Experimental Investigation on Mechanism of Hydrophilic Acrylic Intraocular Lens Calcification

EVANGELOS G. DRIMTZIAS, STAMATINA G. ROKIDI, SOTIRIOS P. GARTAGANIS, AND PETROS G. KOUTSOUKOS

• PURPOSE: To construct a model simulating intraocular lens (IOL) opacification attributable to the formation of calcium phosphate deposits and to investigate the kinetics of deposit formation.

• DESIGN: Prospective laboratory investigation.

• METHODS: SETTING: Department of Ophthalmology, Medical School and Department of Chemical Engineering, Laboratory of Inorganic and Analytical Chemistry, University of Patras, Greece. STUDY POPULATION: Three hydrophilic acrylic IOLs (26% water content) were placed inside a 10-mL double-walled thermostated reactor simulating the anterior chamber. Simulated aqueous humor was injected continuously into the reactor using a pump with variable speed. OBSERVATION PROCEDURES: The observation of IOLs was carried out in situ daily by optical microscopy. Scanning electron microscopy and energy-dispersive radiographic spectroscopy were used for the identification of the morphologic features and the composition of the deposits.

• RESULTS: The lenses were removed and inspected 5, 9, and 12 months after the initiation of the experiment. Investigation showed deposits of calcium phosphate crystallites in the interior of opacified IOLs. However, these deposits were not observed on the surface of the IOLs.

• CONCLUSIONS: In agreement with earlier reports by our group and in the literature, IOL opacification is the result of calcification. It is suggested that the surface hydroxyl groups of the polyacrylic polymeric components of the IOLs are capable of inducing surface nucleation and crystal growth of calcium phosphates. However, most important is the finding that the calcification of IOLs is initiated from their interior through the development of sufficiently high local supersaturation, realized through the diffusion of calcium and phosphate ions. (Am J Ophthalmol 2011;152:824–833. © 2011 by Elsevier Inc. All rights reserved.)

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SMALL-INCISION CATARACT SURGERY WITH FOLDable intraocular lens (IOL) implantation resulted in a new postoperative complication: IOL opacification. Various factors implicated in the phenomenon have been suggested, including inflammation, irrigation solutions, viscosurgical devices, silicone, and fatty acids contamination.[1–14]

Previous reports have demonstrated that IOL opacification is the result of calcification.[3,6,9,10,12–15] The formation of calcific deposits consisting of calcium phosphate salts may be attributed to the fact that the aqueous humor is supersaturated with respect to different calcium phosphate crystalline phases.[15] Modeling in vivo processes by reliable and reproducible in vitro methods is of key importance to understanding the underlying mechanisms. Precise thermodynamic calculations of equilibrium speciation in combination with kinetics measurements at conditions simulating the eye environment are expected to yield mechanistic information concerning the formation of calcium phosphate deposits.

We have developed an experimental model in an effort to investigate in vitro the mechanism of calcification of hydrophilic acrylic IOLs. The nature of the calcium phosphate phases formed in an aqueous medium simulating aqueous humor in relationship to the presence of foreign substrates provided by the IOLs was investigated.

METHODS

AN EXPERIMENTAL MODEL SIMULATING THE ENVIRONment of IOLs into the eye was constructed to investigate the characterization and the kinetics of development of calcified deposits on hydrophilic IOLs.

A double-walled thermostated reactor was constructed, volume totaling 10 mL, made of polyamide. The reactor had glass windows on top and bottom to allow for the direct observation of the IOL specimens in situ using an optical microscope combined with an image analysis system (Quantimet 500; Leica Cambridge, Cambridge, United Kingdom). In the external wall of the reactor, water supplied from a thermostat was circulated to maintain the temperature at 37.0 ± 0.2 C, whereas in the interior of the reactor, constant flow of a simulated aqueous humor solution was ensured with the help of a syringe pump (Fresenius Kabi, Pilot C, Bad Homburg,

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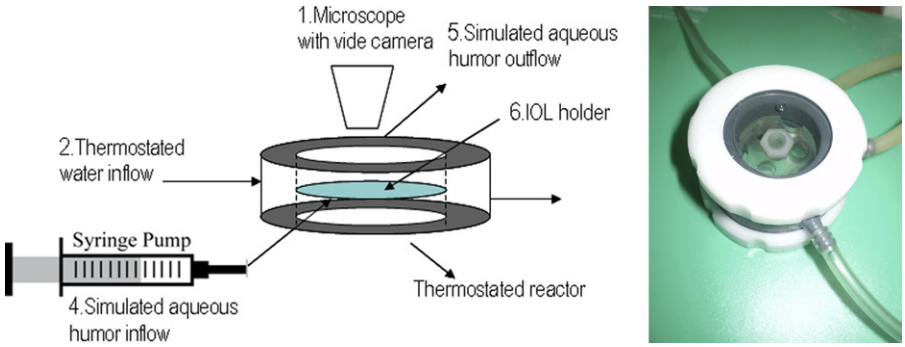

FIGURE 1. Thermostated reactor simulating the anterior chamber's conditions. (Left) Schematic layout of the experimental set-up: (1) recording video camera attached to an optical microscope; (2, 3) inlet and outlet of the water from the thermostat; (4, 5) feed and outlet of the simulated aqueous humor solution; and (6) specimens holder. (Right) Photograph of the actual cell for the intraocular lens (IOL) opacification experiments.

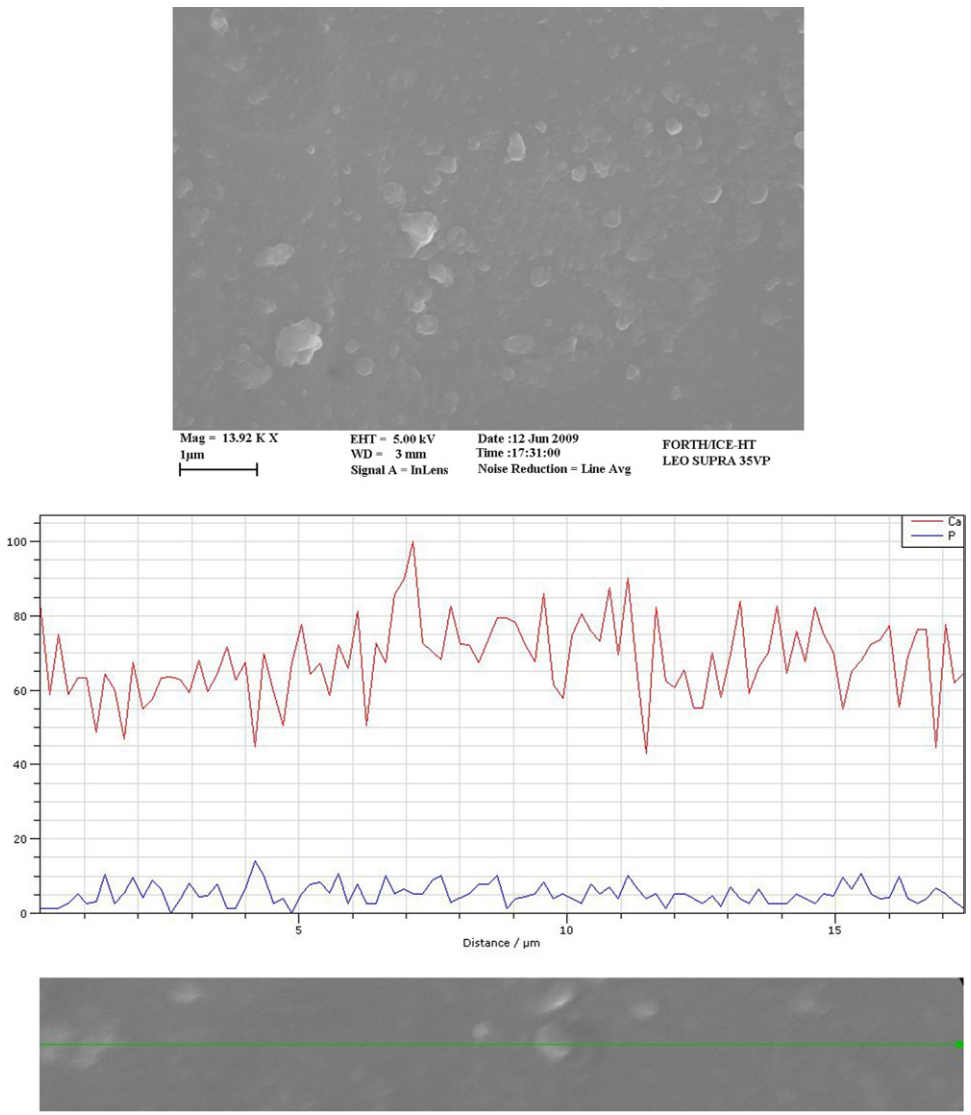

FIGURE 2. (Top) Scanning electron microscopy of the surface of lens A exposed in simulated aqueous humor for 150 days showing granular deposits with appearance similar to calcium-phosphate salts. (Bottom) Energy-dispersive spectroscopy microanalysis of intraocular lens surface deposits showing the presence only of calcium, which in combination with the carbon component, suggested either the presence of filler ($CaCO_3$) or the formation of calcium-polymer salts.

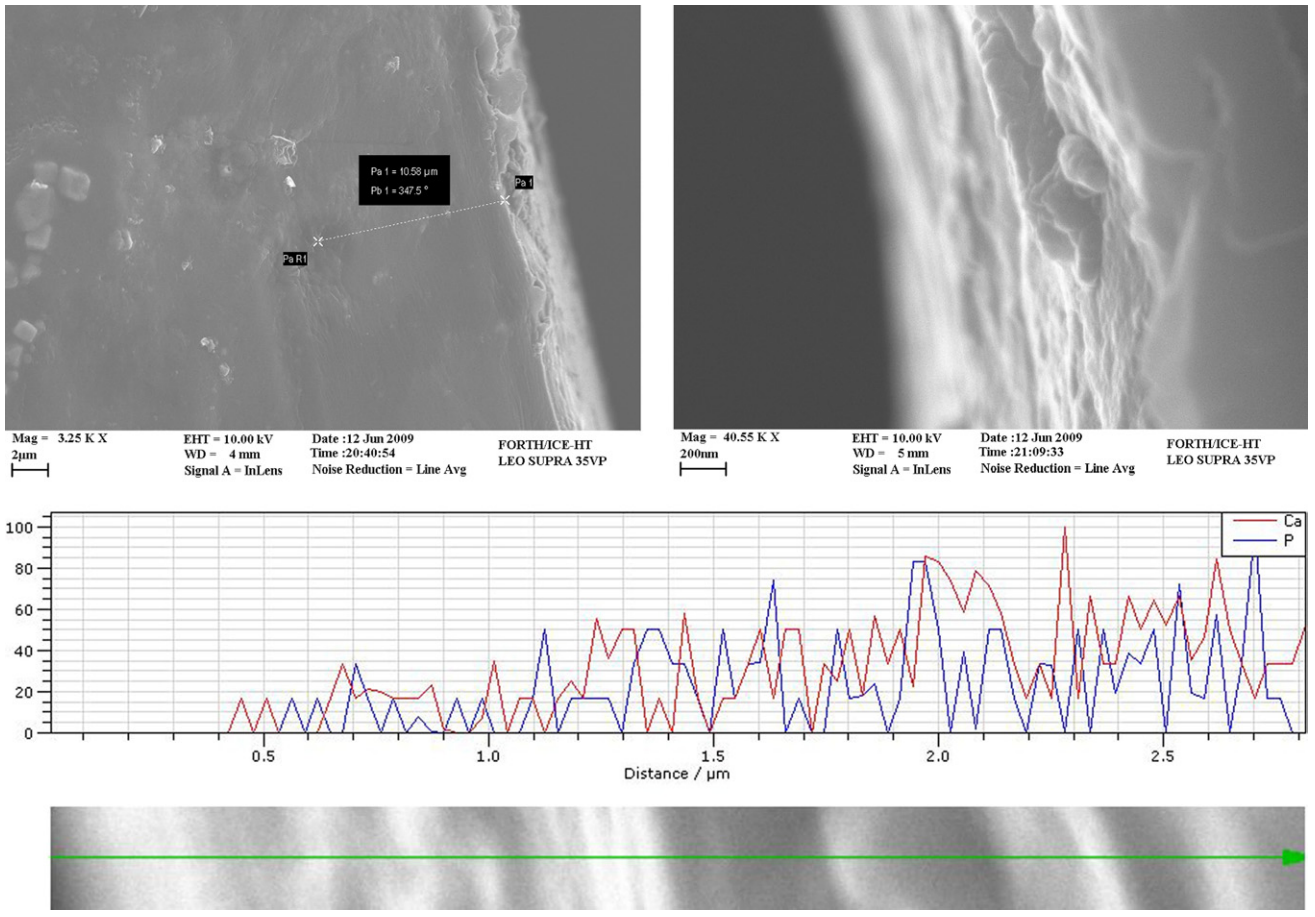

FIGURE 3. (Top left) Scanning electron microscopy investigation after sagittal analysis of lens A showing the development of prismatic nanoparticle deposits in the interior of the intraocular lens, approximately at 10 µm from the surface. (Top right) Size (<100 nm) and morphologic features of the observed deposits were typical of hydroxyapatite. (Bottom) Energy-dispersive spectroscopy microanalysis of the hydroxyapatite deposits formed in lens A exposed to simulated aqueous humor for 150 days at 37 C.

Germany). The composition of simulated aqueous humor solution, which contained only inorganic components, is identical to that of electrolyte concentrations in normal aqueous humor, where the precise concentrations are as follows: sodium (Na^+) = 146 µmol/mL, potassium (K^+) = 5.25 µmol/mL, calcium (Ca^{++}) = 1.70 µmol/mL, magnesium (Mg^{++}) = 0.8 µmol/mL, chloride (Cl^-) = 109.5 µmol/mL, bicarbonate (HCO_3^-) = 33.6 µmol/mL, and phosphate ($H_2PO_4^-$) = 0.62 µmol/mL.[16]

The simulated aqueous humor solution was introduced in the reactor in an once-flow through mode at a flow rate of 0.2 mL/hour, simulating the in vivo flow in the anterior chamber, where aqueous humor is fully renewed within 2 hours.[17] Three-piece hydrophilic acrylic IOLs (A, B, and C) in triplicate (SOFTEC III, LH-5000; LENSTEC Inc, St. Petersburg, Florida, USA), 12.75 mm in total length and 6 mm in optic diameter, made of hydroxyl-ethyl-methacrylate with 26% water content were placed in a special holder to maximize the available total surface exposed to the simulated aqueous humor. The observation of IOLs was carried out in situ daily by optical microscopy for the assessment of the opacification progress. A schematic diagram and a photograph of the experimental setup used for the in vitro calcification experiments of the IOLs are shown in Figure 1.

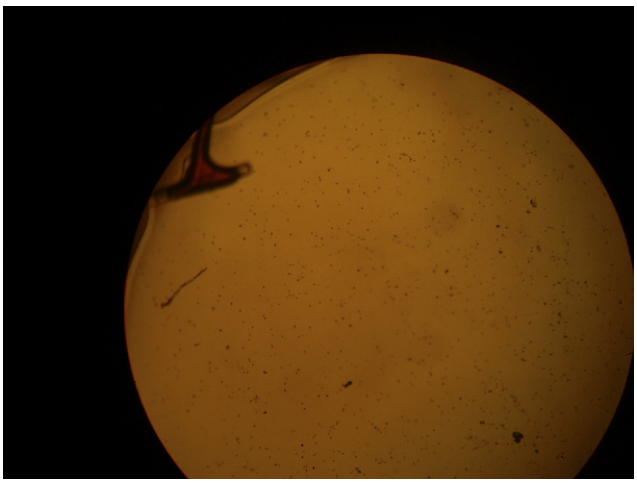

FIGURE 4. Optical micrograph of lens B surface after exposure in simulated aqueous humor at 37 C for 270 days.

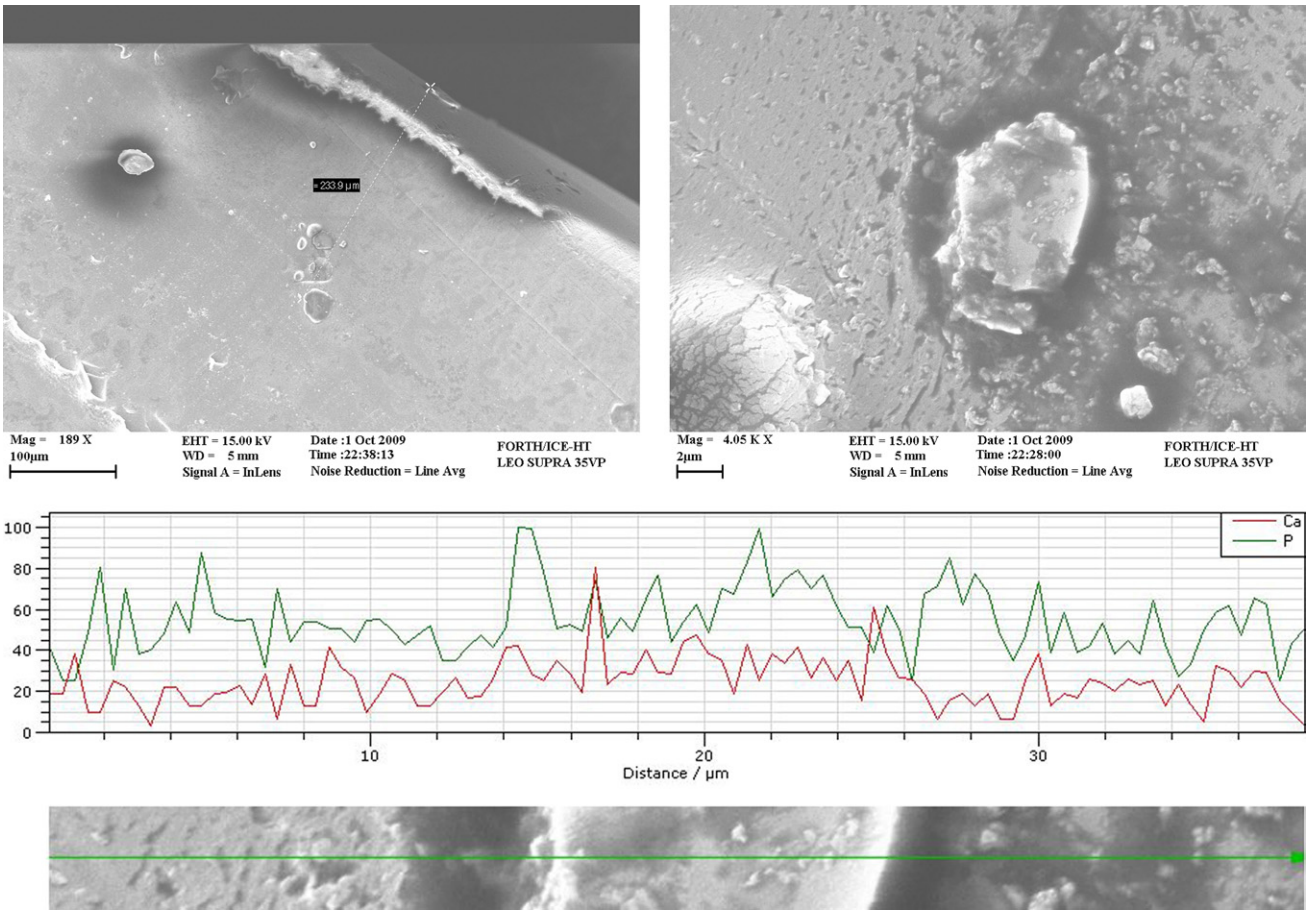

FIGURE 5. (Top left) Scanning electron microscopy of hydroxyapatite prismatic crystals at a depth of 233 µm from the surface of lens B exposed in simulated aqueous humor at 37 C for 270 days. (Top right) Hydroxyapatite prismatic crystals after sagittal analysis of the intraocular lens. (Bottom) Energy-dispersive spectroscopy analysis of the calcific deposits formed in lens B exposed in simulated aqueous humor at 37 C for 270 days.

Five months after the initiation of the experiment, lens A was removed to be inspected, both at the surface and in the interior. The morphologic features of the deposits were examined using scanning electron microscopy (LEO SUPRA VP 35; Carl Zeiss, Oberkochen, Germany). The composition of the deposits was identified by microanalysis with energy-dispersive spectroscopy (JEOL 5200 with Oxford ISIS microanalysis unit; Oxford, United Kingdom). Lens B was removed on the ninth month, whereas lens C was inspected 1 year after the onset of the experiment. Similar studies, including scanning electron microscopy and energy-dispersive spectroscopy analysis, were used for the investigation of both of those lenses.

RESULTS

SCANNING ELECTRON MICROSCOPY ANALYSIS OF THE SURface of lens A showed granular deposits with an appearance similar to that of calcium phosphate salts; despite this, energy-dispersive spectroscopy analysis of the deposit showed the presence only of calcium, which in combination with the carbon component, suggested either the presence of filler ($CaCO_3$) or the formation of calcium polymer salts (Figure 2). The nature of these formations

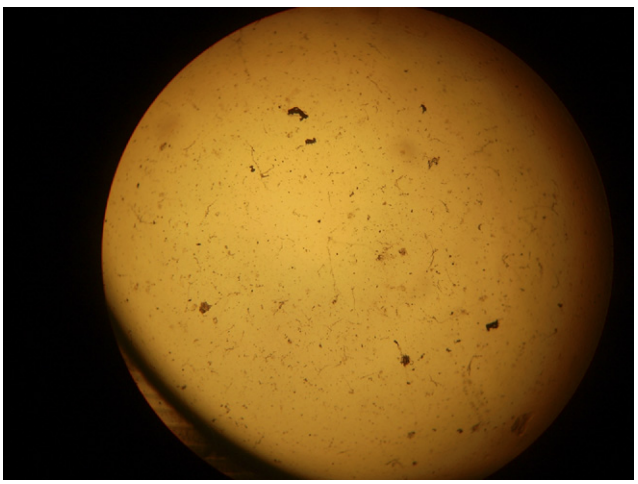

FIGURE 6. Optical micrograph of the lens C surface after exposure in simulated aqueous humor at 37 C for 360 days.

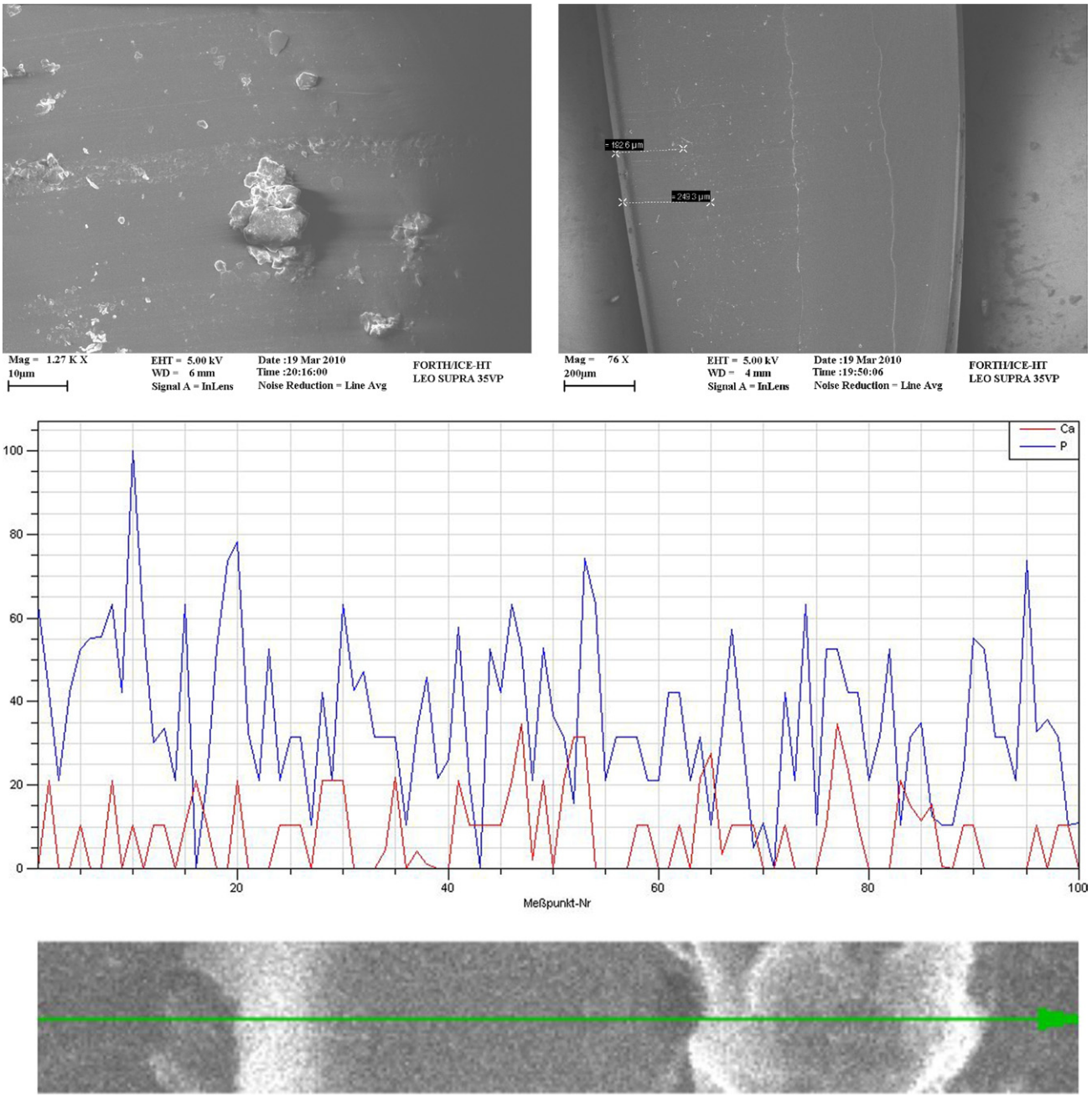

FIGURE 7. (Top left) Scanning electron microscopy investigation of lens C revealing higher density of hydroxyapatite crystallites in the interior of the intraocular lens. (Top right) Distribution of the deposits was noted to be across a line parallel to the surface separated from it by a clear zone, where no evidence of deposition was found. (Bottom) Energy-dispersive spectroscopy microanalysis of the calcific deposits formed in lens C exposed in simulated aqueous humor at 37 C for 360 days.

on the surface of the test specimens needs further investigation.

Subsequently, the IOL was cut for sagittal analysis. Scanning electron microscopy investigation showed the development of prismatic nanoparticle deposits in the interior of the IOL, approximately 10 µm from the surface. The deposits consisted of calcium phosphate crystallites. The size (< 100 nm) and the morphologic features of the observed mineral formation were typical of hydroxyapatite in the interior of the IOL. Energy-dispersive spectroscopy microanalysis confirmed the finding yielding a molar ratio of calcium-to-phospate equal to 1.67, corresponding to hydroxyapatite (Figure 3).

On the ninth month, lens B was removed and the same analytical methodology was applied (Figure 4). The IOL's surface was free of calcium phosphate deposits, as shown by energy-dispersive spectroscopy analysis, although the granular formations observed by scanning electron microscopy

were found to a greater extent in comparison with the previous specimens. Formation of prismatic crystals of hydroxyapatite was found in sections of the lens, reaching depths of 233 μm from the surface (Figure 5). Moreover, the number density of the crystalline deposits was larger in comparison with that of lens A. Lens C was inspected 1 year after the onset of the experiment. No mineral deposits were detected on the IOL's surface, despite the fact that granular deposition was observed to extend over the entire surface (Figure 6). Section analysis of the IOL by using both scanning electron microscopy and energy-dispersive spectroscopy showed deposits consisting of prismatic hydroxyapatite nanocrystals located at a depth of 249 μm from the surface. The distribution of the deposits was noted to be across a line parallel to the surface separated from it by a clear zone where no evidence of deposition was found (Figure 7).

DISCUSSION

THE INCREASING NUMBER OF NEW IOL MATERIALS IMPOSE on every generation of ophthalmologists the need for controlled, prospective clinical studies concerning biocompatibility, stability, and complications of these new materials. In the early 1990s, new foldable hydrophilic acrylic IOL biomaterials became available in cataract surgery, and since 1999 opacification of some hydrophilic IOL designs has emerged as a significant complication.[18] However, crystalline precipitation on the surface of hydrogel lenses was described first by Amon and Menapace in 1991.[19,20] Opacification has been observed in polymethyl methacrylate, silicone, and hydrophilic lenses, and the causes of the deposits can be divided in 3 groups by the time of presentation: those appearing during surgery,[7,8] those appearing in the early postoperative period,[19–21] and those appearing in the late postoperative period (several months after surgery).[2,4–6,10–12,14,22–33]

Opacification of hydrophilic acrylic IOLs resulting from calcification has been reported to occur late after surgery. Moreover, it has been reported that polymethyl methacrylate modified in a way to increase the hydroxyl groups present on the surface resulted in the formation of octacalcium phosphate on its surface.[34]

Different studies and several analytic methods, such as scanning or transmission electron microscopy, elemental analysis by energy-dispersive radiographic spectroscopy, as well as histopathologic and histochemical analysis, have proposed the cause of opacification to be the deposition of calcium phosphate.[2,6,9,10,12,14,24,28,35]

The thermodynamic driving force for the formation of a salt from solution is the difference between the chemical potentials of the salt in solution from the equilibrium (i.e., solubility).[36] Taking into consideration the rate of renewal of the solution in the experimental reactor, the experiments in the present work were carried out at conditions of constant supersaturation, thus providing a good simulation of the in vivo conditions of the patient's eye.

Knowing that calcium content of normal aqueous humor is low and that approximately half of that of the serum,[37] we may assume that any cause of a localized increase in calcium and phosphorus may result in dystrophic calcification.[38–40] As already suggested in earlier reports, calcium and phosphorus may be derived from residual cataractous lens material, where the inadequate cortex cleaning from the capsular bag may predispose the lens to the formation of calcium deposits.[15,21] Besides, phosphorus and calcium increase in cataractous lenses. This was found to be twice the normal amount.[21,41,42]

The role of systemic disease, including diabetes,[43] was implied in the pathogenesis of IOL calcification, although it is unclear whether alteration of the blood-aqueous barrier can result in opacification, given that only some patients with IOL calcification had evidence of systemic diseases. Besides and contrary to the findings of Nakanome and associates, aqueous humor analysis (performed by Yong and associates) has not shown alterations to the chemical composition of the aqueous humor or vitreous.[2,30]

Irrigation solutions used during surgery did not seem to be a factor in the opacification, because it developed months after surgery, presuming that changes in factors such as pH and temperature and changes in concentrations of chemical components could lead to the development of precipitates. Although no analysis of the deposits was performed, only silicone IOLs seemed to be affected.[7]

The role of silicon contamination on calcification of hydrophilic acrylic IOLs was investigated by Werner and associates.[18] In their study, the deposits were characterized by transmission electron microscopy and energy-dispersive spectroscopy analysis, and similarly with the findings of Dorey and associates, silicone was identified centrally in the deposits.[29] The source of the silicone element was not presented convincingly, and it was suggested that its origin was from glassware or small dust particles or from contamination from a packaging system. It has been reported previously that silicone is an important factor in the deposition of calcium, and it seems to be localized physiologically in high concentrations in tissues associated with calcification.[44] However, silicone cannot be regarded as the primary cause of calcification, because its presence was not detected in the microanalysis of the calcified IOLs, performed in different studies.[15,30]

Biological calcification is the deposition of calcium phosphate salts on tissues of living organisms, and it is the primary operation for the formation of teeth and bones. Calcification occurs also on vessel walls, as well as on foreign surfaces after longstanding contact with biological fluids, including implants and bioprosthetic devices. Biological fluids, supersaturated with respect to calcium phosphates, on contact with the foreign substrates (natural, artificial, or both), initiate nucleation and crystal growth of

calcium phosphates on their surface. The issue of biocompatibility merits thorough consideration before the use of prosthetic materials, including bioprosthetic heart valves, vascular grafts, mechanical blood pumps, and crystalline lenses. It has been recognized early that the mechanism of calcification of these implants bears similarities.[45]

The ability of biomaterials to resist calcification warrants testing with both in vivo and in vitro models. The in vivo models have been accepted as a method for predicting calcification of biomaterials. However, in vivo studies have limitations, because they are expensive and time-consuming methods and they are associated with a number of ethical problems. Therefore, in vitro models may be used alternatively to assess quantitatively the kinetics of the calcification process, which in most cases is surface controlled.[46,47] In the in vitro models, simplifications may be carried out so that the respective conditions simulate in vivo to a large extent successfully.

Heterogeneous nucleation, an almost ubiquitous phenomenon, is initiated on the active sites present on the surface of the foreign substrates in contact with the biological fluids. It is often the case that induction times, inversely proportional to the supersaturation of the biological fluids with respect to calcium phosphates, precede the formation of calcific deposits.

Biological fluids, including blood serum and aqueous humor, are supersaturated with respect to a number of different crystalline phases of calcium phosphate in the order of decreasing solubility: dicalcium phosphate dihydrate ($CaHPO_4 \cdot 2H_2O$), octacalcium phosphate ($Ca_8H_2(PO_4)_6 \cdot 5H_2O$), tricalcium phosphate ($Ca_3(PO_4)_2$), and hydroxyapatite ($Ca_5(PO_4)_3OH$). At high supersaturations, it is possible that the formation of the thermodynamically most stable hydroxyapatite is preceded by the formation of 1 or more transient crystalline phases.[48] The tendency for a particular calcium phosphate phase to precipitate in supersaturated solutions may be determined directly from solubility phase diagrams. The formation of transient phases, such as dicalcium phosphate dihydrate and octacalcium phosphate,[49] followed by rapid hydrolysis to hydroxyapatite has been shown in vitro.[50] As the calcification proceeds more mature and stable phases richer in hydroxyapatite, rather than in the transient octacalcium phosphate, phase were found.[51]

However, the calcification of biomaterials also is affected by factors such as polymer structure, porosity, and water content. The surface hydroxyl groups of acrylate polymers through surface complexation with calcium ions may act as sites for nucleation and growth of the mineral phase.[52] The presence of larger numbers of PO_4^{3-} and OH^- groups on the polymers was shown to accelerate hydroxyapatite overgrowth on the respective polymeric substrates. It is possible that calcium ions act as physical cross-linkers between polymer chains, modifying the properties and functions of the implants. As a result, chains open, allowing for the formation of calcium phosphate salts. A closed polymer structure, however, is expected to lead to the reduction of the functional groups available for dissociation or surface complexation, or both, thus making this structure less favorable to initiate nucleation.

The higher extent of hydration in hydrophilic polymeric materials is associated with higher ionization of the surface functional groups, thus promoting calcification through the formation of complexes with ionized calcium. It therefore may be suggested that the larger extent of calcification observed in IOLs with higher water content is the result of the higher extent of dissociation of the surface groups.[52] These polar functional groups (OH^-, COO^-) present in the respective polymeric materials result in a significant increase in electron density on the surface and a reduction of interfacial energy between the polymer and aqueous solution. The energy barrier for the diffusion of calcium and phosphate species from the bulk solution to the substrate is reduced, promoting calcification.[13]

Earlier reports suggested that the calcification occurred either on the surface of the IOL (Hydroview [Bausch & Lomb, Rochester New York, USA] and MemoryLens [Ciba Vision, Duluth, Georgia, USA]) or in the interior (Aqua Sense [Aaren Scientific Inc. Ontario, California, USA] and SC60B OUV [MDR Inc., Clearwater, Florida, USA]).[6,10,12,22,23–26] It should be noted, however, that Yong and associates, in the Hydroview model, noted calcified deposits in the interior of the IOL, just under the surface.[30]

The IOL mineralization experiments in our in vitro model confirmed that the process initiated from the interior, as contrasted with the surface of the IOL, which, in another case where there were disruptions on the surface calcification, might have started on the surface. Scanning electron microscopy examination of the IOLs exposed to the simulated aqueous humor solution in combination with energy-dispersive radiographic spectroscopy microanalysis, confirmed the presence of fewer than 100 nm of the thermodynamically most stable hydroxyapatite crystallites. The molar ratio of calcium to phosphorus calculated from the respective peaks was in good agreement with the value anticipated for hydroxyapatite.

Supersaturation of the aqueous humor with respect to hydroxyapatite is the thermodynamic driving force, sufficient but not necessary for the formation of the respective salt. The formations observed in our experimental setup, which simulated closely in vivo conditions, were found exclusively in the interior of the IOLs and at fronts advancing with time. It therefore may be suggested that the deposits front is the result of diffusion of Ca^{2+}, PO_4^{3-} and OH^- ions through the polymer. Assuming similar values for their diffusion coefficients in the gel (bulk polymer) material, the formation of linear deposits fronts may be explained. The accumulation of the hydroxyapatite lattice ions apparently proceeds until a critical supersaturation is reached. At this point, nuclei form and grow with the arrival of additional ions.

Although in the aqueous humor there is a temperature gradient of approximately 3 C, in our experimental model,

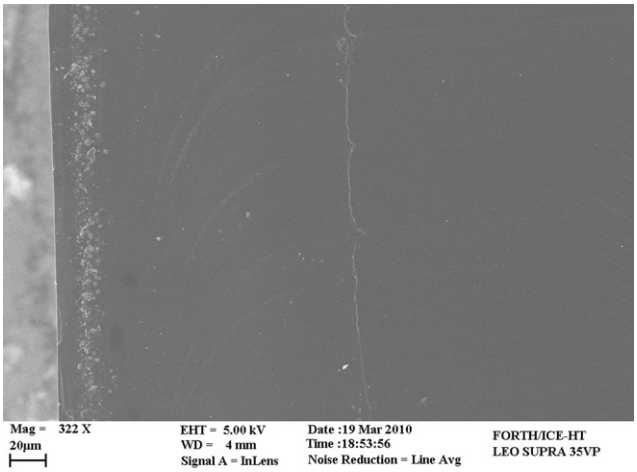

FIGURE 8. Scanning electron microscopy image showing intraoptical deposits distributed in a line parallel to the external optic surface separated by a clear zone just beneath the surface of an explanted calcified intraocular lens, similar with the pattern of our experimental model.

the temperature was kept constant at 37 C.[53] This fact does not affect the results or the supersaturation calculations, because within this relatively small temperature range (34 to 37 C), the solubility of calcium phosphates does not change more than 0.01%. Accordingly, a negligible effect is expected for the rates of growth of the mineral phase or to the mechanism underlying the formation of the supercritical nuclei. It also should be noted that a temperature gradient of 3 C in the aqueous humor is not expected to affect the diffusion coefficients of the aqueous species to more than 0.1%.

The pattern of calcification in our model was similar to that of the SC60B OUV model, where intraoptical deposits were distributed in a line parallel to the external optic surface separated by a clear zone just beneath the surface.[3] These findings also were confirmed after explantation and analysis of an calcified SC60B OUV IOL in our laboratory (Figure 8). IOL calcification is an ongoing process after IOL implantation, and the longer the process proceeds, the more the density of the deposits in the interior of the IOL increases. In all cases, the surface was free of deposits, and the distortions that were observed are thought to be the result of changes in the polymer structure in the IOL interior. The surface can be affected only in late phases of calcification and many years after IOL implantation. At this stage, crystals may outgrow, especially at places in which the polymer's surface has developed fissures.[14] This observation moreover is being confirmed in a total patient recall, 3 years after IOL implantation, where evidence of calcification was reported in 14.5% of the operated eyes, even if patients remained asymptomatic.[54]

The issue of the initiation of the calcification process (interior or surface) needs further investigation. Different studies suggest the phenomenon to be initiated on the IOL surface.[9,13] In our experiment, where low supersaturation and low flow rate conditions have been achieved, diffusion is being favored and calcification takes place in the interior. It should be noted, however, that special care was taken to preserve the surface of the IOLs intact, to avoid inducing surface nucleation of the mineral deposits.

In conclusion, late postoperative IOL opacification causes a severe loss of visual acuity. Because the calcification process seems to be initiated past an initial delay, it is important to be vigilant in the long-term follow-up of these patients. The progressively increasing specks may provide evidence for progressive nucleation and crystal growth of calcium phosphate nanocrystals to microcrystals. Many ophthalmologists are not aware of this clinical problem, and recognizing this phenomenon will help to prevent patients from undergoing useless procedures. IOL exchange is the only therapeutic approach in such patients, because patients with calcified IOLs have gradual deterioration of their visual acuity, and no case of spontaneous recovery has been observed.

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Biosketch

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