Comparison of in vivo dissolution processes in hydroxyapatite and silicon-substituted hydroxyapatite bioceramics

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Abstract

The incorporation of silicate into hydroxyapatite (HA) has been shown to significantly increase the rate of bone apposition to HA bioceramic implants. However, uncertainty remains about the mechanism by which silicate increases the in vivo bioactivity of HA. In this study, high-resolution transmission electron microscopy was used to observe dissolution from HA, 0.8 wt% Si-HA and 1.5 wt% Si-HA implants after 6 and 12 weeks in vivo. Our observations confirmed that defects, in particular those involving grain boundaries, were the starting point of dissolution in vivo. Dissolution was observed to follow the order 1.5 wt% Si-HA > 0.8 wt% Si-HA > pure HA and it was found to be particularly prevalent at grain boundaries and triple-junctions. These observations may help to explain the mechanism by which silicate ions increase the in vivo bioactivity of pure HA, and highlight the enhanced potential of these ceramics for biomedical applications.

Keywords: Silicon; Hydroxyapatite; Solubility; Bioactivity; Transmission electron microscopy (TEM)

1. Introduction

Hydroxyapatite, [Ca$_{10}$(PO$_4$)$_6$(OH)$_2$; HA], has achieved significant application as a bone graft material in a range of medical and dental applications. However, a disadvantage of using HA implants in comparison to bioactive glasses and glass ceramics is that its reactivity with existing bone is low [1] and the rate at which bone apposes and integrates with HA is relatively slow [2–4]. These properties could have implications for the time required for patient rehabilitation [5]. Bone mineral has a similar chemical composition to synthetic HA, but additionally, contains several ionic substitutions [6]. These substitutions induce complex structures at the unit-cell level and play a role in influencing the dissolution rate of apatites, which may favour osseointegration [3]. The effects of various ionic substitutions on the bioactivity of HA, have been the subject of in vitro [7] and in vivo studies [8,9].

A series of experiments by Carlisle, using electron probe microanalysis, reported the presence of silicon (~0.5 wt%) in vivo within the mineralising osteoid regions, i.e. the active calcification sites, of normal tibiae from young mice and rats [10], suggesting that silicon plays a critical role in the bone calcification process.

In vitro studies by Gibson et al. demonstrated that the substitution of silicate ions for phosphate ions into hydroxyapatite enhances osteoblast cell activity, compared to phase pure HA. Silicate ion substitution was also reported to enhance the formation of a poorly crystalline surface apatite layer on HA, incubated in simulated body fluid (SBF) [11]. Furthermore, an in vivo study by Patel et al., comparing the rates of bone apposition to HA and silicon-substituted HA (Si-HA) ceramic implants demonstrated bone apposition to be significantly greater at the surface of Si-HA implants [8]. Nevertheless, the mechanism by which silicate ions increase the in vitro and in vivo bioactivity of HA is still unresolved.

The study of in vivo dissolution is essential to improve our understanding of the processes leading to the enhanced bioactivity of these biomaterials. The commonly proposed mechanism underlying the phenomenon of the bioactivity of HA involves the dissolution of calcium and phosphate ions from the HA [12]. This

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process may occur through the surrounding environment (extracellular fluid) and may also be actively mediated by osteoclast cells [13]. Dissolution generates increased concentrations of calcium and inorganic phosphate in the spaces between the existing bone and the implant [14]. Precipitation of HA into this space will ensure incorporation of the implant into the existing bone. Any strategy to accelerate this process will make a significant improvement to the quality of life of the patient.

Several studies have demonstrated that the bioactivity of HA ceramics is dependant upon their microstructure and, in particular, on the relative number and type of defect structures present [15–18]. A previous study comparing dissolution of calcium and phosphate ions from HA ceramics and bone apatite showed that dissolution processes were initiated at dislocations and grain boundaries in vivo [17]. Wen et al. suggested that grain boundary structure has a predominant influence on the dissolution behaviour of biological apatites [19]. Furthermore, it has been suggested that incoherent grain boundaries, without lattice continuity, could be more sensitive to dissolution than semi-coherent grain boundaries with some lattice continuity [20]. In the present study, we used high-resolution transmission electron microscopy (HR-TEM) to compare dissolution, particularly at defect structures, in phase pure HA and Si-HA of two different compositions. The impetus for this study was based on findings in a previous study comparing the ultrastructure of HA and Si-HA which suggested that the substitution of silicate ions into the HA lattice increases the number of defect structures [15].

When preparing sections containing the bone-HA interface for TEM, it is essential that the sample preparation procedure does not alter the elemental composition of the bone nor that of the HA. Procedures using aqueous solutions for dehydrating and embedding bone in preparation for ultramicrotomy can alter the crystalline phase [21,22] of HA. In this study, samples containing the bone-HA interface were fixed and dehydrated in anhydrous ethylene glycol and ethanol, and TEM sections were sectioned onto deionised water at pH 7.3 on the trough of a diamond knife. The sections were retrieved either immediately or after various intervals of time to model dissolution. Dissolution of HA in vivo was then compared to dissolution in water. Imaging at 300 kV with the TEM minimised beam damage to the crystals and maximised the resolution from the moderately thick sections.

The main objective of this study was to use HR-TEM to compare dissolution of HA and Si-HA granules in vivo. We hypothesise that the incorporation of silicate ions into HA increases its bioreactivity by increasing the number of defect structures. The defect structures are the specific sites within the HA-ceramic that are most vulnerable to dissolution. Therefore, by increasing the number of defect structures the solubility of the HA ceramic in a biological environment is increased, as is its rate of osseointegration.

2. Materials and methods

2.1. Chemical synthesis

Phase pure HA with a Ca/P molar ratio of 1.67 was prepared by a precipitation reaction between calcium hydroxide, [Ca(OH)$_2$], and orthophosphoric acid, [H$_3$PO$_4$] solution, according to the methods described elsewhere [23]. Si-HAs (0.8 and 1.5 wt%) were also prepared by acid–base neutralisation reactions, but in addition to calcium hydroxide and orthophosphoric acid, silicon acetate was incorporated into the reaction mixture as a source of silicate ions. Quantities of reactants were calculated by assuming that silicate would substitute for phosphate in the HA lattice [24]. Therefore, the number of moles of H$_3$PO$_4$ in phase pure HA was the same as the number of moles of (H$_3$PO$_4$ + silicon acetate) for the Si-HA samples, with the number of moles of Ca(OH)$_2$ kept constant. Precipitation reactions were carried out at room temperature and the pH was maintained at 10.5 by the addition of ammonium hydroxide solution. After complete mixing of the reactants, the suspensions were aged overnight. The resulting precipitates were filtered, washed and dried at 80°C overnight.

2.2. Sample preparation

HA and Si-HA were prepared both as powders to compare dissolution in water and as granules to compare dissolution in vivo.

2.3. Preparation of HA and Si-HA powders

Aged, filtered and dried precipitates of pure HA and 1.5 wt% Si-HA were ground into a fine powder. The powder was subsequently ball milled, using a porcelain mill pot with alumina milling balls, for 1 h. The powder was then removed from the mill pot and passed through a series of sieves; as a result of this process, the maximum particle size of the final powder that was used in this study was less than 75 μm.

2.4. Preparation of HA and Si-HA granules

HA and Si-HA filter cakes were processed into granules (1–2 mm) by partial grinding and mechanical sieving.
2.5. Sintering and characterisation of HA and Si-HA granules and powders

After preparation, powders and granules of HA and Si-HA were sintered at 1200°C for 120 min using a ramp rate of 2.5°C/min.

The phase composition of the sintered powders and granules for all HA and Si-HA samples were assessed by X-ray diffraction using a Phillips D500 diffractometer with CuKα radiation. Data was collected over the 2θ range 25–40° with a step size of 0.02° and a count time of 2.5 s. Identification of the phases was achieved by comparing the diffraction patterns of HA and Si-HA with ICDD (JCPDS) standards [25]. The Ca/P molar ratios of HA and Si-HA were calculated from X-ray fluorescence (XRF) spectroscopy results.

The bulk density of sintered HA and Si-HA granules were assessed using a Micromeretics Accupyc pycnometer.

2.6. Embedding of the HA and Si-HA powders

Powders of HA and Si-HA were treated with three changes of 100% ethanol and three of propylene oxide over an hour, and then infiltrated with Spurr’s resin (Agar Scientific, Essex, UK) over several days: Spurr’s resin was prepared with 10 g epoxy monomer vinyl cyclohexene dioxide (ERL), 4.5 g diglycidyl ether of polypropylene glycol (DER-736), 26 g nonenyl succinic anhydride (NSA), and 0.7 g benzylidimethylamine (BDMA). The samples were agitated at room temperature in 1:1 solutions of propylene oxide and Spurr’s resin for 2 days, 1:3 propylene oxide:Spurr’s for 1 day, then 100% Spurr’s for 2 weeks under vacuum. The Spurr’s resin was changed every 24 h. Samples were then cured in fresh Spurr’s resin for 23 h at 60°C. Pre-casting a ~200 μm layer of Spurr’s resin into the truncated beam capsules before adding the HA granules facilitated sectioning of the blocks.

2.7. Scanning electron microscopy of the HA and Si-HA granules

Sintered HA and Si-HA granules were dispersed onto the surface of aluminium stubs and subsequently sputter coated with 10 nm of gold. Scanning electron microscopy (SEM) in secondary electron mode was performed in a Philips XL30 FEG operated at 5 kV, using a 30 μm thin foil final aperture.

2.8. Surgical procedure and tissue processing

The guidelines for the care and use of laboratory animals [Animals (Scientific Procedures) Act 1986] were observed throughout implantation procedures. Sintered granules of HA, 0.8 wt% Si-HA and 1.5 wt% Si-HA were implanted into 2–3 year old Texcel X Continental sheep weighing between 70 and 80 kg. The implants were placed bilaterally into the femoral condyle. This site was selected as it presented a large volume of load bearing cancellous bone within the animal. An incision was made adjacent to the femoral condyle, and the soft tissue was dissected to reveal the bone. A defect 0.9 cm in diameter and 0.9 cm in depth was drilled into the bone and washed with sterile saline solution. The defect was then filled with the granular implant material, and the subcutaneous tissues and skin were sutured to encapsulate the granules. After the operation, the animals were placed in pens in groups of 3–4 and were allowed full use of their legs. Implant compositions were studied at time points of 6 and 12 weeks.

Following sacrifice, segments containing the bone–HA interface were sawed and trimmed to a size that could be embedded. The specimens were fixed in anhydrous ethylene glycol for 24 h from the time of trimming and were rinsed in 100% ethanol twice for 5 min. Sections were embedded using the same procedure described previously for embedding of HA powders.

2.9. Preparation for transmission electron microscopy

Pure HA and 1.5 wt% Si-HA powders were also dispersed in ethanol, sonicated, and collected on lacey carbon 300 mesh copper grids.

Sections (90 nm) of HA and 1.5 wt% Si-HA powders were cut onto a water bath using a Leica Ultracut E and collected immediately, 1, 5 and 30 min post-sectioning. The deionised water in the bath had a pH of 7.3 and a resistivity of >15 mΩ/cm.

Silver to gold sections (70–90 nm) containing the bone–HA interface, were similarly cut onto distilled water with an ultramicrotome using a 45° diamond knife. Sections were collected immediately on lacy carbon 300 mesh copper grids, and dried for an hour at 37°C.

2.10. Transmission electron microscopy

TEM and selected area electron diffraction (SAED) were performed in a Phillips CM30 operated at 300 kV. Zero-loss, energy filtered TEM (EFTEM) was performed on a Phillips CM300 operated at 300 kV. Diffraction contrast was employed for bright-field imaging. Montages of all bone–HA interfaces at 6 and 12 weeks in vivo were mapped out from these images, to facilitate the location of regions for higher resolution imaging.
3. Results

3.1. Materials characterisation

XRF analysis of HA showed the calcium/phosphorus (Ca/P) molar ratio to be 1.67, which is equivalent to stoichiometric HA. The Ca/P molar ratios of 0.8 wt% Si-HA (1.76) and 1.5 wt% Si-HA (1.85) were significantly higher than that of stoichiometric HA.

XRD measurements for HA powders indicate that the sintered HA, 0.8 and 1.5 wt% Si-HA were phase pure, with no additional phases present (Fig. 1(a–c)).

Sintered granules of HA and Si-HA exhibited densities of approximately 96–97% of the theoretical maximum of 3.156 g/cm³. SEM images indicate that the morphology of the granules were similar, irrespective of chemical composition. A representative image of the pure HA and Si-HA granules is illustrated in Fig. 2.

3.2. In vitro transmission electron microscopy observations

SAED of the crystallites confirmed that they were HA. Dissolution was defined as a reduction of contrast and loss of lattice fringes from the crystals. These changes occur at sites of dissolution because these sites contain less mineral per unit volume of section and therefore experience less electron scattering with mass-thickness contrast accordingly reduced. Observations suggested a loss of material in the region of dissolution that is unrelated to beam damage, as adjacent regions of HA did not show a similar loss of contrast after irradiation with the electron beam at 300 kV.

3.3. Effect of dispersing powders in ethanol

Dispersion of the pure HA and 1.5 wt% Si-HA powders in ethanol revealed smooth, discrete edges with no loss of mineral at the sub-grain boundaries or triple-junctions. An example of a representative crystallite of pure HA is illustrated in Fig. 3. Similar features were observed in the 1.5 wt% Si-HA.

3.4. Effect of sectioning powders onto water

When the powder was sectioned onto water and allowed to sit for periods of up to 1 min, there was no obvious disruption to the ultrastructure of the pure HA and 1.5 wt% Si-HA (Fig. 4a and b). There was also no observed loss of mineral at triple junctions and their associated sub-grain boundaries in the crystallites of the Si-HA. Comparison of Figs. 3 and 4a suggests that sectioning with the diamond knife induced fracture of the crystallites along grain boundaries aligned parallel to
the long axis of the crystallites. However, after periods of 5 or 30 min in contact with water, the edges of some of the pure HA crystallites appeared scalloped (Fig. 4c) and a loss of mineral was observed at several of the triple-junctions in Si-HA. This degradation was more extensive after 30 min (Fig. 4d). SAED of the individual grains showed that there was no loss of symmetry or intensity of the spots at any of the time points.

3.5. In vivo dissolution of HA, 0.8 wt% Si-HA and 1.5 wt% Si-HA

Several general observations were made from analysing montages of the HA–bone interface from at least two sections from each sample. These results were compared to results from a previous study in which the ultrastructure of the bulk HA and Si-HA were characterised using HR-TEM [2].

Fig. 5 illustrates an example of a montage through the bone into the depth of the implanted 1.5 wt% Si-HA ceramic at 12 weeks post-implantation. A greater depth of dissolution was observed at the surface of the 1.5 wt% Si-HA grains within the implant when compared to HA samples at both time points in vivo. As indicated in Fig. 6a and b, dissolution of the HA and Si-HA grains was not observed at the interface (I) of any of the ceramics, after 6 or 12 weeks of implantation, although extensive dissolution was observed within the bulk of the implant (B) (Fig. 6b).

3.6. Pure HA

No signs of dissolution were observed on the surfaces of the HA crystallites at 6 weeks in vivo, with grains appearing uniformly dense without loss of material. These images were similar to the images of Si-HA illustrated in Fig. 4a. After 12 weeks in vivo, many voids were observed on the surface of crystallites (Fig. 7a and b). The contrast of these voids suggested that they were related to a loss of material, which could be associated with early stages of dissolution from the HA ceramic. An investigation was carried out to assess whether these voids could be related to beam damage. It was found that voids were not generated after the same dose of irradiation at 300 kV for samples that had not been implanted. This strongly suggests that these voids were related to dissolution and not to beam damage. Furthermore, these voids were particularly prevalent in grains containing several dislocations.

3.7. 0.8 wt% Si-HA

After 6 and 12 weeks in vivo, extensive dissolution of the 0.8 wt% Si-HA grains had occurred (Fig. 8a and b). Needle-like apatite crystallites appeared to emanate from the surface of the Si-HA grain, and appeared to be connected to the Si-HA grains by an interfacial region with a mottled appearance (indicated by a black arrow). A notable observation was the presence of grain boundary dissolution in some of the crystallites at 12 weeks in vivo (Fig. 8c).
3.8. 1.5 wt% Si-HA

After 6 weeks in vivo, more observations of dissolution for the 1.5 wt% Si-HA crystallites were seen compared to HA or 0.8 wt% Si-HA implants (Fig. 9a). In some regions, dissolution appeared to connect the grains together, with dissolution appearing to extend along the long-axis of the crystallites (SAED confirmed this to be the c-axis). Furthermore, fewer grain boundaries and triple-junctions were observed on the 1.5 wt% Si-HA crystallites after 6 weeks in vivo when compared to non-implanted samples that had been sectioned on water for 10 s to 1 min. After 12 weeks in vivo, needle-like crystallites were observed to emanate from the surface of many of the Si-HA crystallites, indicating that extensive dissolution had occurred (Fig. 9b). A more extensive mottled effect was observed on the surface of the 1.5 wt% Si-HA samples than on the 0.8 wt% Si-HA, localised between the needle-like crystallites and the dissolving grains (Fig. 9b). Lattice imaging showed these fringes to extend from the surface of Si-HA grains to the needle-like crystallites. SAED of the dissolving Si-HA reflected the larger size of the microcrystals. Fig. 9c illustrates that dissolution occurred predominantly at the smallest grain at triple junctions. Furthermore, energy-filtered, high resolution imaging of dissolving grain boundaries revealed a loss of material at these grain boundaries (Fig. 9d).
4. Discussion

4.1. TEM sample preparation of the bone–HA interface

It is essential in TEM imaging that the sample preparation procedure creates as little damage to the sample ultrastructure as possible. The standard technique for preparing biological TEM samples containing the bone-HA interface is by ultramicrotomy, i.e. sectioning ultrathin (70–90 nm) sections with a diamond knife and collecting them in a water trough. There has been some debate as to whether or not HA dissolves in water. A study by Landis et al. suggested that it is essential that the sample preparation technique remains totally anhydrous at all stages [22]. Nevertheless, it is very difficult to cut dry sections of the bone–HA interface that are of suitable thickness to image at high resolution. Furthermore, an in vitro dissolution experiment by Lin et al. showed negligible dissolution of phase pure HA after soaking in distilled water at 37°C for 30 days [26]. In this study, we observed minimum alteration to the ultrastructure of HA if powders were sectioned onto water and collected after time periods of no longer than 1 min. Powders, and not granules, were used for the in vitro study since it is very difficult to section dense granules with a diamond knife. Comparison of the ultrastructure of specimens of HA and Si-HA implanted in vivo, sectioned and floated on water for 30 min, demonstrated differences in morphology in the dissolving region. Needle-like crystallites were observed at the “dissolution front” in vivo, whereas, although there was also a notable loss of mineral at the grain boundaries on the samples sectioned onto water, the needle-like crystallites were absent. These results are significant, as it is very difficult to cut thin (<100 nm) TEM sections with a dry knife that will contain sufficient interface to image.

4.2. Role of silicate ions in increasing the dissolution rate of Si-HA in vivo

In our current study, dissolution was observed to follow the order 1.5 wt% Si-HA > 0.8 wt% Si-HA > pure HA, suggesting that silicate ions increase the solubility of HA. If bioactivity does follow the proposed dissolution–reprecipitation mechanism, the combination of these current findings with those of a recent study by Patel et al. [8] suggests that the increased solubility of Si-HA increases the rate of bone apposition to these bioeramics. These findings highlight the significance of dissolution of HA to the in vivo bioactivity of Ca–P biomaterials.
4.3. Role of defects in increasing the bioactivity of Si-HA in vivo

In a previous HR-TEM study, we characterised dislocations (edge, screw and mixed), grain boundaries and triple-junctions in HA and Si-HA [15]. This study illustrated more triple-junctions and sub-grain boundaries in Si-HA samples compared to pure HA. It was proposed that the increased number of defect structures, in particular triple-junctions, in Si-HA compared to HA might be a possible mechanism by which silicate ions increase the rate of bone apposition to HA ceramic implants. In our current study, dissolution was clearly observed to initiate preferentially at grain boundaries and triple-junctions. Hence, our study confirms that an increase in the number of defects in Si-HA may play a key role in increasing the rate of in vivo dissolution.

HR-TEM studies on biological and synthetic apatites have all highlighted the role of defects to in vivo dissolution [17]. But none of these studies have given any significance to the prominence or the role of different defect types. For the higher 1.5 wt% Si-HA, loss of material from grain boundaries and surfaces was the predominant mechanism by which dissolution occurred. In contrast, grain boundary dissolution was not observed for phase pure HA. Instead, the presence of voids in grains of phase pure HA containing dislocations at 12 weeks post-implantation suggests that dissolution from dislocations may be the major initiation sites for dissolution. These observations on the dissolution of HA and Si-HA thus indicate further that there is a difference in grain boundary structure between pure HA and Si-HA.

This study has demonstrated the important role of defects in in vivo dissolution. Nevertheless, it is well established that there are several other mechanisms by which in vivo dissolution occurs [27,28]. In particular, differences in crystal size give rise to differences in dissolution rate and may affect subsequent cellular responses [27]. Observations demonstrating the dissolution of the smallest grains of triple-junctions suggests that decrease in grain size increases the solubility of the material. Furthermore, recent scanning electron microscopy (SEM) results from our group showed a significant decrease in grain size in Si-HA compared to pure HA [29]. If the incorporation of silicate ions decreases the grain size of HA, this could present another potential mechanism by which silicate ions increase the in vivo bioactivity of HA.

4.4. Comparison of dissolution of HA at the bone–HA interface and on the surface of HA grains in the bulk of the implant

The precipitation of biological apatite on the surface of HA ceramics in vivo and in vitro has been extensively reported [17,30–35]. An important finding in this study was the observation of larger, needle-like crystallites on the surface of the 1.5 wt% Si-HA in the deeper regions of the implant when compared to the smaller plate-like apatite crystallites at the bone–HA interface. This difference suggests that these two ultrastructural characteristics arise as a result of two different biological processes. The progression through lattice fringes to the needle-like crystallites at grain surfaces implies that the needle-like crystallites are generated by a loss of material from the grains of Si-HA and not due to the heterogeneous nucleation of biological apatite. Specifically, this suggests that structural variations arise from a “dissolution front” advancing perpendicular to the
surface of the HA grains. The dissolution front could be the result of dissolution extending from the surface of the grains along dislocation lines [36], for example at low angle grain boundaries, composed of a wall of edge dislocations. The fact that dissolution from the surface of the crystallites was observed within the implant, and not at the interface between the bone and the HA, highlights the difference in biological milieu of the crystallites within the implant as opposed to that at the bone–HA interface. At the implant–bone interface, the ceramic material is in contact with a variety of biological materials, including proteins, which adsorb onto and coat the surface of the ceramic particles [37]. The observed differences in ultrastructure suggest that adsorbed proteins may prevent degradation of sintered crystals, which is normally required for the formation of new phases via solution-mediated physicochemical reactions [37]. The biological environment of the crystallites in the implant is more analogous to that of an acellular in vitro medium. Hence, it is not surprising that similar ultrastructural features such as the dissolution front are observed in the implant and in vitro [35]. The precipitation of smaller, plate-like biological apatite crystallites, closely associated with the surface of the

Fig. 7. (a) TEM micrograph of grains of pure HA within the implant at 12 weeks in vivo. Black arrows show dislocations and electrolucent spots possibly related to dissolution. (b) Higher magnification TEM lattice image of grains of pure HA within the implant, 12 weeks post-implantation. Black arrows show voids possibly related to dissolution.
HA, suggests that a biologically mediated mechanism of mineralisation may be involved in the formation of these phases.

4.5. Comparison of dissolution of HA in water and in vivo

In vivo observations suggested that dissolution initiates at grain boundaries and at the surfaces of grains in the Si-HA. Nevertheless, after 6 and 12 weeks in vivo extensive dissolution had already occurred and so it was difficult to confirm whether dissolution had proceeded at grain boundaries or at the surface of the grains. After floating sections on a water bath for 30 min, there was a preferential loss of mineral at grain boundaries, particularly at triple-junctions and their associated sub-grain boundaries. Although the in vitro environment does not directly model the biological milieu in vivo, comparison of these results does suggest that they have similar features. There was a loss of mineral at grain boundaries both in vivo and in vitro. This in vitro model may therefore provide further evidence for our proposed dissolution model for Si-HA in vivo.

5. Conclusions

This study highlighted the role of defects in the in vivo dissolution of HA and Si-HA ceramic implants. Defect type was also observed to play a significant role in influencing the rate of in vivo dissolution. Furthermore, dissolution in the bulk regions of an implant followed the same order as the percentage bone apposition at the ceramic surface, i.e. 1.5 wt% Si-HA > 0.8 wt%
Si-HA > pure HA. We propose that the incorporation of silicate ions into HA leads to an increased rate of dissolution of Si-HA. The Ca, P and Si ions subsequently diffuse through the ceramic grains to the bone–HA interface, driven by a concentration gradient. The increased concentration of Ca, P and Si ions at the HA–ceramic interface accelerated the precipitation of biological apatite and induced bone apposition at the surface of the ceramic. These observations may explain the mechanism by which silicate ions increase the in vivo bioactivity of HA, and highlight the enhanced potential of Si-HA ceramics for biomedical applications.

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