

# The effect of long-term wear of soft lenses of low and high oxygen transmissibility on the corneal epithelium

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## Abstract

**Purpose** To measure the effects of long-term wear of soft lenses of low and high oxygen transmissibility (Dk) on basal epithelial appearance and epithelial thickness.

**Methods** Sixty-three subjects were enrolled in a cross-sectional study. Seventeen high Dk lens wearers and 24 low Dk lens wearers who had worn lenses on an extended wear basis for more than 3 years (range: 3–22) were compared to a group of 22 age-matched subjects who had never worn contact lenses. Cell regularity and the intensity of light backscattered by the basal epithelium were assessed using confocal microscopy. Epithelial thickness was measured at the centre and at four peripheral locations using modified optical pachometry.

**Results** Epithelial basal cells appeared less regular in low Dk lens wearers than high Dk wearers or controls (Mann–Whitney *U*-test,  $P = 0.001$ ). The intensity of backscattered light did not differ across groups (Kruskal–Wallis test,  $P = 0.37$ ). Low Dk wearers had the thinnest epithelium (46 (10)  $\mu\text{m}$ ), followed by high Dk wearers (54 (14)  $\mu\text{m}$ ) and controls (58 (9)  $\mu\text{m}$ ; ANOVA,  $P \leq 0.006$ ). Topographical position did not affect epithelial thickness (ANOVA,  $P = 0.10$ ).

**Conclusions** Visible alterations to the basal epithelial cells can only be detected in long-term extended wearers of low Dk soft lenses. Extended wear of high Dk soft lenses results in topographically uniform epithelial thinning that is significantly less than the thinning seen with low Dk lenses. Confirmation of these findings using groups with evenly matched duration of lens wear is required.

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**Keywords:** epithelial thickness; basal epithelium; contact lens wear; hypoxia; *in vivo* confocal microscopy

## Introduction

The corneal epithelium is one of the major components of the ocular defense system against infections. Maintenance of good epithelial health is therefore of great significance. Soft lenses alter the epithelium in a myriad of ways. These include central<sup>1–5</sup> and peripheral<sup>3,6</sup> epithelial thinning, basal cell fragility,<sup>7</sup> reduced surface cell shedding,<sup>1,2,8</sup> and cell death,<sup>1,9,10</sup> reduced mitosis,<sup>11</sup> a lower number of epithelial cell layers,<sup>4,7</sup> and reduced oxygen uptake.<sup>5</sup> Increases in surface cell size,<sup>1,2,8,12–15</sup> bacterial adhesion,<sup>1,2,8</sup> epithelial permeability,<sup>16</sup> and the number of microcysts<sup>5,17</sup> have also been observed. Although alterations to the corneal epithelium in the short term have been well described, the appearance of the epithelium after long-term lens wear is often poorly characterized, particularly in the case of lens materials and modalities of wear introduced to the market in more recent years.

Because of difficulties in obtaining good resolution *in vivo*, knowledge of the impact of soft lens wear on the deeper epithelium at the cellular level has until now been mostly limited to *in vitro* experiments.<sup>4,7</sup> The technique of confocal microscopy<sup>18</sup> allows for observations of the basal epithelium *in vivo*.<sup>19</sup> Therefore, the purpose of this study was to measure the effect of long-term wear of soft lenses on the corneal

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epithelium, most particularly on the *in vivo* basal epithelial appearance.

## Materials and methods

### Subjects and study conduct

A prospective cross-sectional study was designed. All active patient files from the research clinic were examined to locate subjects who had worn either low oxygen transmissibility (Dk) hydrogel or high Dk silicone hydrogel lenses on an extended wear basis continuously for a minimum of 3 years. Subjects were excluded if they had worn both hydrogel and silicone hydrogel lenses or if they had previously worn any other lens types, such as PMMA or RGP lenses. Forty-one subjects (24 low Dk and 17 high Dk) met this inclusion criterion and agreed to participate. Eight low Dk subjects reported mixed soft lens wear experience. For those subjects, previous low Dk daily wear was considered equivalent to half a year of extended wear. On the basis of this, total wear experience for the low Dk group was 14 (4) years (range: 8–22). Four low Dk subjects wore lenses on a 13 nights/week extended wear schedule with fortnightly replacements. The remainder wore lenses on a six nights/week extended wear schedule with weekly replacements. Nineteen subjects wore an etafilcon A lens (Vistakon, Jacksonville, FL, USA) and five wore a polymacon lens (Bausch & Lomb, Rochester, NY, USA) in the measured eye. The 17 subjects in the high Dk silicone hydrogel group had worn lenses for a mean of 5 (1) years (range: 3–6). None had prior experience with low Dk hydrogels or any other type of lens wear. As such, length of wear experience was significantly less for high Dk than low Dk wearers (*t*-test,  $P < 0.001$ ). All high Dk subjects wore lenses on a 29–30 nights per month extended wear basis with monthly replacement. One subject wore a balafilcon A lens (Bausch & Lomb, Rochester, NY, USA) and 16 subjects wore a lotrafilcon A lens (CIBA Vision, Atlanta, GA, USA) in the measured eye. Lens power worn for the low Dk group averaged  $-3.73$  D (1.37; range:  $-1.25$  to  $-6.50$  D) and was significantly higher than the average of  $-1.84$  D (0.82; range:  $-1.00$  to  $-3.50$  D) in the high Dk group (Wilcoxon rank-sum test,  $P < 0.001$ ). The oxygen transmissibility of the lens worn by each subject was estimated by measuring the centre thickness of a sample of 4–6 lenses using a micrometre gauge. The mean age of low and high Dk wearers was 40 (7) and 35 (8) years old, respectively.

Lens wearing groups were compared to a control group of 22 subjects (age 37 (7) years) who had never regularly worn contact lenses. Control subjects for whom a complete data set was available were retrospectively selected from the research clinic database. Individual

matching was not performed. The male-to-female ratio was 11:13 for the low Dk group, 9:8 for the high Dk group, and 10:12 for the controls. There were no significant differences between the three groups in age (one-way ANOVA,  $P = 0.06$ ) or gender distribution (Pearson's  $\chi^2$ -test,  $P = 0.88$ ).

All subjects were free of apparent ocular pathology. Subjects were examined at least 4 h after waking to account for any possible diurnal variation in measurements. Measurements were performed at the end of their routine contact lens examination, within 2 h of lens removal.

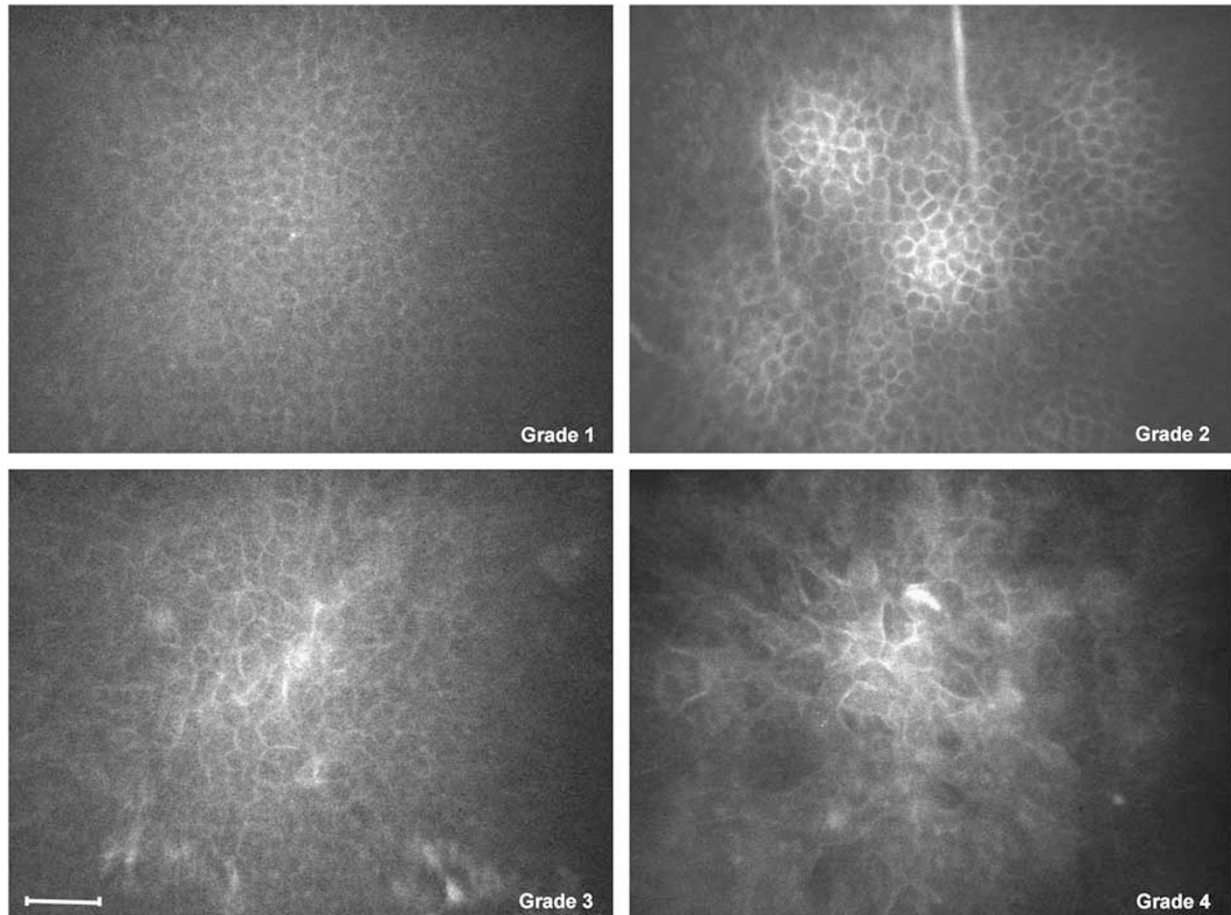
### Study procedures

A single trained examiner (IJ) performed measurements in one randomly selected eye.

The cornea was imaged using a slit-scanning *in vivo* confocal microscope (Confoscan 2, Fortune Technologies, Virgona, Italy) with constant light sources and camera settings, which remained unchanged throughout the study. Care was taken to ensure that possible sources of variations in the backscattered light intensity measurements were controlled. The objective lens was disinfected and cleaned with 70% isopropyl alcohol and fresh cool (4 °C) coupling gel reapplied between each individual scan. Because subjects from various groups were examined randomly, it was assumed that unavoidable variations in the light source intensity and camera sensitivity over time would be spread across groups and that any changes observed could be safely attributed to real differences between groups.

Used with a 40 times objective, the confocal microscope captures digital images of an area measuring approximately  $340 \times 255 \mu\text{m}$ . Depending on scan quality, one to three images of the basal epithelial cell layer of each subject were available for measurement. A single masked observer (IJ) assessed cell regularity based on the 1–4 grading scale (0.5 steps) displayed in Figure 1. On the basis of the minimum available sample size of 15 subjects per group, a clinically relevant effect size of 1 grade, a standard deviation of cell regularity measurements of 0.5, and an assumption that the grading scale follows a normal distribution, the power to detect differences with a 98% confidence level (adjusted for multiple comparisons) is 72%. The backscattered light intensity (0–255 greyscale) of each image measured by the confocal microscope was also noted. Based on the minimum available sample size of 15 subjects per group, a clinically relevant effect size of a 10-greyscale unit and a standard deviation of greyscale measurements of 10 U, the power to detect differences with a 98% confidence level (adjusted for multiple comparisons) is 61%.

Modified optical pachometry<sup>20</sup> was used to measure epithelial thickness. Although a subject's group assignment was unmasked, the examiner remained



**Figure 1** Scale (grades 1–4) for basal epithelial cell regularity. Bar represents 100  $\mu\text{m}$ .

masked to pachometry results throughout the procedure. One central and four peripheral (nasal, temporal, superior, and inferior) measurements were made using a series of fixation light-emitting diodes. As the same fixation targets were used for both eyes, distances from the centre of the cornea differed slightly between the right and left eye. Expressed as the distance from the visual axis, these were located 3.7 mm nasal, 4.3 mm temporal, 3.6 mm superior, and 3.6 mm inferior for the right eye, and 4.0 mm (2.9 mm for four subjects) nasal, 3.5 mm (4.1 mm for four subjects) temporal, 3.6 mm superior, and 3.6 mm inferior for the left eye. Five consecutive measurements were averaged for each position with the exception of the central cornea where five measurements each taken from three separate locations (right eye 0.0 mm, 0.7 mm nasal and temporal; left eye 0.1 mm and 0.7 mm temporal and 0.6 mm nasal) were averaged.

#### Statistical analyses

A Kruskal–Wallis test was used to determine differences in basal epithelial cell regularity and backscattered light

intensity and when appropriate, a Mann–Whitney *U*-test used to determine where any significant differences lay. For analysis of epithelial thickness, a two-way mixed design ANOVA was conducted with group assignment and topographical position as factors. The assumptions of normality and equality of variances were verified before analysis. Missing data were substituted using the expectation–maximisation approach. *Post hoc* analysis was carried out using a Bonferroni correction. Standard multiple linear regression analysis was performed to determine whether lens oxygen transmissibility and length of wear experience contributed to the epithelial thinning.

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

#### Results

Analysis of the regularity of basal epithelial cells (Figure 2) revealed significant differences between groups (Kruskal–Wallis test,  $P = 0.01$ ).

Low Dk wear was associated with a decrease in cell regularity compared to high Dk wear and controls (Mann–Whitney *U*-test,  $P=0.01$ ). The high Dk lens wearing did not affect basal epithelial cell regularity (Mann–Whitney *U*-test,  $P=0.82$ ). Highly irregular basal epithelium (ie, grade 3.5 or 4.0) was not observed in any of the two groups of normal lens wearers or in the non-lens wearing controls. Interestingly, none of the high Dk wearers or controls was rated higher than 2.0, whereas 45% of low Dk wearers were rated 2.5 and above.

The intensity of backscattered light (median (interquartile range)) did not differ across groups (Kruskal–Wallis test,  $P=0.37$ ) and was 38.7 (23.5–53.9) greyscale in low Dk wearers, 39.8 (27.3–52.3) greyscale in high Dk wearers and 38.3 (33.0–43.6) greyscale in non-lens wearers.

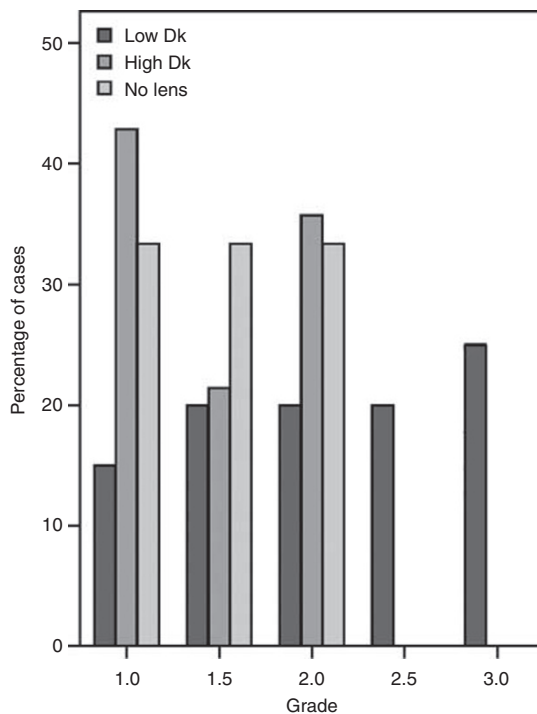
The thickness profiles of long-term lens wearers and controls are displayed in Figure 3. ANOVA analysis revealed significant differences between groups ( $P<0.001$ ). The epithelium of low Dk extended wearers was thinner than both high Dk wearers ( $P<0.001$ ) and controls ( $P<0.01$ ). Wearers of high Dk lenses also had thinner epithelium than controls ( $P=0.006$ ). Topographical position, however, did not have a

significant effect, indicating that the epithelium is roughly uniform in the central 8 mm of the cornea ( $P=0.10$ , power = 62%). An interaction between wear group and topographical position could not be detected with the current sample size ( $P=0.99$ , power = 10%). Compared to controls (58 (9)  $\mu\text{m}$ ), the central epithelium was 7% thinner in high Dk wearers (54 (14)  $\mu\text{m}$ ) and was 21% thinner in low Dk wearers (46 (10)  $\mu\text{m}$ ).

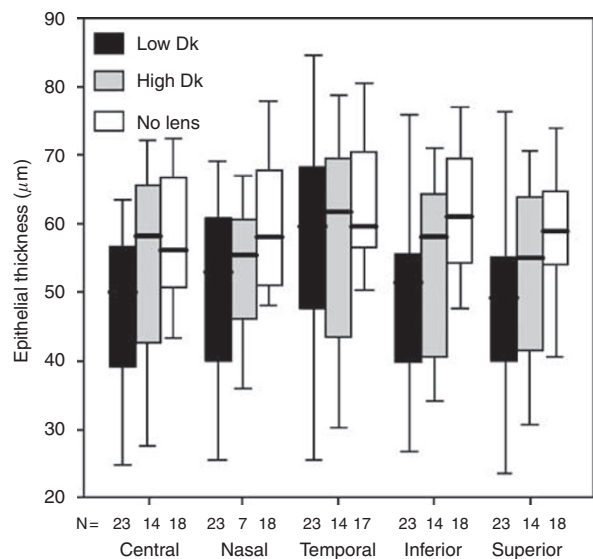
Lens oxygen transmissibility ( $P=0.55$ ) and wear duration ( $P=0.36$ ) were poor predictors of epithelial thickness and could only explain 6% of the variance ( $P=0.14$ ).

### Discussion

This study demonstrates for the first time *in vivo* that morphological alterations to the regularity of basal epithelial cells are present in extended wearers of low Dk hydrogel lenses and that the same changes are not observed during extended wear of high Dk soft silicone hydrogel lenses. Monkey experiments had previously shown epithelium thinning without oedema during low Dk soft lens wear because of a loss of superficial cells and a flattening of the remaining ones.<sup>4</sup> The morphological changes observed in this study appear to confirm that



**Figure 2** Basal epithelial cell regularity in long-term low Dk hydrogel and high Dk silicone hydrogel extended wearers. Cells were rated more irregular in low Dk wear than high Dk ( $P=0.01$ ), or no wear ( $P=0.01$ ). High Dk wear did not affect regularity (images could not be obtained for five low Dk, three high Dk, and seven control subjects).



**Figure 3** Epithelial thickness in long-term low Dk hydrogel and high Dk silicone hydrogel extended wearers. The epithelium was significantly thinner in low and high Dk wearers than non-lens wearing controls ( $P<0.06$ ), and thinning was more pronounced in wearers of low Dk lenses compared with the wearers of high Dk lenses ( $P<0.001$ ; data were not obtained for one low Dk, three high Dk, and four control subjects). Nasal thickness was not obtained for seven high Dk subjects.

flattening of the columnar basal epithelial cells is also occurring in soft lens wearing humans. Cell density was not assessed but other investigators have been unable to demonstrate any reduction in the number of basal epithelial cells during long-term lens (soft and rigid) wear.<sup>21</sup> Although epithelial swelling is a possible confounding factor, it is only known to enhance visibility of the basal epithelial cell borders and has not been associated with alterations in basal epithelial cell morphology.<sup>18,22</sup> The finding of uniform backscattered light reflectivity across all groups further supports the assumption that any residual epithelial swelling present is minimal.

This study confirms that long-term wear of silicone hydrogel lenses produces epithelial thinning, but to a significantly lower degree than hydrogel lenses. The epithelial thickness results for the low Dk group replicate previous findings.<sup>3,5</sup> Conversely, Patel *et al* could not demonstrate central epithelial thinning in long-term wearers of daily wear soft and rigid low Dk lenses.<sup>6</sup> Their study protocol included a minimal delay of 12–24 h between lens removal and confocal microscopy examination. This may have been sufficient time for epithelial thickness to recover from any adverse effects caused by lens wear. A similar difference in thinning between wearers of hydrogel and silicone hydrogel lenses has been demonstrated after the first month of extended wear in a prospective study, followed by a partial adaptive recovery over the next 11 months.<sup>1,2</sup> Although it is possible that partial adaptive recovery occurred in the subjects enrolled in this study, our observations after 5 years of silicone hydrogel wear indicate that total recovery of epithelial thickness to levels equivalent to those of non-lens wearers may never occur. Although the examiner remained unaware of thickness results throughout the pachometry measurements, the possibility of bias remains as this investigator knew which group the subjects were from. The unequal wear experience of the low and high Dk soft lens wearers is also a possible confounding factor in this study. As wearers of low Dk had worn lenses on average for a longer time than wearers of high Dk lenses, it is possible that the lower amount of thinning observed in silicone hydrogel wearers may go on to progress to levels observed in hydrogel wearers over the longer term. Confirmation of these results in subjects with matched wear experience is required.

Hypoxia, direct lens pressure and modulation of epithelial homeostasis are possible mechanisms underlying the epithelial changes observed during soft lens wear. The technique of orthokeratology convincingly illustrates how malleable and quickly responsive the corneal epithelium can be to direct pressure.<sup>23</sup> Indeed, it has been postulated that this underlies the refractive

changes observed during high Dk soft lens wear.<sup>24</sup> In a series of innovative experiments, Cavanagh<sup>25</sup> was able to show that simple eye closure as well as any type of lens wear can significantly alter the normal epithelial homeostasis. Evidence of a greater thinning effect with low Dk lenses compared to the stiffer high Dk silicone hydrogel lenses combined with the finding that morphological changes to the basal epithelial cell layer could only be detected in hydrogel lens wearers in this study suggest that hypoxia remains the driving factor in soft lens wearers.

Compared with low Dk soft lenses, high Dk silicone hydrogel lenses appear to limit the degree of epithelial thinning and to prevent significant changes to the basal epithelial cell layer regularity from occurring.

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