Clinical highs and lows of Dk/t

Part 1 – Has oxygen run out of puff?

In the first of a two-part series, Professor Noel Brennan and Dr Philip Morgan look at the latest terminology and theories about oxygenation of the cornea through silicone hydrogel lenses.

Although silicone hydrogel (SiH) contact lenses have fallen short of their original goal, solving the continuous wear-infectious keratitis problem, they undeniably provide a superior environment than hydrogels by promoting normal corneal metabolic activity. While there is consensus on this benefit, it is less clear how high we have to go in terms of oxygen transmissibility (Dk/t) within the SiH category to achieve an optimal physiological result. (For simplicity, units of 10^-9 (cm/sec)(mlO_2/ml.mmHg) are omitted where Dk/t values are given in the text.)

Theoretical modelling backed up by equivalent oxygen percentage (EOP)-based empirical data suggests that there will be little difference between any of the SiH lenses.1-6 However, some authors argue that one should expect continuing benefits by increasing Dk/t within the SiH range.7,9

While the modelling and laboratory findings are important to contemplate, the ultimate test of these differences will be found in clinical performance. In this, the first of a two-part series, we address the clinical perspective to arrive at the conclusion that there is little to be gained in strict physiological terms by pushing Dk/t values beyond those provided at the low end of the SiH range. In part two, we will highlight important differences in performance within the SiH category that are not oxygen based and should be the real consideration for selecting between different lens brands.

The law of diminishing returns

The law of diminishing returns must apply when considering the relation between oxygen reaching the cornea and Dk/t. Let us suppose a contact lens with Dk/t equal to 100 leads to a partial pressure of oxygen at the front surface of the cornea of 100 mmHg (from available data, this is most probably a conservative estimate). Under normal open eye wearing conditions, doubling the Dk/t to 200 will not lead to a partial pressure of 200 mmHg. It cannot, because the partial pressure of atmospheric oxygen at sea level is about 159 mmHg (at STP) and the pO_2 at the corneal surface will never exceed this. We can keep doubling the Dk/t, but it will never lead to a pO_2 of greater than that in the atmosphere. Data from Bonanno et al in Figure 1 exemplify this by showing that pO_2 at the anterior surface increases only gradually above a Dk/t level of about 85.8,10

Figure 2 demonstrates that as the modelling of corneal oxygenation from Dk/t to EOP to flux to consumption.
Efron and our own unpublished measures†

<table>
<thead>
<tr>
<th>Material</th>
<th>Brand name</th>
<th>Water content (%)</th>
<th>Modulus (MPa)</th>
<th>Maximum Dk/t †,13,14†</th>
<th>Minimum Dk/t †,13,14†</th>
<th>Surface modification</th>
<th>Other technology</th>
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<td>Plasma-polymerisation</td>
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becomes more sophisticated, continuing to increase Dk/t shows increasingly marginal benefits (see panel). Hence, there is no question that the law of diminishing returns applies, the only real question is, at what point do increases in Dk/t cease to have real clinical benefit? Research on oxygen consumption and the clinical evidence presented below suggests that this level is below the lowest Dk/t value found in SiH lenses.

In analysing the implications of oxygen on corneal tissue, it is appropriate to refer to a set of lens parameter values. Such information is provided in Table 1. It should be remembered that the Dk/t value cited for most lenses applies to the centre of the lens alone. A lens with a central Dk/t of 20 may well have a peripheral Dk/t of 10 or less. Central and peripheral Dk/t values provided in Table 1 are estimates derived from various sources of permeability and thickness values, including manufacturer data, Bruce, Efron et al and our own unpublished measures.† Maximal Dk/t data may vary from manufacturer stated values as these are commonly presented at 0.30mm across a wide range of powers and this rule-of-thumb can be useful for estimating the worst case Dk/t on higher-powered lenses. For speciality lenses, such as torics, the same maximal thickness values will tend to apply, so the general conclusions made in this paper for spherical lenses will be generally applicable to specialty lenses.† Dk/t values used in the discussion below will refer to central Dk/t unless otherwise stated. Acuvue Advance and PureVision exhibit minimum Dk/t data for SiH lenses generally recommended for daily wear (DW) and continuous wear (CW) respectively and these lenses will be referred to in this context below.

**Known oxygen-related effects**

Realistically, all hydrogel lenses induce corneal hypoxia. Short-term closed eye wear of hydrogel lenses leads to corneal edema, limbal hyperemia and endothelial blebs.²⁶ A period of hydrogel lens CW sees the development of microcysts and vacuoles, vascularisation of the cornea, stromal thinning, endothelial polymegathism, and myopic creep.²⁸²⁹ Open-eye wear of hydrogel lenses produces less effect than closed eye wear but evidence suggests that there is virtually always some degree of hypoxia somewhere in the cornea. Limbal hyperemia is the most obvious sign and occurs in most people during hydrogel lens wear.²⁰²¹ Long-term DW of hydrogel lenses has also been shown to cause endothelial polymegathism,²² but it is unclear whether the extent is uniform across the oxygen transmissibility (Dk/t) range of hydrogels (about 0 to 30) as studies to date have only considered the various modalities by group. Lower Dk/t hydrogel lenses (less than about 20) are known to cause corneal swelling even with the eyes open.²³ Lenses at the low end of the Dk/t range (a peripheral Dk/t of less than about 10) may also lead to vascularisation.²⁴²⁵ It is therefore likely that lenses at the upper end of the Dk/t range (above a Dk/t of about 20) produce minimal change to the cornea aside from limbal hyperemia. Since most contact lens wearers around the world use thin, medium-water content hydrogel lenses with a central Dk/t of 20 or thereabouts, it is reasonable to state that elimination of limbal hyperemia constitutes the outstanding, if not only, reason for switching from DW hydrogels to SiH lenses.

**Oedema, striae and endothelial folds**

There is a strong link between the thickness of the cornea and its oxygen supply.³²³³ During open-eye wear, the cornea will swell if the contact lens Dk/t is under about 20.³⁴ Hydrogels will therefore generally produce some
corneal swelling even when the eyes are open. If this amount is more than about 5 per cent, the clinician will also be able to see posterior stromal striae and when it swells by more than about 10 per cent, endothelial folds appear. None of the SiH lenses would be expected to produce any corneal swelling while the eyes are open and there is evidence to support this contention.37 During overnight eye closure, there will be some swelling of the cornea even without contact lens wear. The amount has been estimated to be between 0.7 and 5.5 per cent.38 The amount varies with lens wearing experience; Cox et al found 3.8 per cent swelling in non-contact lens wearers, 2.0 per cent in subjects adapted to DW hydrogel lenses and 0.7 per cent in those adapted to CW hydrogel lenses.39 All contact lenses will cause further swelling in the closed eye state above these baselines. The medium-water content hydrogels will generally cause about 8 per cent further swelling and hydrogels with lower Dk/t than these will cause greater amounts.40 SiH lenses cause much less edema. The SiH lens with the lowest Dk/t that is approved for CW, PureVision, only causes about 2 per cent swelling additional to the baseline amount.40 The SiH with the highest Dk/t, Focus Night & Day, causes about 1 per cent more swelling.41 It is unclear whether these small amounts of 1 to 2 per cent swelling seen with SiH lenses in addition to that which occurs without a contact lens in place are indicative of harmful hypoxic stress and whether the small differences between these lenses are important. In the absence of a known link between swelling and corneal pathology and given the large proportional difference between SiH and hydrogel lenses, we propose that the degree of swelling occurring with SiH lenses is of no consequence.

Microcysts
Holden et al stated that, of various compromises that CW of hydrogels may produce, ‘the most easily observable condition indicative of epithelial compromise is microcysts’.42 Sweeney et al state that ‘in clinical trials microcysts are used as the classic marker of hypoxia’. Hickson and Papas measured the incidence of microcysts in people who do not wear contact lenses to be 49 per cent, although none showed more than 5 microcysts per cornea.43 DW of hydrogel lenses does not seem to influence this incidence.42,44 Consequently DW of SiH lenses would not be expected to increase this prevalence, a premise based on the default that no-one has deemed it worthy of measuring. In contrast, the mean number of microcysts in subjects wearing hydrogel contact lenses after five years of CW has been reported as 17 ± 21, with virtually all eyes showing at least one microcyst.23 Microcyst numbers inversely correlate with Dk/t during closed eye wear, with the Dk/t level at which they fall to baseline numbers estimated at around 50.45 Given that the central Dk/t of the PureVision is about 90, it is no surprise that microcysts are not generally reported as a problem with SiH lenses. Brennan et al reported on wear of 3 different type of SiH lenses and found an incidence of 30 to 59 per cent, which is consistent with the Hickson-Papas baseline but a higher incidence of 9 to 17 per cent with greater than 10 microcysts.46 They studied the lenses with highest and lowest Dk/t values in the EW category for SiH but found no evidence of a relation between this most important marker of hypoxia and Dk/t within this group.

Vascularisation
Vascularisation is important because it is the only, serious, contact lens-related threat to vision other than microbial keratitis (Figure 3). It can occur with both DW and CW of hydrogels. Because it takes some time to develop and is non-acute in nature, incidence and relative risk data are very patchy. Lenses with even modest peripheral Dk/t values, say around 10 as is found in some thin high-water content lenses, may induce some minor sprouting of vessels but do not appear to induce significant vascularisation in DW. It is therefore most unlikely that any hypoxic related vascularisation would be found with SiH lenses in DW and we are unaware of any such reports.

Dumbleton et al considered vascularisation over nine months of CW and found significant vascularisation in wearers of low Dk/t lenses (peripheral Dk/t about 10) and none in wearers of high Dk/t (peripheral Dk/t values in the region of 60 to 100) lenses,47 confirming the general relationship between vascularisation and Dk/t. However, there have been very few studies enabling assessment of the impact of Dk/t within the SiH category. Over a period of one year of CW, Brennan et al found near zero percent incidence of significant vascularisation in either eye among 212 subjects wearing PureVision and Acuvue lenses contralaterally.48 Further analysis of a one-year CW study of PureVision, Night & Day and Biofinity reported by Brennan et al46 found that almost half of the subjects, who were from a mixed history of previous wearers, were graded as having some degree of vascularisation on entry to the study. At subsequent visits, recorded vascularisation decreased considerably but more or less equally between the different lens types. At the final visit, 25 per cent of subjects wearing PureVision still showed some degree of vascularisation versus 21 per cent of subjects wearing Night & Day. Santodomingo et al do not even mention vascularisation in their 18-month comparison of PureVision and Night & Day, restricting comments entirely to hyperaemia.49,50

In summary, SiH lenses seem to have eliminated hypoxically-induced vascularisation. Further, there is no evidence of differences within the SiH category with regard to propensity to induce vascularisation.

Limbal redness
As noted earlier, limbal redness is the primary hypoxic sign in DW of thin, medium-water content, hydrogel lenses. Papas derived a critical peripheral lens Dk/t value of 125 to avoid limbal redness in open eye wear51 and this proposal is one of the main pillars for advocates of higher Dk/t. However, the methodology used to derive this criterion has shortcomings. In keeping with Holden and Mertz,52 the mathematical approach seeks to identify an intercept between what is essentially an asymptotic curve and its asymptote, an inherently imprecise exercise. There are also serious doubts over the quality of the control used by Papas. The baseline was taken to be the eye without a contact lens. But mechanical effects and temperature during lens wear may confound limbal redness measures over

**Figure 3 SiH contact lenses do not appear to induce vascularisation (shown here) at all**
and above the influence of Dk/t.

To this end, we surveyed the literature for support to Papas’ criterion of 125. Our search identified seven studies that compared differences between two different SIH lenses in the degree of induced limbal hyperaemia in both DW and CW. Since the peripheral Dk/t values of all the SIH lenses fall below 125 and no two values are the same, we would expect to find significant differences in the degree of limbal redness in all of these studies if Papas finding is clinically important. In none of these studies was there a difference reported. This suggests that, not only is the criterion of 125 of little relevance in the clinical world, but that a figure of 37, the minimum peripheral Dk/t found in DW silicone-hydrogel lenses, is adequate to avoid clinically important open-eye limbal redness.

Endothelial blebs

Within minutes of insertion of a contact lens, dark regions known as blebs appear in the specular reflection of the endothelium. Although they are not regarded as being of pathological concern on their own, blebs constitute an immediate index of hypoxia with the area of the endothelium comprising blebs during wear of a contact lens being inversely proportional in general to the Dk/t of that lens. However, we recently tested whether there were differences in bleb response within the SIH category. We examined bleb formation following 20 minutes wear of SIH lenses in East Asian eyes under open and closed eye conditions and were unable to demonstrate differences across Dk/t.

Endothelial polymegathism

Most studies agree that endothelial cell density is not affected by either daily or continuous contact lens wear; however, the distribution of cell sizes and shapes does change, effects known as polymegathism and pleomorphism respectively. Of the clinical markers that potentially indicate long-term physiological compromise to the cornea through chronic hypoxia, endothelial polymegathism would seem to be the most sensitive. Microcyst numbers tend to peak after several months of CW (not counting the rebound effect if this mode of wear is interrupted), stromal and epithelial thinning are generally modest in magnitude compared to population variance, vascularisation only arises in individual cases and usually requires severe hypoxia but polymegathism seems to continue to worsen linearly over time. It also seems to increase with intensity of wear. Figure 5 shows the endothelial appearance of a 25-year veteran hydrogel lens wearer compared to young and older non-wearers. The development of endothelial polymegathism appears to be related to the degree of hypoxia as there is considerable change in wearers of PMMA lenses, during CW of hydrogel lenses and to a lesser extent in DW of hydrogel lenses; however, there is minimal change in wearers of silicone elastomer lenses. Yet, it is unclear at what Dk/t level polymegathism begins. It is also yet to be determined whether SIH lenses induce this phenomenon and also whether switching to these materials allows recovery from hydrogel lens induced endothelial polymegathism.

Corneal thinning

Both epithelial and stromal thinning may occur in response to CW of hydrogel lenses but an effect with DW is less obvious. It is uncertain how much of the thinning can be attributed to mechanical effects as opposed to hypoxic effects. Orthokeratology is known to thin the cornea centrally and the major effect of this is independent of Dk/t. There is no evidence that there is hypoxic related corneal thinning with SIH lenses.

Myopic creep

Small myopic shifts have been previously identified with DW and CW wear of hydrogel lenses and the degree to which these occur would seem to be greater than with spectacles. These changes are not apparent with wear of at least one brand of silicone-hydrogel lens. However, the degree to which myopic changes are attributable to hypoxia remains open to conjecture. There is no apparent increase in central corneal curvature associated with hydrogel lens-induced myopic shift. It is theorised that peripheral retinal refraction is responsible for ocular growth. Wear of standard design contact lenses may change the aberration profile leading to a greater degree of optically stimulated myopic increase than if spectacles were worn. This effect may be counterbalanced in the case of wear of higher modulus silicone-hydrogel lenses, which will have a tendency to mechanically flatten the central corneal region.

Summary

There is little evidence of physiologically-based performance variation within the silicone-hydrogel lens category. That which is known to exist comprises small differences of unknown significance in the closed eye corneal swelling response between SIH lenses and laboratory differences in limbal hyperaemia that do not seem to manifest in clinical reports for either DW or CW. In part two of this series, we will consider those differences in lens performance between SIH brands which are important and show that these are related to material properties other than oxygen transmissibility.

References

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