ortho-k study has utilised a daily wear rigid corneal lens control, in a crossover design [542]. It is now readily accepted by both scientific and clinical consensus that single-vision distance corrections, of any form, do not reduce axial or refractive myopia progression in children [543,544].

5.3. Impact of rigid corneal lenses on axial length and ocular growth in myopia control

The evidence for overnight ortho-k rigid corneal lens wear to reduce the excessive axial elongation seen in childhood myopia is relatively new. Reports from 2005 [545] and 2009 [546] reported 47 % and 55 % less axial elongation over 2 years of wear when compared to historical controls. Several other two-year controlled trials have taken place since, the results of which are summarised in Table 3. A novel cross-over study design involving a daily wear, alignment fit rigid corneal lenses worn in one eye and overnight ortho-k worn on the contralateral eye demonstrated a complete halt in myopic progression in the ortho-k treated eye for both six-month phases [542]. Two meta-analyses of ortho-k studies concurred in examining seven controlled trials over two years duration, concluding that ortho-k reduced axial elongation by 0.27 mm over two years (95 % CI 0.22 to 0.32 mm) [547,548].

The longest ortho-k intervention data reported is a retrospective study of 203 eyes from 66 ortho-k wearers and 36 spectacle wearing controls aged 7–17 years at baseline and with a mean follow up time of 6.32 ± 0.15 years. Across the first two years, the ortho-k group progressed 0.17 ± 0.02D while the control group progressed 0.52 ± 0.03D. This statistically significant difference was maintained from year-2-to-4 and year-4-to-6 of follow up, albeit reducing from a 0.35D difference in the first two years to a 0.19D difference in year-4-to-6. From year-6-to-8 of follow up, there was no statistically significant difference between groups [549].

5.3.1. Orthokeratology influence on ocular component growth other than axial length

Vitreous chamber depth changes in step with axial length changes in ortho-k intervention studies, with a similar significant reduction in growth compared to historical controls [545,546]. Very similar vitreous chamber depth and axial length changes were also found in another study, however no comment was made on the contribution of vitreous chamber depth to axial length changes [545]. Vitreous chamber depth changes accounted for around 60 % of axial length changes and by eliminating the effects of change in anterior chamber depth through vitreous chamber depth quantification, this confirmed the slowing of eye growth with ortho-k wear [546]. The latter authors measured additional ocular component changes in their study, finding that change in anterior chamber depth over time was not statistically significant in ortho-k wearers, but a small increase of 0.06 mm per year in soft contact lens wearers was noted. Crystalline lens thickness changes were not different between the groups [546]. Ortho-k can also impact corneal nerves as detailed above in Section 4.1.6.

The sum of the available literature indicates that ortho-k consistently reduces myopia progression by around 45 % compared to single vision spectacle and contact lens corrections over several two-year studies, with a statistically significant myopia control effect likely maintained over several years of wear.

5.4. Impact of soft contact lenses on axial length and ocular growth in myopia control

While ortho-k rigid corneal lenses currently enjoy the largest scientific volume of evidence for myopia control efficacy [547,548], the

Table 3

Summary of results for key myopia control intervention studies evaluating ortho-k. Adjusted means are presented with (standard deviations) as detailed in each paper. N = total participants at final analysis visit; Ortho-k = orthokeratology; SV = single vision; SCI = soft contact lens. Studies 1 and 2 measured axial length using A-scan ultrasound; studies 3-7 employed interferometry measurement (IOL Master in all cases).

<table>
<thead>
<tr>
<th>Intervention study</th>
<th>Control intervention</th>
<th>N (total)</th>
<th>Duration (years)</th>
<th>Axial length change (mm)</th>
<th>Efficacy for reducing axial elongation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho et al. 2005 [545]</td>
<td>SV spectacles (historical)</td>
<td>70</td>
<td>2</td>
<td>0.29 (0.27)</td>
<td>0.13 (46)</td>
</tr>
<tr>
<td>Walline et al. 2009 [546]</td>
<td>SV SCLs (historical)</td>
<td>56</td>
<td>2</td>
<td>0.25 (0.19)</td>
<td>0.16 (56)</td>
</tr>
<tr>
<td>Kakita et al. 2011 [550]</td>
<td>SV spectacles</td>
<td>92</td>
<td>2</td>
<td>0.39 (0.27)</td>
<td>0.11 (36)</td>
</tr>
<tr>
<td>Cho &amp; Cheung 2012 [551]</td>
<td>SV spectacles</td>
<td>78</td>
<td>2</td>
<td>0.36 (0.24)</td>
<td>0.14 (43)</td>
</tr>
<tr>
<td>Santodomingo 2012 [552]</td>
<td>SV spectacles</td>
<td>53</td>
<td>2</td>
<td>0.47 (0.23)</td>
<td>0.11 (32)</td>
</tr>
<tr>
<td>Charm 2013 [553]</td>
<td>SV spectacles</td>
<td>28</td>
<td>2</td>
<td>0.19 (0.21)</td>
<td>0.51 (32)</td>
</tr>
<tr>
<td>Chen 2013 [554]</td>
<td>SV spectacles</td>
<td>58</td>
<td>2</td>
<td>0.31 (0.27)</td>
<td>0.64 (31)</td>
</tr>
<tr>
<td><strong>META-ANALYSES</strong></td>
<td><strong>Absolute difference in progression between treatment and control groups (mm)</strong></td>
<td></td>
<td></td>
<td>0.27 (95 % CI 0.22, 0.32)</td>
<td>0.14 (45)</td>
</tr>
<tr>
<td>Sun et al. 2015 [547]</td>
<td>7 studies</td>
<td>2</td>
<td></td>
<td>0.26 (95 % CI 0.21, 0.31)</td>
<td>0.13 (45)</td>
</tr>
<tr>
<td>Si et al. 2015 [546]</td>
<td>7 studies</td>
<td>2</td>
<td></td>
<td>0.26 (95 % CI 0.21, 0.31)</td>
<td>0.13 (45)</td>
</tr>
</tbody>
</table>
largest volume of recent innovations in contact lens myopia control are in various designs of soft multifocal designs. The terminology ‘multifocal’ is here used to denote any ‘simultaneous image’ optical design where dioptric power varies either smoothly or discontinuously with zonal radius [555].

Studies investigating bifocal and multifocal spectacles for myopia control in children showed limited success in the late 20th and early 21st century [535]. The first publications investigating multifocal soft contact lenses for myopia control employed designs originally designed for presbyopia. An abstract [556] and a twin study case report [557] investigated a commercially available multi-zone simultaneous vision design, being distance centred with alternating near and distance zones. The results indicated a halting of myopia progression in the twin case report and a reduction of progression by around 2/3rds in the abstract of a one-year randomised clinical trial. Another commercially-available, distance-centred, continuous aspheric design was demonstrated to reduce refractive progression by 50 % and axial elongation by 29 % compared to single vision soft contact lenses in a two year study [558]. A prospective, randomized controlled trial on this same lens design revealed a 36 % reduction of axial elongation in wear of a +2.50 Add, with no significant effect of the +1.50 Add, both in comparison to a single vision soft contact lens control [559].

Clinical trial results for the two first myopia-control specific designed soft contact lenses were reported in 2011. The first, a dual-focus alternating design, showed promise in a cross-over trial of two 10-month phases in 2011 [560]. The second [561] is reported in Table 4, along with several more controlled trials of at least one-year duration which quantified axial length. Most of these studies employed novel multifocal soft contact lenses designs rather than commercially-available presbyopic designs.

5.5. Potential mechanisms of contact lens myopia control

The mechanism of how ortho-k reduces the rate of axial elongation in childhood progressive myopia is not known. The main theory involves peripheral retinal input, involving differential optical stimulus between localised peripheral and central retinal signals creating a ‘slow down’ signal for retinal growth, as has been shown in numerous animal models. However there is conjecture that shifts in relative peripheral refraction correlate with myopia progression in humans [570,571]. Ortho-k and multifocal soft contact lenses both shift relative peripheral refraction towards more myopia – although not equivalently [572] – and both show statistically significant myopia control efficacy. It has also been demonstrated that when viewing a near target in multifocal soft contact lenses wear and foveal hyperopic defocus is experienced, peripheral defocus instead tended towards emmetropia [573].

Similarly, on-axis simultaneous defocus occurs through the depth of focus created by ortho-k or multifocal soft contact lenses, due to pronounced shifts in spherical aberration [574,575]. Changing spherical aberration in turn changes accommodative demand at near [576,577] and a single study for each of ortho-k [578] and multifocal soft contact lenses [579] have indicated a relationship between improved accommodative response and a better myopia control effect in myopia control contact lens wear.

Future research in myopia controlling contact lenses will likely further explore these mechanisms and their specific influence in individual myopes, ideally leading to improved efficacy across all wearers.

Table 4

<table>
<thead>
<tr>
<th>Intervention study</th>
<th>Control intervention</th>
<th>N (total)</th>
<th>Duration (years)</th>
<th>Axial length change (mm)</th>
<th>Efficacy for reducing axial elongation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Sankaridurg et al. 2011 [561]</td>
<td>SV spectacles (non-concurrent)</td>
<td>82</td>
<td>1</td>
<td>0.24 (0.17)</td>
<td>0.39 (0.19)</td>
</tr>
<tr>
<td>2 Walline et al. 2013 [558]</td>
<td>SV SCLs (historical)</td>
<td>54</td>
<td>2</td>
<td>0.29 (0.03)</td>
<td>0.41 (0.03)</td>
</tr>
<tr>
<td>3 Lam et al. 2014 [562]</td>
<td>SV SCLs</td>
<td>128</td>
<td>2</td>
<td>0.25 (0.23)</td>
<td>0.37 (0.24)</td>
</tr>
<tr>
<td>4 Fujikado et al. 2014 [563]</td>
<td>SV SCLs</td>
<td>24</td>
<td>1</td>
<td>0.09 (0.08)</td>
<td>0.17 (0.08)</td>
</tr>
<tr>
<td>5 Paune et al. 2015 [564]</td>
<td>SV spectacles</td>
<td>40</td>
<td>2</td>
<td>0.38 (0.21)</td>
<td>0.52 (0.22)</td>
</tr>
<tr>
<td>6 Aller et al. 2016 [565]</td>
<td>SV SCLs</td>
<td>78</td>
<td>1</td>
<td>0.05 (0.14)</td>
<td>0.24 (0.17)</td>
</tr>
<tr>
<td>7 Cheng et al. 2016 [566]</td>
<td>SV SCLs</td>
<td>106</td>
<td>1</td>
<td>0.23 (0.15)</td>
<td>0.37 (0.16)</td>
</tr>
<tr>
<td>8 Chamberlain et al. 2019 [567]</td>
<td>SV SCLs</td>
<td>109</td>
<td>3</td>
<td>0.30 (0.27)</td>
<td>0.62 (0.30)</td>
</tr>
<tr>
<td>9 Sankaridurg et al. 2019 [568] (# designs tested)</td>
<td>SV SCLs</td>
<td>234</td>
<td>2</td>
<td>0.41 to 0.46 (across 4 designs)</td>
<td>0.58 (0.27)</td>
</tr>
<tr>
<td>10 Walline et al. 2020 [559] (results given for high add power MFCL + 2.50)</td>
<td>SV SCLs</td>
<td>292</td>
<td>3</td>
<td>0.42 (95 CI 0.38, 0.47)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

META-ANALYSIS (does not include 2019 & 2020 papers)

Li et al. 2017 [569] studies

<table>
<thead>
<tr>
<th>N (total)</th>
<th>Duration (years)</th>
<th>Axial elongation (mm)</th>
<th>Efficacy for reducing axial elongation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>1</td>
<td>0.27 (95 CI 0.22, 0.32)</td>
<td>0.135</td>
</tr>
</tbody>
</table>

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levels of attention and, given their possible relationship with contact medical usage. The third area is the growing level of interest and lenses beyond the more traditional refractive correction and more niche mensions as seen in ortho-k and myopia control. These forms of changes to ocular surface sensitivity which have received increasing ocular surface. Emerging from this small group are LWE, interactions understanding of the mechanical interaction between contact lens and certainly a potentially important observation and may help further un is likely to be a requirement for ECPs into the foreseeable future.

Some changes of the eye to contact lens wear have remained stubbornly intransigent to improvements in both lens materials and designs. Bulbar conjunctival hyperaemia and cellular changes at the ocular sur face visualised by the use of sodium fluorescein and lissamine green are sensitive and somewhat non-specific indicators of the physiological impact of lens wear. Monitoring such changes during contact lens wear is likely to be a requirement for ECPs into the foreseeable future.

A number of identified changes have received relatively little attention in recent times and their significance and/or clinical management is not well understood. These include blinking (which has received very limited attention in the literature) and LIPCOF which is certainly a potentially important observation and may help further un understanding of the mechanical interaction between contact lens and ocular surface. Emerging from this small group are LWE, interactions between lenses and the Meibomian glands, and contact lens-induced changes to ocular surface sensitivity which have received increasing levels of attention and, given their possible relationship with contact lens discomfort, seem likely to be areas of strong research interest in the coming years.

This report has highlighted three particular areas of interest which may transform the contact lens field in future years, in rather different ways. The first two relate to the programmed alteration of ocular di mensions as seen in ortho-k and myopia control. These forms of refractive manipulation provide distinct reasons for the use of contact lenses beyond the more traditional refractive correction and more niche medical usage. The third area is the growing level of interest and expertise in the assessment of the sub-clinical inflammatory response to contact lens wear. Insights provided by techniques such as in vivo confocal microscopy have been able to demonstrate features of the immunological response to contact lens wear and these is reason to believe that such research may be key to revealing the mechanisms behind various physiological responses, adverse events and that cause of many drop-outs: contact lens discomfort.

Acknowledgement

The CLEAR initiative was facilitated by the BCLA, with financial support by way of Educational Grants for collaboration, publication and dissemination provided by Alcon and CooperVision.

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