EXTENDED REPORT

Ultrastructural evaluation of explanted opacified Hydroview (H60M) intraocular lenses

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Aim: To describe the ultrastructural appearance of explanted opacified Hydroview H60M intraocular lenses.
Methods: 14 explanted lenses were examined by scanning electron microscopy, and their appearance compared with a non-implanted H60M lens from the same time period. Wavelength-dispersive x ray spectroscopy (WDX) was performed on two opacified lenses.
Results: Subsurface deposits were seen in all explanted opacified lenses. These deposits broke only onto the surface of more densely opacified lenses. WDX confirmed that the deposits contained both calcium and phosphorous, consistent with their being calcium apatite.
Conclusion: These findings challenge the widely accepted opinion that H60M intraocular lens opacification begins on the surface of the optic.

Since the first intraocular lens (IOL) was implanted in 1949,¹ prosthetic lens implantation has become routine with cataract surgery. Lens-related complications are uncommon. Cataract surgery is the most commonly performed procedure in the UK (with >306 000 operations in England during 2004–5²). IOL implants are the most commonly used prosthetic devices. The drive to improve the quality and reliability of IOLs will continue the trend to develop new materials and designs. The potential for unforeseen problems will remain for the future and cannot be fully eliminated. Any complication related to implanted lenses will have considerable implications for public health, clinical governance and health service resources.

On rare occasions, IOLs implanted during cataract surgery can become opacified.^{3–11} In 2004, the UK Medicines and Healthcare Products Regulatory Agency recognised that H60M Hydroview IOLs manufactured between December 1997 and May 2001 displayed an increased incidence of postoperative opacification.¹² During this period, 88 527 H60M lenses were supplied to hospitals in the UK.¹²

In this report, the ultrastructural appearance of explanted opacified H60M Hydroview IOLs (Bausch and Lomb Surgical, Rochester, New York, USA) was compared with that of a non-implanted (non-opacified) H60M lens manufactured during the same time period.

Patients typically present with symptoms of reduced visual acuity or glare from 12 to 36 months postoperatively.¹² This is longer than the experimental lifetime of animals in which biocompatibility may be studied. In some patients, this opacification causes sufficiently severe symptoms to necessitate lens exchange surgery.¹³

The 6 mm hydrophilic optic of the H60M lens was made from a copolymer of 2-hydroxyethylmethacrylate and 6-hydroxyhexylmethacrylate combined with a small quantity of 1,6-hexanediol and an ultraviolet blocker.^{13 14} The optic was polymerically linked to two modified C-loop haptics to form a one-piece design. The haptics were made from a polymethylmethacrylate cross linked with ethylene glycol dimethacrylate and coloured blue.^{13 15} H60M lenses were designed to be folded and implanted into the capsular bag through a 3.5–4 mm corneal incision using special forceps.

It is not known why H60M lenses opacify. Most studies have shown surface calcification on opacified H60M lenses^{13 15} and one study has shown subsurface calcium deposition.¹⁴ In extraocular physiological systems, it has been shown that the presence of silicone promotes calcification.^{16–18} Before May 2001, H60M lenses were delivered in SureFold packaging (Bausch and Lomb Surgical), which contained a silicone gasket. Surface calcification has been attributed to the migration of silicone from this gasket on to the lens' surface.¹³ Others have suggested that the 2-hydroxyethylmethacrylate–6-hydroxyhexylmethacrylate copolymer has a high affinity for calcification.¹⁴ For these reasons, it has been suggested that, although multifactorial, the mechanism of opacification depends on the presence of silicone on the surface of the H60M lens. Although no cases of H60M opacification were considered to occur before the introduction of this packaging^{13 19} and none was thought to occur since the change from it, this theory alone is unable to explain why opacification affects the lens optic, but entirely spares the lens haptic (made from a different material but similarly exposed to silicone), why the rate of opacification varies considerably by date of implantation and between centres,¹⁵ or why it is unusual for an individual to have bilateral H60M opacification even when both eyes received lens implants during the "at-risk" period.¹³

PATIENTS AND METHODS

Patients who self-presented, were referred by opticians or general practitioners, or were identified within the Bristol Eye Hospital, Bristol, UK, because of symptomatic reduction in visual acuity, were offered lens exchange surgery. All patients gave informed consent for their explanted lenses to be examined.

This study was approved by the Bath Local Research Ethics Committee (reference number 04/Q2001/255) with site-specific approval from the Central and South Bristol Research Ethics Committee, and performed in accordance with the tenets of the Declaration of Helsinki. The study was approved by the Bristol

Abbreviations: IOL, intraocular lens; SEM, scanning electron microscopy; WDX, wavelength-dispersive x ray spectroscopy

Figure 1 Scanning electron micrographs of non-implanted (control) lens (A, C) and a severely affected lens (B, D–F). Bars are 1 mm in (A) and (B), and 20 μ m in (C–F). (A) Low-power image of the junction between the optic (O) and the haptic (H) showing the smooth appearances of the surfaces. (B) Low-power view of one half of a severely affected lens showing the optic (O) and the haptic (H). (C) Detail from the periphery of the cut surface of the lens showing the smooth appearance of the upper and lateral surfaces of the lens. (D) Detail from enclosed area 1 in (B) in which a number of small deposits on the upper and lateral surfaces of the lens can be seen (arrows). (E) Detail of enclosed area 2 showing the large number of closely packed deposits and the elongated region where the deposits appear fused (arrows). (F) Detail of enclosed area 3 showing the junction between the optic (O) and the haptic (H). Note the numerous deposits on the optic (arrows), but their complete absence from the haptic.

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Several different surgeons explanted lenses, and no standard technique was used. In most cases, the optic was bisected using scissors to facilitate removal through a small clear corneal incision. Fourteen explanted opacified H60M lenses were studied. One non-implanted H60M lens from the same period was used as control.

At the initiation of this study, we examined various processing protocols to ensure that accurate information was obtained by scanning electron microscopy (SEM) and x ray analysis, and to establish a standard protocol for future studies. It was found that the transport medium could be variable and that fixation was not essential. Preliminary studies found that allowing the lens to air dry after removal was detrimental and resulted in adherent material not present *in situ* (cellular debris blood and proteinaceous material) contaminating the surface of the lens. This could compromise electron microscopy and result in erroneous x ray microanalysis findings. Certain unusual findings reported in previous studies could result from contamination with adhering material subsequent to removal. In addition, the need for critical point drying before SEM was examined and found to be unnecessary.

Lenses needed to be placed immediately in transport fluid. The lenses were transported for SEM in various fluids including 4% glutaraldehyde in 0.1 M phosphate buffer, formalin or saline. If not already cut in half for surgical removal, the lenses

were divided into two equal halves equidistant between the haptics, washed in distilled water and air dried. The two halves were mounted on stubs using double-sided tape, in such a manner that one half had the anterior surface exposed and the other the posterior surface. The samples were sputter coated with gold before examination under a Philips 505 scanning electron microscope. Lenses were examined by SEM, and the presence and location of abnormalities were noted.

For wavelength-dispersive x ray spectroscopy (WDX) analysis, the samples were mounted in Struers Specifx 20 epoxy resin so that cross sections through the lens could be polished, using standard metallographic methods down to 1 μ m diamond. Polished blocks were then coated with carbon and examined using a JEOL 8800 electron-microprobe with an accelerating voltage of 15 kV and a probe current of 5 nA.

RESULTS

On SEM, the surface of the optic and haptics of the control lens appeared extremely smooth, with no evidence of any surface roughening or the presence of any organic or inorganic deposits (fig 1A). After hemisection, and when examined in cross section, no abnormality of the underlying plastic of the optic was evident (fig 1C).

SEM of the explanted opacified lenses showed numerous deposits both below and on the surface of the optic, completely sparing the haptics (figs 1 and 2). A comparison of opacified lenses in this series found a similar pattern of deposition on all

Figure 2 Scanning electron micrographs of less severely affected lenses (A–E) and a sample examined by wavelength-dispersive x ray spectroscopy (WDX; F–H). Bars are 10 μ m. (A) Central region of the optic of a mildly affected lens showing a number of indistinct subsurface deposits (arrowheads) and a few deposits on the surface (arrow). (B) More severely affected lens showing an increase in the number and size of the subsurface deposits (arrows). (C) Image of the cross-cut surface of same lens as in (A) showing the subsurface deposits (arrows). (D) Image of the cross-cut surface of same lens as in (B) showing the increased size of the subsurface deposits. (E) Image of the cross-cut surface of same lens as in (B) showing the subsurface (arrows) and surface (arrowheads) deposits. (F) Backscatter image of a cross section through the surface of a lens embedded in epoxy resin for WDX showing deposits (arrows) just below the surface (arrowheads). (G) WDX analysis of the same area as in (F) examined for calcium. The highest concentration (red/yellow) of calcium coincides with the subsurface deposits (arrows). (H) WDX analysis of the same area as in (F) examined for phosphorous. The highest concentration (red/yellow) of phosphorous coincides with the subsurface and calcium deposits (arrows).

Figure 3 A diagrammatic representation of the hypothesised progression of H60M lens opacification from an initial subsurface focus within the plastic of the optic (A), which enlarges (B) before making contact with the surface (C). As the focus enlarges further, it causes surface elevation (D) and then surface distortion (E) before breaking through the surface (F) after which part of the exposed deposit may break away (G).

lenses. There were marked differences in the size and density of deposits and area of lens optic involved. In all cases, irrespective of the overall density of deposition, the largest concentrations of deposits were located in the central region of the optic, with progressively reduced levels towards the periphery (contrast fig 2C,D). When the deposits on the anterior and posterior surfaces were compared, no marked differences were observed; both surfaces of a given lens showed a similar degree of deposition. In the more severely affected lenses, the deposits formed an almost confluent layer in the central region (fig 1E), whereas they were well separated in the peripheral regions (fig 1D,F). In the most opacified lens (on clinical and macroscopic examination), in a few areas, the deposits had a cratered appearance, as if part of the deposits had broken away from the lens surface.

The less severely affected lenses showed mild surface elevations associated with numerous focal areas of increased electron discharge (fig 2A, arrowheads). This is characteristic of a subsurface location of inorganic deposits and contrasted with the sharp contours of the surface deposits (cf figs 2A and 1D,E). When the lenses were cut and examined in cross section, it was confirmed that these areas represented subsurface deposits (fig 2C–E). All deposits were within 5 μm of the surface. Although a range of deposit sizes was seen in each lens, there was a consistent relationship between the maximum deposit diameter and the density of opacification seen in any particular lens.

The smallest deposits, with diameters $<1\ \mu\text{m}$, were present in the least densely opacified lenses, and were situated beneath the surface of the optic and caused no disturbance of the lens surface (fig 2C, arrowheads). Larger deposits were found with increasing frequency in more densely opacified lenses. There was a tendency for these larger deposits to be closer to the lens surface and deposits of approximately 2–3 μm diameter were commonly seen in the immediate subsurface region causing surface elevations (fig 2C, arrows). Even larger deposits were associated with surface layer distortion and elevation (fig 2C,D). In the most densely opacified lenses, most deposits had erupted through the surface of the optic and appeared as discrete structures on the face of the optic.

On several severely affected lenses, bands of surface deposits had coalesced to form paired curvilinear bands (fig 1E). These bands were at right angles to the axis between the base of the haptics, and each band was approximately 50 μm wide and at least 2 mm long. Individual pairs of bands exhibited symmetry with each other along their long axis. The shape of these bands corresponded to the shape of the forceps used to fold the H60M lens for implantation. There was no evidence of surface damage or depression in these areas to suggest that the surface or the lens had been damaged by this process.

In two lenses, cross sections through the surface and subsurface deposits were examined by WDX. The subsurface deposits could be identified by their atomic number contrast in the backscatter image (fig 2F). When elemental maps were examined, these deposits were shown to have high levels of calcium (fig 2G) and phosphorous (fig 2H), consistent with calcium apatite. These elements were concentrated in the surface layer although smaller concentrations were observed deeper within the lens (fig 2G,H).

DISCUSSION

Ultrastructural examination of H60M IOLs showed that deposits occurred only on the lens optic, with complete sparing of the haptics (made from a different polymer, which were never affected). The size and area occupied by the deposits varied between lenses. By examining a series of 14 lenses, we could infer that there was progressive growth of the crystalline deposits (fig 3). However, this study does not offer any

information about the temporal changes in individual lenses. In clinically and macroscopically less densely opacified lenses, the lens surface was unaffected, but small deposits consistent with calcium apatite seemed to form just beneath the surface of the optic within the superficial 5 μm . In more densely opacified lenses, the increasingly larger subsurface deposits seemed to have broken through to the lens surface to form a surface crust. This difference in ultrastructural appearance between H60M lenses with different degrees of opacification suggests that the process of opacification may be progressive. This hypothesis is supported by unpublished clinical observations from Bristol Eye Hospital, where serial observations of affected patients found that progressive increases in lens opacification occurred.

The increased opacification in the shape of the lens-folding forceps seen here by SEM contrasts with the clinical appearance of reduced opacification in these areas and the finding that H60M opacification appears less dense in these areas when examined with the light microscope.¹¹ We suggest that the increased transparency in these areas may result from a greater confluence of surface deposits, resulting in less light scattering, giving the paradoxical clinical and light microscopic appearance of reduced opacification. No surface irregularity was evident in these areas other than those due to the accumulation of deposits. It may be assumed that the process of folding altered the lens surface either directly through pressure or indirectly through flexion, which may affect the pattern of opacification in the underlying area.

These findings challenge the current opinion that H60M opacification originates on the lens surface. Additionally, the correlation between the overall density of opacification and the number of larger opacities may imply that H60M opacification is a progressive process.

Previous reports from energy dispersive x ray analysis of opacified H60M lenses consistently report the presence of calcium and phosphorous,¹⁵ although additional reports of fluorine, magnesium and sodium²⁰ may imply that not all deposits are the same. The Wavelength Dispersive x ray (Spectroscopy) findings in this series support the previously described view that calcium and phosphorous are components of the deposits that develop in these lenses.

The reason for the initiation of calcification remains unclear, but an abnormality of the plastic of the lens optic, or its interaction with an unknown variable, could be responsible for starting the process. This hypothesis is similar to that proposed for the opacification of the S60B-OUV lens manufactured by Medical Developmental Research (Clearwater, Florida, USA), another hydrophilic IOL in which delayed postoperative opacification was observed.^{21–22} These findings are incompatible with the silicone nidus theory, unless the silicone can penetrate into the surface of the optic, as this seems to be the site of initial deposition of calcium and phosphorous. To date, the crystals formed on opacified lenses have not been compared directly with similar crystalline material generated *in vitro*. Calcium phosphate generated *in vitro* varies according to the conditions in which it is generated.²³ Calcium phosphate from simulated body fluids forming on osteogenic ceramics is only detected inside pores at physiological flow rates, as opposed to within the pores and on the surface with simple immersion.²⁴ Although the generation of calcium phosphate *in vivo* does not always correlate with the findings *in vitro*,²⁵ this raises the question of whether yttrium–aluminium–garnet (YAG) capsulotomy may alter fluid currents through implanted IOLs and hence affect the speed and pattern of calcium phosphate deposition. The probable initial deposition of calcium phosphate below the optic surface may conceivably occur independently of silicone from the packaging gasket. If this were the case, we might expect these lenses to continue to show a

tendency to opacification beyond the time period of silicone removal from the packaging.

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