Bonding behavior of ultrahigh strength unsintered hydroxyapatite particles/poly(L-lactide) composites to surface of tibial cortex in rabbits

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Abstract: Unsintered hydroxyapatite particles/poly(L-lactide) (u-HA/PLLA) composites with an initial bending strength of up to 270 MPa were developed based on the hypothesis that inclusion of u-HA particles in a PLLA matrix might enhance bone bonding. The purpose of this study was to examine the bonding strength and behavior of these u-HA/PLLA composites on the surface of the bone cortex. Composites containing 30 (u-HA30), 40 (u-HA40), or 50 wt % (u-HA50) of fine u-HA particles (3-μm average particle size) were prepared. Semicolumnar plates of these composites and control PLLA plates were fixed with metal screws to the surface of both proximal tibial cortices in 45 rabbits. The loads required to detach the plates from the bone cortex surface, defined as the bonding strengths, were measured at 4, 8, and 25 weeks after implantation. Bonding strengths in the u-HA30 group at 8 weeks and in the u-HA40 and u-HA50 groups at each postimplantation time were significantly greater than in the PLLA group (*post hoc* test using Fisher's protected least significant difference method). At each postimplantation time histological examinations revealed direct contact between the bone and the u-HA/PLLA composite plates without any intervening fibrous tissue. There was no evidence of any inflammatory or foreign-body response in any group throughout the follow-up periods. The results of this study suggest that the biodegradable PLLA fixation plates amended with u-HA particles could be functionally superior to PLLA plates without particles. J Biomed Mater Res, 47, 412–419, 1999.

Key words: poly(L-lactide); hydroxyapatite; composite; bonding strength; bone cortex

INTRODUCTION

The treatment of long bone fractures frequently involves surgical intervention to fix osteosynthetic metal plates. Because there is a large difference in mechanical strength between bone and a metal plate,[1] the porosity of the bone beneath the plate increases due to stress protection.[2,3] Additional disadvantages of using a metal plate include the need for a second operation to remove the plate and the problem of metal corrosion.

Recently, resorbable materials that retain good mechanical properties during the healing period were investigated for the treatment of fractured bones.[4–8] A Finnish group reported successful resorbable fixation by polyglycolide (PGA) rods in human ankle fractures.[9–12] We examined high-strength poly(L-lactide) (PLLA) screws[13,14] that were applied clinically.[15] Tissue reactions to PLLA are described by several authors.[16–19] Some authors reported a nonspecific foreign-body reaction to the degraded PLLA material,[16] while other authors reported the absence of any inflammatory foreign-body reaction.[17,18]

Osteosynthetic plates made from resorbable materials were also investigated. Unfortunately, there are few successful reports on the fixation of long bone fractures using resorbable plates in high load-bearing situations, because of their poor mechanical strength.[19] We previously reported that in rabbits the union rate of femoral shaft transverse osteotomies fixed with PLLA plates with an initial bending strength of about 240 MPa was 67%, whereas the union rate of those fixed with stainless steel plates was 80%.[20] In that report we strongly suggested that for stress shielding PLLA plates were ideal for restoring

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the mechanical strength and density of the united bone; however, the stress concentration around the screw holes of the PLLA plates resulted in a 14% rate of plate failure.[20] Therefore, we concluded that bioresorbable osteosynthetic plates require greater initial mechanical strength in order to reduce plate failure.

Hydroxyapatite (HA) is the crystalline portion of natural bone mineral. Synthetic HA has the ability to become chemically bonded to bone via natural-appearing bone cementing mechanisms.[21–25] A major disadvantage is that synthetic HA is brittle and has insufficient strength for use in weight-bearing situations. Because ceramics are highly rigid but too brittle and polymers are flexible but not strong enough to meet the mechanical demands for an internal fixation device, composites of polymers and inorganic materials may offer the desired compromise in both stiffness and ductility. Attention was recently paid to the application of HA in combination with polymeric substances. Polyethylene, polybutyrate, and PLLA are the most frequently used polymers in such composites.[26–29] We developed a new resorbable osteosynthetic implant, a reinforced composite of sintered HA (s-HA) and PLLA, that has the highest mechanical strength to date of any reinforced bioactive ceramic fiber or particle/polymer composite implants.[30] The bending strength of this new composite reached 280 MPa. Furthermore, we reported that HA crystals deposited and grew on the surface of this material at 3–6 days after immersion in simulated body fluid, suggesting that this material had the ability to bond directly to bone.[30]

Unsintered HA (u-HA) and α- or β-tricalcium phosphate are classified as bioresorbable bioceramics, while s-HA is classified as a surface bioactive group.[31] We also developed an u-HA/PLLA composite, which possesses an initial bending strength of about 270 MPa.[32] We hypothesized that the inclusion of u-HA particles in the PLLA matrices would enhance bone bonding. The purpose of this study was to examine the bonding strength and behavior of this ultrahigh-strength u-HA/PLLA composite on the surface of the tibial cortex in rabbits for up to 25 weeks.

MATERIALS AND METHODS

Preparation of materials

To synthesize u-HA[33] by hydrolysis, an aqueous solution of pure calcium hydrogen phosphate and calcium carbonate was heated at 90°C, matured for 5 h, and fully dried for 10 h after filtering. The equation for the chemical reaction is

$$6CaHPO_4 + 4CaCO_3 \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 4CO_2 + 2H_2O$$

The clusters, ranging in size from 5 to 50 μm, were aggregates of microhexagonal crystals with an aspect ratio of about 4–10 (2–3 μm length/0.3–0.5 μm width). The clusters were milled and sieved off, and the resulting particle size ranged from 0.3 to 20 μm and had a mean of 3 μm. The molar ratio of 1.69 of Ca/P was very close to that of pure HA, which is 1.67.

The u-HA was identified as apatite containing carbonate (CO_3^{2-}) and having particles with medium crystallinity using Fourier transform IR absorption spectra (FTIR) and X-ray diffraction, respectively.

The PLLA was polymerized as described previously.[34] The viscosity-average molecular weight ($\overline{M}_v$) of the PLLA powder was 400 kDa before blending with the u-HA particles. The PLLA powder was purified several times by precipitation from a polymer/dichloromethane solution using ethanol by dropping the ethanol in small amounts into the solution.

Preparation of composites and implants

The small granules of uniformly distributed u-HA microparticles within a PLLA matrix were collected by precipitation from a polymer solution using ethanol as described for purifying the PLLA powder. The granules were extruded to make thick billets that were then molded into thin billets by a new process for compression molding at 103°C. The composites contained 30, 40, and 50% by weight of u-HA particles, which we termed u-HA30, u-HA40, and u-HA50, respectively. The bending strengths (S_b) and the bending moduli (E_b) of 3.2-mm diameter rods made of these composites were measured in accordance with Japanese Industrial Standard methods (Table I). The molded billets were cut into semicolumnar 4 × 10 × 8 mm plates with a 2-mm diameter hole in the center [Fig. 1(a)]. The flat bases of the plates were 70 mm^2 [Fig. 1(b)]. PLLA-only plates produced by the same process were used as the control group. Their surfaces were roughened with #100 sandpaper to increase their surface area, and they were cleaned with ethanol in an ultrasonic cleaner for 20 min.

All the implants used in this study were sterilized with ethylene oxide (EOG 20 wt %, CO_2 80 wt %) at 45°C for 5 h with 50% H_2O. The remaining gas was removed by aeration at 45°C until the gas could no longer be detected by gas chromatography.

Animal operation

Maintenance of the rabbits and the animal experiments were conducted at the Institute of Laboratory Animals, Kyo-

TABLE I
Initial Bending Strengths and Moduli of u-HA/PLLA Composites

	u-HA/PLLA (wt ratio)	u-HA/PLLA (vol ratio)	$\overline{M}_v$ (kDa)	S_b (MPa)	E_b (GPa)
u-HA30	30/70	17/83	210	269	7.6
u-HA40	40/60	24/76	208	270	9.1
u-HA50	50/50	32/68	202	268	12.3

Viscosity average molecular weight, $\overline{M}_v$, bending strength, S_b; bending modulus, E_b. The u-HA30, u-HA40, and u-HA50 u-HA/PLLA composites have 30, 40, and 50 wt % u-HA particles, respectively.

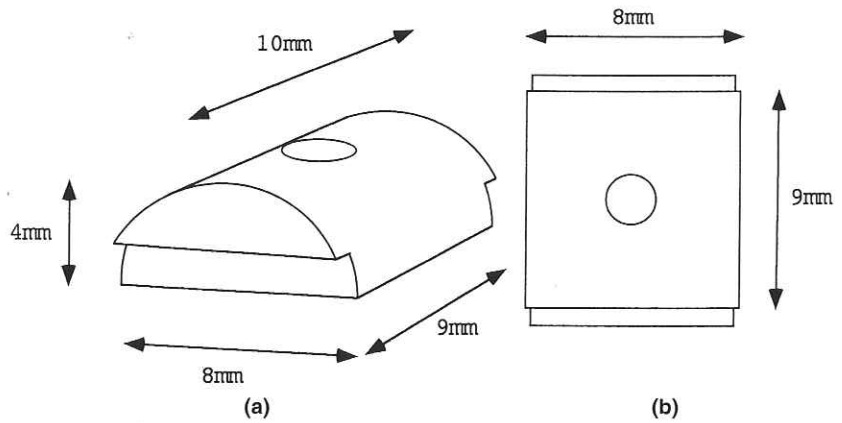


Figure 1. Preparation of implants. (a) Diagram of an implant and (b) the base of an implant.

to University. In the present study 45 mature male Japanese rabbits, which weighed 3.0–3.5 kg were used. The rabbits were anesthetized with an intravenous injection of 0.5 mL/kg Nembutal (Abbott, North Chicago, IL). The operations were performed under aseptic conditions. A 2 cm long skin incision was made on the anteromedial aspect of the proximal tibial metaphyses of each rabbit, and a 10 × 10 mm area of the tibial cortices were exposed subperiosteally; 1.8-mm diameter holes were drilled at the center of the exposed cortices. AO screws (2.0-mm diameter, 16.0-mm length; OR-211, ASIF, Davos, Switzerland) were driven into the drilled holes at a torque of 1.5 kg · f · cm using a Kanon 5 DPSK torque driver [Nakamura Mfg. Co., Ltd., Nagoya, Japan; Fig. 2(a)]. The wounds were cleansed with sterile saline solution during the operation and then closed in layers.

Plates of u-HA30, u-HA40,and u-HA50 were implanted on the surface of the bilateral tibial cortices of 12 rabbits each. Plates of PLLA were implanted in the same fashion in nine rabbits. NIH Guidelines for the Care and Use of Laboratory Animals were observed. The rabbits were housed in a temperature- and humidity-controlled room with a 12-h light cycle. Food and water were given freely. No rabbits died during the follow-up period. Four rabbits from each of the u-HA/PLLA composite groups and three rabbits from the PLLA group were sacrificed with lethal doses of Nembutal at 4, 8, and 25 weeks after implantation and samples containing the implants were excised.

At each follow-up time five samples from the PLLA group and six samples from each u-HA/PLLA composite group were subjected to the detachment test immediately after sacrifice to evaluate the bonding strength of the bone-implant interface (Table II). At each follow-up time a sample from the PLLA group and two samples from each u-HA/PLLA composite group were prepared for histological examination (Table II).

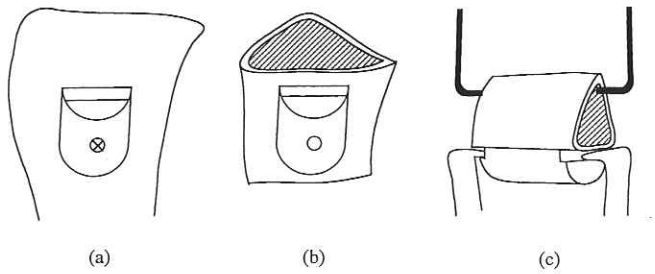


Figure 2. Method used to test implant bonding strength. (a) Fixation of the implant to bone cortex with a screw, (b) excision of the tibia with implant, and (c) measuring bonding strength.

Evaluation of bonding strength

The samples were cut transversely at 3 mm proximal and distal to the implant. The bone tissue covering the margin of each implant was removed completely so the implant was in contact with the bone only at its base. The screws were gently removed [Fig. 2(b)].

The implant–bone samples were connected with hooks to an Instron-type tensile load tester [Autography S-500, Shimazu Seisakusho Ltd., Kyoto, Japan; Fig. 2(c)]. The implants were pulled perpendicularly to the base of their contact with the bone cortex at a crosshead speed of 3.5 cm/min. The loads required to detach the implants from the bone, defined as the bonding strengths, were expressed as mean ± 1 standard deviation. Possible differences between the 12 groups were investigated in a *post hoc* test using Fisher's protected least significant difference (Fisher's PLSD; Stat

TABLE II
Numbers of Samples Subjected to Mechanical and Histological Evaluation

Implant	4 Weeks	8 Weeks	25 Weeks
	Mechanical Evaluation		
PLLA	5	5	5
u-HA30	6	6	6
u-HA40	6	6	6
u-HA50	6	6	6
	Histological Evaluation		
PLLA	1	1	1
u-HA30	2	2	2
u-HA40	2	2	2
u-HA50	2	2	2

View, Version 4.5, Abacus Concepts, Inc., CA). Differences at $p < 0.05$ were considered to be statistically significant.

Histological evaluation

Samples for histological examination were fixed in 10% phosphate-buffered formalin for 3 days, dehydrated with a graded ethanol series [70, 80, 90, 99, and 100% (v/v)], soaked with styrene to remove the ethanol, and then embedded in polyester resin.

Each resin block was sectioned perpendicular to the longitudinal axis of the bone with a diamond band saw (EXAKT cutting system, Germany). Three 500-μm thick cross-sectional slices were taken from each block (proximal to the screw hole) at the screw hole and distal to the screw hole. Therefore, at each postimplantation period, six and three slices were examined from the u-HA/PLLA composite groups and the PLLA group, respectively. The slices were polished and the bone–implant interface was examined using a scanning electron microscope (SEM, Hitachi S-2460N, Japan) connected to an electron probe microanalyzer (EPMA, Horiba EMAX, Japan) system. The slices were ground with a speed lap (Marto Ltd., Tokyo) to a thickness of 150 μm for contact microradiography and to a thickness of 80 μm for Giemsa surface staining. The slices were then examined using light microscopy. Direct contact was defined as contact between the bone and implant over a distance greater than 100 μm in a slice.

RESULTS

None of the implants broke during the bonding strength tests. Table III and Figure 3 show the bonding strengths between the implants and the surfaces of the bone cortices. Significant differences between the implants at each postimplantation period were determined using Fisher's PLSD and are also listed in Table III.

The bonding strengths of the PLLA, u-HA30, and u-HA40 groups increased with time and reached maximum values of 0.93 ± 0.60, 2.19 ± 1.15, and 3.49 ± 1.27 kg/cm^2, respectively, at 25 weeks after implantation. In the u-HA30 group the bonding strength at 8 weeks was significantly greater than that at 4 weeks ($p = 0.0445$). In the u-HA50 group the bonding strength at 8 weeks was significantly greater than that at 4 weeks ($p = 0.0005$) and reached a maximum value of 4.32 ± 1.87 kg/cm^2. However, by 25 weeks the bonding strength had decreased significantly compared with that at 8 weeks ($p = 0.0227$). There were no other statistically significant differences between the temporal partitions for any of the implants. The bonding strength in the u-HA30 group was greater than that in the PLLA group at each postimplantation time; however, the differences among these groups were statistically significant only at 8 weeks (Table III). The bonding strengths in the u-HA40 and u-HA50 groups were significantly greater than that in the PLLA group at each postimplantation time (Table III).

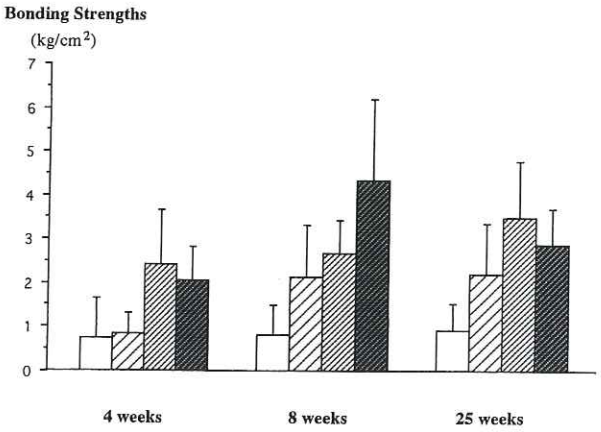


Figure 3. Bonding strengths at the bone–implant interface. (□) PLLA, (▨) u-HA30, (▨) u-HA40, and (▨) u-HA50. For all PLLA data points, $n = 5$; for all u-HA/PLLA composite points, $n = 6$.

Contact microradiographs showed direct contact between the bone and the plate in all u-HA/PLLA composite groups at each postimplantation time (Fig. 4). Contact microradiographs for the PLLA group yielded no information regarding the bone–implant interface because PLLA is radiolucent.

No direct contact between the bone and the PLLA plate was observed at any postimplantation time using Giemsa surface staining [Fig. 5(a)]. In contrast, direct contact between the bone and the plate was observed in all u-HA/PLLA composite groups at each postimplantation time using this method [Fig. 5(b–e)]. Tissue responses to the implants showed the same pattern in all the u-HA/PLLA composite groups. Bony tissue had grown on the surface of the implant at 4 weeks [Fig. 5(c)]. By 8 weeks this newly formed bony tissue had spread over the surface of the implant and the fibrous layer had diminished [Fig. 5(d)]. Direct contact was maintained at the bone–implant interface, and remodeling of the cortical bone was observed at

TABLE III
Average Interfacial Bonding Strength (kg/cm^2) ± 1 Standard Deviation

Implant	4 Weeks	8 Weeks	25 Weeks
PLLA	0.74 ± 0.92	0.83 ± 0.66	0.93 ± 0.60
u-HA30	0.86 ± 0.47	2.12 ± 1.21*	2.19 ± 1.15
u-HA40	2.44 ± 1.25*	2.69 ± 0.74†	3.60 ± 1.27†
u-HA50	2.05 ± 0.80*	4.32 ± 1,87†,‡,§	2.89 ± 0.81†

*$p < 0.05$, significantly different from PLLA.
†$p < 0.01$, significantly different from PLLA.
‡$p < 0.01$, significantly different from u-HA30.
§$p < 0.01$, significantly different from u-HA40 (Fisher's PLSD).

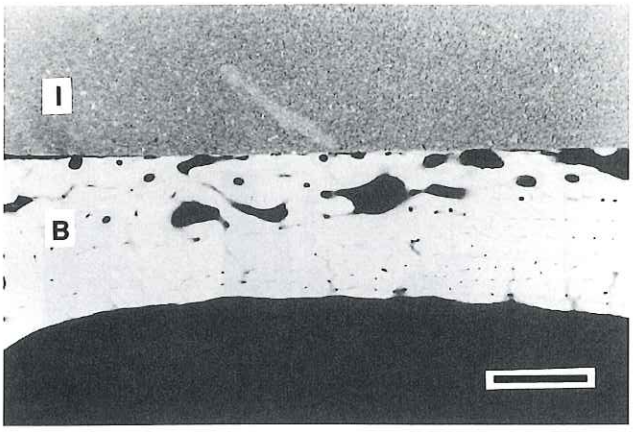


Figure 4. Contact microradiograph of the bone–implant interface. The 8-week u-HA50 sample shows bone directly bonded to the implant. B, bone; I, implant. Original magnification ×40; scale bar = 500 μm).

25 weeks [Fig. 5(e)]. No biodegradation of the implants had occurred in any of the groups at 8 weeks. At 25 weeks signs of degradation, such as cracking or surface separation of the implant, were observed in the u-HA50 group; however, there was no fragmentation of the implant in any of the groups. The u-HA particles did not dissociate from the implant into the tissue in any group. There was no evidence of inflammatory or foreign-body response in any group throughout the follow-up periods.

In the SEM study the bone tissue was seen to be connected directly to the u-HA/PLLA composite implants without any intervening tissue [Fig. 6(a)]. In the SEM-EPMA study the X-ray intensities of calcium (Ca), phosphorus (P), and carbon (C) across the bone–implant interface were analyzed and were shown to change at the bone–implant interface [Fig. 6(b)].

DISCUSSION

If an osteosynthetic implant applied to the surface of bone cortex for fracture repair could bond to the bone, it would be one of the most favorable methods for the secure fixation of implants to the bone cortex. Verheyen et al. used the push-out test to examine the bonding strengths of implants made of s-HA particles/PLLA composites to bone.[28] However, the push-out test cannot evaluate the bonding strength between the implant and the surface of the bone. Furthermore, the values obtained with this method are variable and depend on such factors as the position of the implant, the tapering angle of the plug itself, and the position of the plug aligned with the jig for pushing out. The values obtained with the present method were not affected by these problems. Essentially, the present method was thought to directly examine the bonding strength of osteosynthetic plates to bone.

The HA particles/PLLA composites used in Verheyen et al.'s study possess an initial bending strength of up to 100 MPa and an initial bending modulus of up to 8.0 GPa; thus, they might be useful in non-load-bearing applications.[27] In contrast, the u-HA/PLLA composites used in the present study possess an initial bending strength of up to 270 MPa and an initial bending modulus of up to 12 GPa (Table I). These properties mean that they are the first composites of this type with the potential for use as osteosynthetic plates.

In the present study no direct contact between the PLLA plate and bone cortex was detectable on histological examination at any postimplantation time. The detaching strength of the PLLA group reached a maximum of only 0.93 ± 0.60 kg/cm^2 at 25 weeks. This may be explained by the anchoring effect between the roughened surface of the implants and the intervening soft tissue. The bonding strength in the u-HA30 group was significantly greater than that in the PLLA group at 8 weeks. The bonding strengths in the u-HA40 and u-HA50 groups were significantly greater than that in the PLLA group at each postimplantation time. These differences in the bonding strength between the u-HA/PLLA composite groups and the PLLA group were considered to be due to the inclusion of u-HA particles in the implants.

Yoshii et al. reported previously that the bonding strengths of apatite and wollastonite containing glass ceramics (AW-GC) to the surface of bone cortices reached a maximum of 15.1 ± 3.1 kg/cm^2, whereas those of alumina-ceramic implants reached a maximum of only 1.4 ± 0.7 kg/cm^2.[35] They also reported that the bonding behavior of AW-GC was comparable to that of dense HA.[36] The bonding strength of the u-HA50 composite corresponded to a little less than 30% of that of that of dense HA. This may be because the u-HA particle content of the u-HA50 composite was about 32% by volume (Table I) and would occupy the same proportion of the surface area.

The bonding strength in the u-HA50 group decreased significantly between 8 and 25 weeks, whereas bonding strength was maintained in the u-HA40 group. This might be explained by more rapid degradation of the u-HA50 implants, leading to a fall in their mechanical strength, because these u-HA/PLLA composite implants contained the lowest concentration of PLLA. However, further detailed *in vivo* studies of these composite implants will be needed to clarify the mechanism underlying their degradation.

Two research groups previously reported the absence of any inflammatory foreign-body reaction to PLLA implants.[17,18] Although inflammatory foreign-body reactions were more rarely reported with PLLA than with PGA implants,[15,37,38] phagocytosis by histiocytes is characteristic of the final stages of PLLA

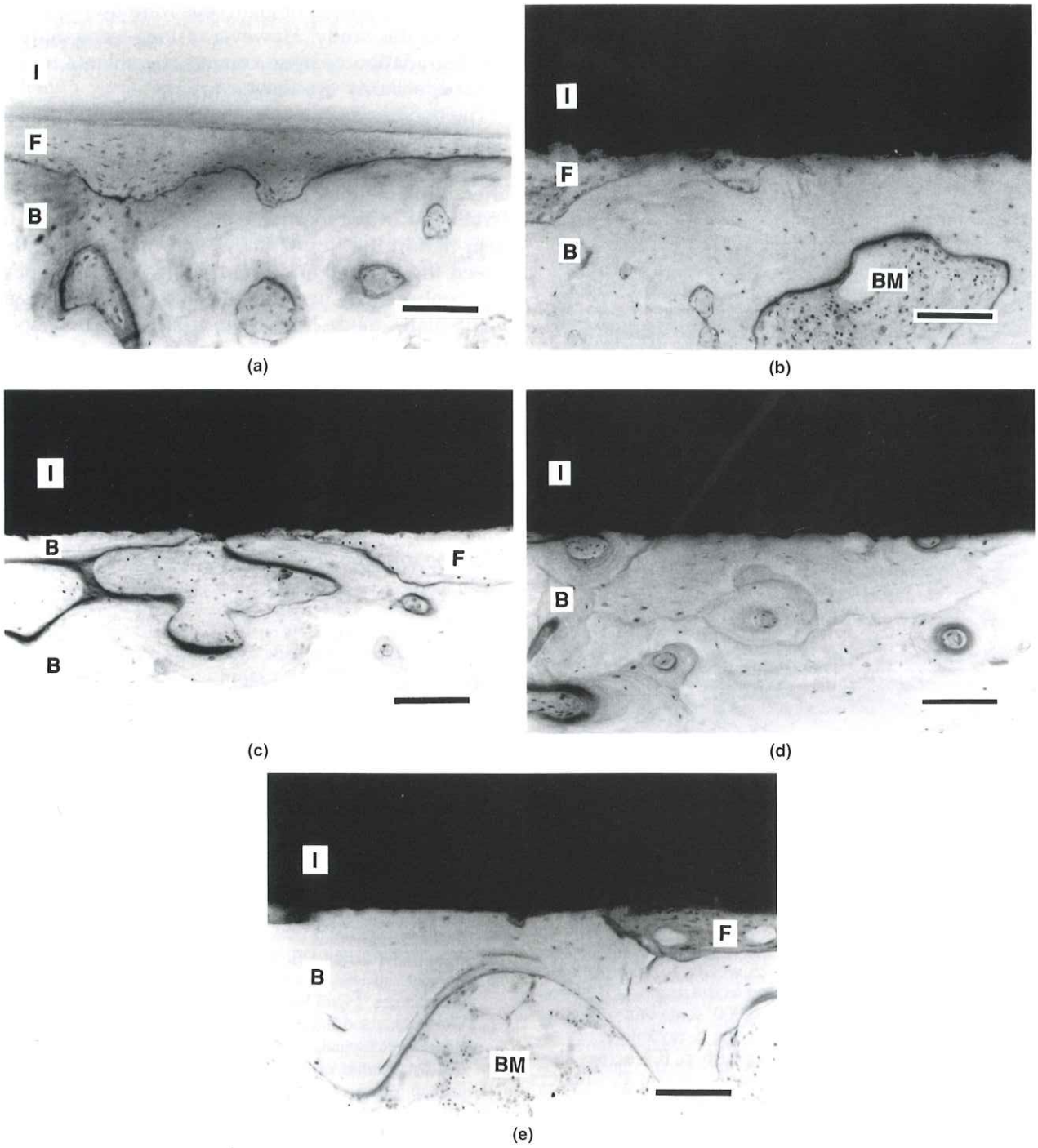
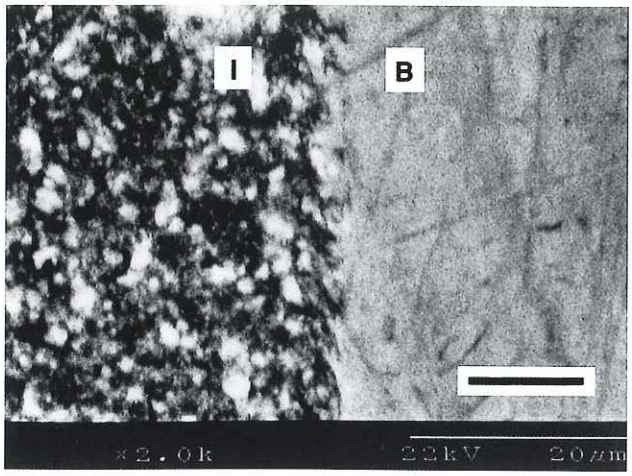


Figure 5. Giemsa surface staining of the bone–implant interface. B, bone; I, implant; BM, bone marrow. Original magnification ×200; scale bar = 100 μm. (a) An 8-week PLLA sample. Intervening fibrous tissue (F) was approximately 50 μm thick. (b) An 8-week u-HA30 sample. Direct contact between the bone and the implant was observed in part. Intervening fibrous tissue (F) was observed in another part. (c) A 4-week u-HA50 sample. Bony tissue grew on the surface of the implant. Intervening fibrous tissue was (F) partly observed. (d) An 8-week u-HA50 sample. Newly formed bony tissue is directly spread over the surface of the implant and the fibrous tissue layer is diminished. (e) A 25-week u-HA50 sample. Direct contact of the bone–implant interface was maintained. Remodeling of cortical bone containing bone marrow tissue was observed. There was no evidence of inflammatory or foreign-body response in any sample.

biodegradation.[39] Cracking of an implant in the u-HA50 group was observed at 25 weeks, suggesting some biodegradation. However, there was no fragmentation of the implants in any group throughout the follow-up periods. Also, there was no evidence of inflammatory or foreign-body response in any group throughout the follow-up periods during this study. This may be because the PLLA component of these



(a)

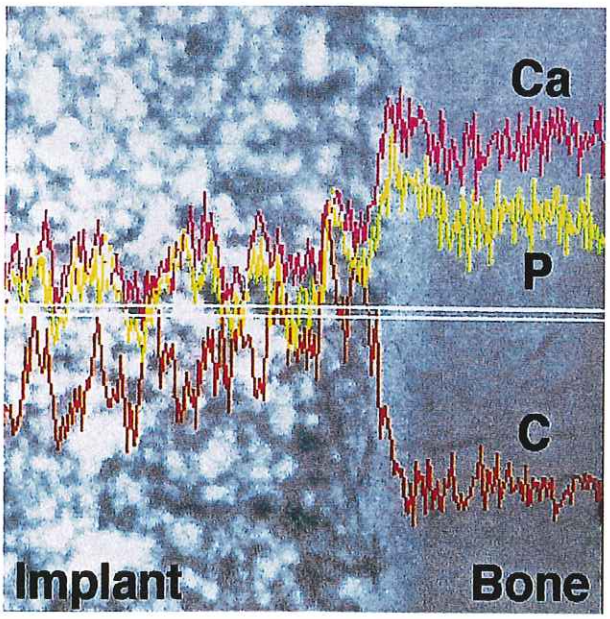


Figure 6. SEM-EPMA study of the interface between the u-HA50 implant and the bone at 25 weeks. (a) SEM photograph showing bone directly bonded to the implant. B, bone; I, implant. Original magnification ×2000; scale bar = 10 μm. (b) SEM-EPMA photograph showing the X-ray intensities of calcium (Ca), phosphorus (P), and carbon (C) across the bone–implant interface. The amounts of Ca, P, and C changed at the bone–implant interface.

u-HA/PLLA composites maintains a viscosity average molecular weight of over 50 kDa for up to 25 weeks, and it takes a long time to be fully degraded. Regarding the HA particles, several authors reported that sintered HA particles can evoke inflammatory reactions such as osteolysis and aseptic loosening of implants following total hip arthroplasty using HA-coated implants.[40,41] Therefore, we chose u-HA particles as a filler, because these are considered to be bioresorbable.[31] No dissociated u-HA particles were found between the implants and the bony surface, and no phagocytosis of the particles by inflammatory cells such as macrophages or giant cells was observed by 25 weeks in this study. However, a long-term study of the degradation of these composite implants will be needed to clarify the above concerns.

The bonding behavior of the u-HA/PLLA composite plates, which had an initial bending strength of 270 MPa, was studied up to 25 weeks. Even by 4 weeks after implantation the bonding strengths in the u-HA40 and u-HA50 groups were significantly greater than that in the PLLA group, and direct contact between the u-HA40 and u-HA50 plates and the bone was confirmed by histological examination. Osteosynthetic plates made from these u-HA/PLLA composites can therefore be expected to bond directly to bone during the healing period, thus reinforcing stability after fractures. In conclusion, the inclusion of u-HA particles into a PLLA matrix within a range of 30–50% by weight appears to enhance the bone bonding of bone fixation plates. This property was exploited in the development of biodegradable PLLA fixation plates supplemented with u-HA particles, which could be functionally superior to PLLA plates without particles.

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