Comparison of Hydroxyapatite and Beta Tricalcium Phosphate as Bone Substitutes After Excision of Bone Tumors

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Abstract: Long-term results are reported in 23 patients and short-term results in 30 patients presenting with bone tumors treated by curettage or resection followed by implantation of hydroxyapatite (HA) or highly purified beta-tricalcium phosphate (β-TCP), respectively. Mean follow-up was 97 and 26 months in cases involving HA implantation and β-TCP implantation, respectively. Radiographs revealed HA incorporation into host bone in all but two cases; moreover, no obvious evidence of HA biodegradation was observed. A single patient exhibited late deformity following implantation of HA. All grafted β-TCP was, at least partially, absorbed and replaced by newly formed bone. The mean period required for the disappearance of radiolucent zones between the ceramics and host bone was 17 weeks in HA and 9.7 weeks in β-TCP. Highly purified β-TCP appears to be advantageous relative to HA for surgical intervention in bone tumors consequent to the nature of remodeling and superior osteoconductivity. © 2004 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 72B: 94–101, 2005

Keywords: hydroxyapatite; tricalcium phosphate; bone graft; osteoconduction; bone tumor

INTRODUCTION

A variety of synthetic bone grafts have been utilized to fill osseous defects following removal of bone tumors. Calcium phosphate ceramics are synthetic scaffolds that have been employed in orthopedics since the 1980s. Hydroxyapatite (HA) is prepared by precipitation and subsequent sintering at temperatures above 1000°C (Ca-to-P ratio is 1.67). Beta-tricalcium phosphate (β-TCP), which possesses stoichiometry similar to amorphous biologic precursors to bone mineral, displays a Ca-to-P molar ratio of 1.5.[1–3]

Numerous basic studies have demonstrated that calcium phosphate ceramics are biocompatible, bioactive, and osteoconductive.[1–7] The first clinical application of calcium phosphate entailed the successful repair of a bony defect by Albee in 1920.[2,4] Subsequently, development of ceramics as biomaterials for bone repair, substitution, and augmentation became the subject of intense scrutiny.[2] Reports appear in the literature describing the clinical utility of calcium phosphate ceramics to fill cavities following excision of bone tumors; however, data regarding long-term results of the grafted ceramics are limited.[8–18] Based on composition, calcium phosphate may be classified as (1) HA, (2) β-TCP, (3) biphasic calcium phosphate, an intimate mixture of HA and β-TCP, or (4) unsintered calcium phosphate or calcium-deficient apatite $(Ca,Na)_{10}(PO_4)_6(OH)_2$.[2] In our institute, HA was employed as a bone graft substitute between 1992 and 1998; since 1999, highly purified β-TCP has been used in bone tumor surgery. This investigation compares the clinical and radiological outcome of tumor surgery involving these two types of grafted materials.

MATERIALS AND METHODS

HA (Bonfil®, Mitsubishi Materials, Chichibu, Japan) [Figure 1(A)] in the form of porous cubes (porosity of 70%, pore size of 90–200 μm, 900°C sintering temperature) was used between 1992 and 1998. Since 1999, highly purified β-TCP was utilized. β-TCP (OSferion® Olympus, Osaka, Japan) (porosity of 75%, pore size of 100–400 μm, 1050°C sintering temperature) [Figure 1(B)] was manufactured to an extraordinarily high degree of purity.[19]

No benefit of any kind will be received either directly or indirectly by authors.

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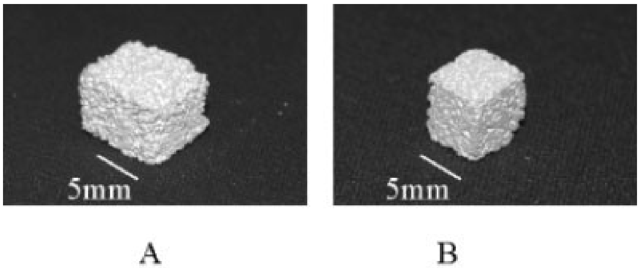

Figure 1. Photographs of the two materials. (A) Hydroxyapatite (Bonfil®); (B) β-TCP (OSferion®).

Clinical findings are summarized in Tables I and II. HA was employed on a single occasion in each of 23 patients (12 women, 11 men). Patient age at surgery was 2–67 years with mean of 27 years (standard deviation: SD = 19). The sample population consisted of six, five, four, and two cases of simple bone cyst, giant cell tumor, enchondroma, and fibrous dysplasia, respectively. Additionally, six cases were classified as "other." Tumors were located in the femur (11 patients), humerus (3), ilium (3), tibia (3), and at other sites (3). Maximum dimensions of the tumors ranged from 3 to 12 cm; mean size was 7.1 cm (SD = 2.9). The mass of implanted HA ranged from 2 to 26 g (mean = 11 g, SD = 5.9). HA was used exclusively in 13 patients; in contrast, in 10 subjects, HA was combined with a corticocancellous autograft for relatively large defects. Mean follow-up was 97 months (35–130 months).

β-TCP was employed in 30 patients (13 women, 17 men). Patient age at surgery was 5–73 years with a mean of 32 years (SD = 20). The sample population consisted of 10, 5, 3, and 3 cases of fibrous dysplasia, simple bone cyst, giant cell

TABLE I. Summary of the Patients Who Were Implanted With Hydroxyapatite

Case No.	Age	Sex	Diagnosis	Location	Tumor Size (cm)	Amount of Ceramics (g)	Autograft	Disappearance of Radiolucent Zone (Weeks)	Postop. MRI (Months)	Follow-up (Months)	Complication
1-1	12	F	Parosteal osteosarcoma	Femur	10	8	Fibula	16		130	
1-2	13	M	Parosteal osteosarcoma	Femur	12	10	Fibula	16	24	128	
1-3	41	M	Giant cell tumor	Sacrum	10	10	Fibula	20		122	
1-4	5	F	Simple bone cyst	Humerus	5	7		20		122	
1-5	2	F	Eosinophilic granuloma	Radius	3	2		8		121	
1-6	9	M	Simple bone cyst	Femur	10	10		8		111	
1-7	6	M	Simple bone cyst	Humerus	7	10		16		110	
1-8	10	M	Simple bone cyst	Humerus	5	10		12		110	Fracture postop. 3w
1-9	24	M	Giant cell tumor	Femur	7	7	Ilium	16	24	109	
1-10	28	F	Simple bone cyst	Ilium	10	26	Fibula	[a]		108	
1-11	37	M	Fibrous dysplasia	Femur	5	20		16		99	
1-12	61	F	Enchondroma	Tibia	4	10		20	36	98	
1-13	12	F	Enchondroma	Ilium	10	13		24		98	
1-14	42	M	Hemangioma	Ischium	5	20		20		96	
1-15	12	F	Osteoid osteoma	Femur	3	6		8		92	
1-16	56	M	Enchondroma	Femur	12	20	Ilium	20	60	90	
1-17	40	F	Fibrous dysplasia	Femur	7	2		20		88	
1-18	16	M	Chondronblastoma	Femur	3	9		16	44	88	
1-19	42	F	Giant cell tumor	Tibia	7	10	Ilium	[a]		80	Late deformity
1-20	67	F	Enchondroma	Tibia	3	8	Ilium	20		76	
1-21	9	F	Simple bone cyst	Femur	10	20		12		70	Fracture postop. 4w
1-22	36	F	Giant cell tumor	Ilium	7	8	Ilium	20	38	39	Local recurrence
1-23	45	M	Giant cell tumor	Femur	8	10	Fibula	16	32	35	Local recurrence
Mean	27				7.1	11		16		97	
SD	19				2.9	5.9		4.4		24	
Range	2–67				3–12	2–26		8–24[b]		35–130	

[a] Clear zone were still present at final follow-up.
[b] Two cases (1-10, 1-19) were excluded.

TABLE II. Summary of the Patients Who Were Implanted With Beta-Tricalcium Phosphate

Case No.	Age	Sex	Diagnosis	Location	Tumor Size (cm)	Amount of Ceramics (g)	Autograft	Disappearance of Radiolucent Zone (Weeks)	Total Resorption of β-TCP	Postop. MRI (Months)	Follow-up (Months)	Complication
2-1	16	M	Aneurysmal bone cyst	Ischium	9	30	Ilium	12			50	
2-2	29	M	Fibrous dysplasia	Femur	5	7	Fibula	12			46	
2-3	47	M	Fibrous dysplasia	Femur	4	8		16			42	
2-4	56	M	Fibrous dysplasia	Femur	10	14		12		12	40	Fracture postop.4w
2-5	60	M	LSMFT[a]	Ilium	7	17		12			39	
2-6	17	M	Simple bone cyst	Femur	15	30	Fibula	16			39	
2-7	11	F	Osteofibrous dysplasia	Tibia	5	2		8	+		35	
2-8	33	F	Fibrous dysplasia	Femur	8	10		8	+		32	
2-9	14	M	Fibrous dysplasia	Humerus	5	4		8	+		29	
2-10	68	M	LSMFT	Femur	7	5		12		18	27	
2-11	42	F	Simple bone cyst	Ilium	10	10		8	+		26	
2-12	28	F	Fibrous dysplasia	Humerus	5	4		8	+	12	25	
2-13	35	F	Simple bone cyst	Pubis	3	5		12			25	
2-14	5	F	Simple bone cyst	Femur	4	5		12	+		25	
2-15	13	M	Osteofibrous e-dysplasia	Tibia	5	7		8			25	
2-16	16	M	Metastatic cancer	Ilium	5	4		8			24	
2-17	30	F	Fibrous dysplasia	Femur	9	12		12		12	23	
2-18	15	M	Osteosarcoma	Tibia	3	2	Fibula	16			22	
2-19	47	F	Enchondroma	Femur	5	7		8			22	
2-20	18	M	Giant cell tumor	Femur	7	10	Ilium	12	+	12	21	
2-21	55	F	Enchondroma	Finger	2	2		4	+		21	
2-22	10	M	Fibrous dysplasia	Femur	15	14	Fibula	8	+		21	
2-23	73	F	Giant cell tumor	Femur	7	10		8		8	21	
2-24	35	M	Enchondroma	Femur	5	11		8	+		16	
2-25	5	M	Simple bone cyst	Humerus	4	5		6	+		16	Local recurrence
2-26	23	F	Fibrous dysplasia	Rib	3	1		8	+		14	
2-27	72	F	Fibrous dysplasia	Femur	12	10		8			12	Fracture postop. 2w
2-28	35	M	Giant cell tumor	Radius	3	2	Ilium	8			12	
2-29	23	F	Fibrous dysplasia	Radius	3	3		4	+	12	12	
2-30	18	M	Osteoid osteoma	Tibia	3	2		8			12	
Mean	32				6.3	8.4		9.7			26	
SD	20				3.9	7.1		3.1			10	
Range	5–73				3–15	1–30		4–16			12–50	

[a] LSMFT = liposclerosing myxofibrous tumor.

tumor, and enchondroma, respectively. In addition, nine cases were classified as "other." Tumors were located in the femur (15 patients), humerus (3), ilium (3), tibia (3), and at other sites (6). Maximum dimensions of the tumors ranged from 2 to 15 cm; mean size was 6.3 cm (SD = 3.9). The mass of implanted β-TCP ranged from 1 to 30 g (mean = 8.4 g, SD = 7.1). β-TCP was used exclusively in 23 patients; in contrast, in seven subjects, it was combined with a corticocancellous autograft for large defects. Mean follow-up was 26 months (10–50 months).

All patients underwent curettage or resection of the tumor and filling of the defect with blocks and granules of HA or β-TCP.

Patients were scheduled for follow-up evaluations, which included clinical and radiographic studies, at 2-, 4-, and 8-week intervals. Subsequently, subjects were examined every 2–6 months. Radiographs were assessed to determine changes in the radiolucent zone surrounding the grafted materials. Postoperative magnetic resonance imaging (MRI) was conducted in order to disclose local recurrence in seven and six patients receiving the HA and the β-TCP grafts, respectively.

RESULTS

HA group

Neither postoperative infection nor toxic complications were observed. Postoperative radiographs revealed radiolucent

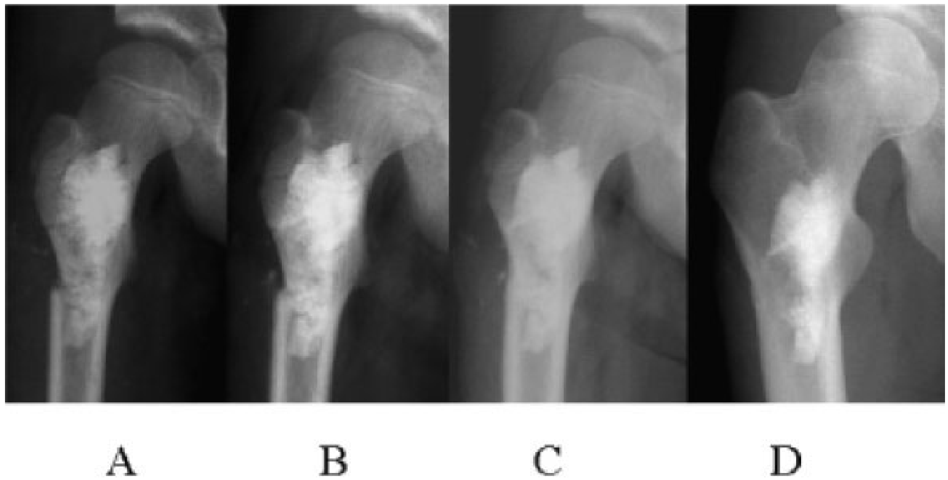

Figure 2. Radiographs of a simple bone cyst in a 9-year-old male (Case 1-6). (A) Immediate post-operative radiograph displaying granules of HA and surrounding radiolucent zone. (B) The radiolucent zone was present after 8 weeks. (C) The radiolucent zone vanished after 16 weeks. (D) One hundred eleven months later, increased radiographic density at HA implant sites and diminished discrimination between HA blocks or granules were apparent. However, no obvious evidence of biodegradation was detected.

zones between implanted HA and the surrounding bone immediately after surgery. Over time, radiolucent zones disappeared and new bone developed in 21 of 23 patients. Two cases exhibited continuous radiolucent zones at the final follow-up. Among the 21 cases, the mean period required for disappearance of the zones was 16 weeks (range 8–24 weeks). Periodic radiographic assessment demonstrated an apparent increase in radiographic density at HA implant sites and diminishing discrimination between HA blocks or granules. However, no obvious evidence of HA biodegradation at a maximum of 130 months follow-up was detected (Figures 2–4).

Postoperative MR imaging was performed in seven patients. Duration of MR examination and surgery ranged from 24 to 60 months (mean = 37 months). On both T1- and T2-weighted images, all areas of implanted HA in these seven subjects displayed low signal intensity to surrounding cancellous bone [Figure 4(C, D)].

Two patients presenting with giant cell tumors of the femur and ilium developed local recurrence; subsequently, these malignancies were excised 35 and 39 months, respectively, after initial surgery. Postoperative fractures occurred in two patients within four weeks following surgery. One individual exhibiting a simple bone cyst of the proximal humerus fell three weeks following surgery, whereas the second individual displaying a simple bone cyst of the proximal femur fell four weeks after the procedure. Both fractures united as a result of conservative treatment.

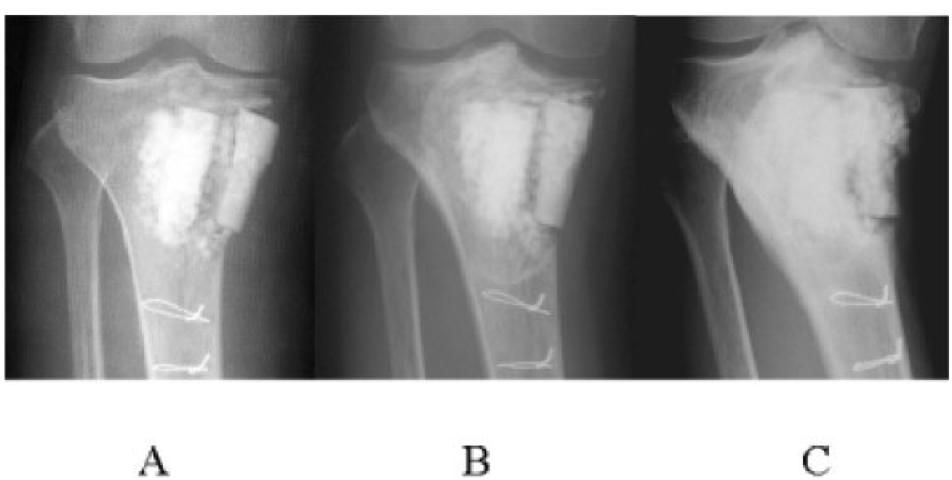

Figure 3. Radiographs of a giant cell tumor of the tibia in a 42-year-old woman (Case 1-19). (A) Immediate postoperative radiograph displaying granules and blocks of HA and surrounding radiolucent zone. (B) The radiolucent zone remained after 7 months. (C) The radiolucent zone and varus deformity are present after 2 years.

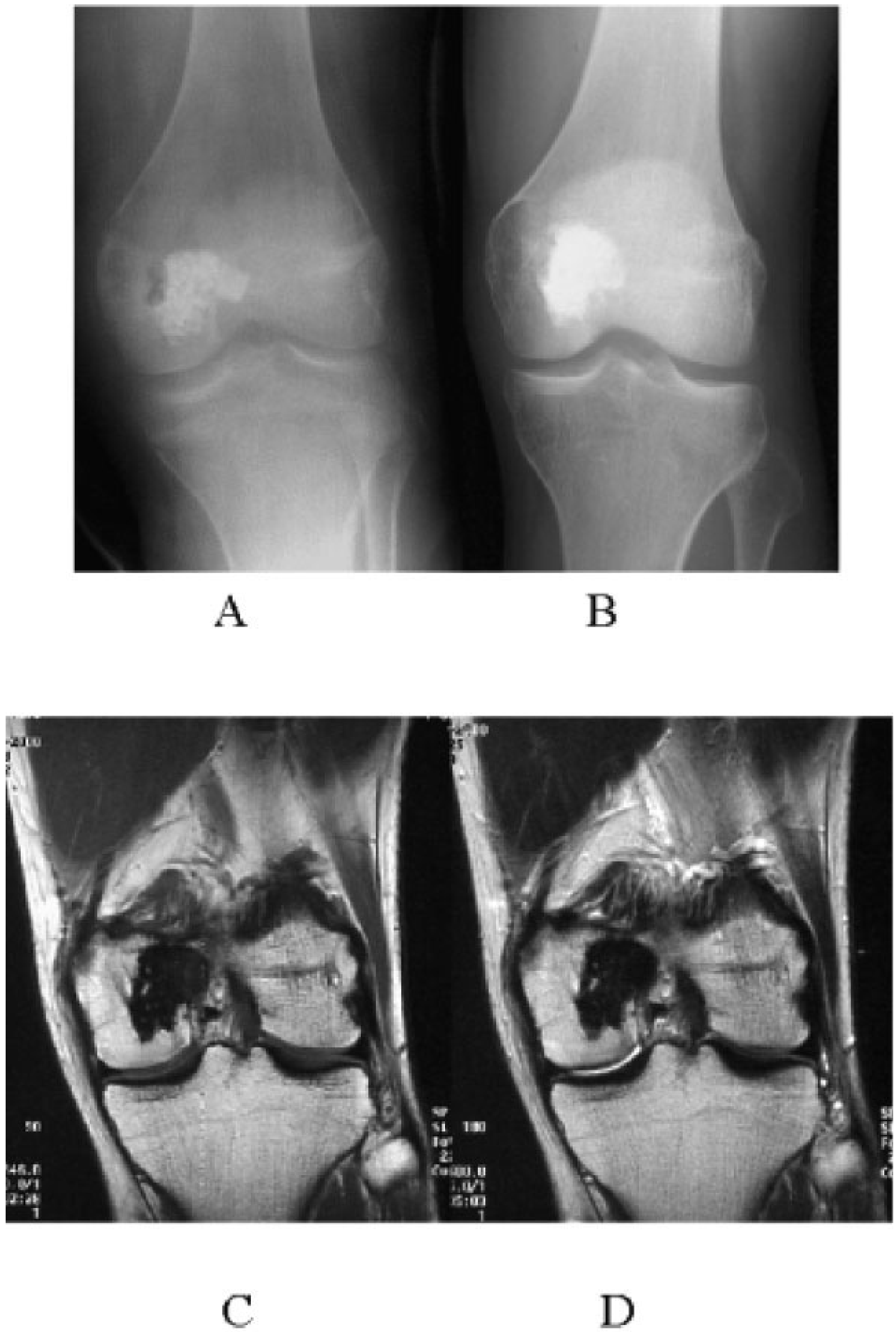

Figure 4. Radiographs and MR images of a chondroblastoma of the femur in a 16-year-old male (Case 1-18). (A) Immediate postoperative radiograph exhibiting granules and blocks of HA and surrounding radiolucent zone. (B) Four years later, the radiolucent zone has vanished. However, no obvious evidence of biodegradation is apparent. (C) T1-weighted and (D) T2-weighted MR images demonstrating signal voids at the grafted area.

One patient with giant cell tumor of the proximal tibia displayed late varus deformity of the tibia two years after surgery. The radiolucent zones between HA and the surrounding bone never disappeared in this case; moreover, removal of grafted HA corticocancellous autograft and correction osteotomy were conducted 35 months after the initial operation (Figure 3). No bone ingrowth to the implanted HA blocks was observed during revision surgery.

No patient complained of local pain at final follow-up (Table I).

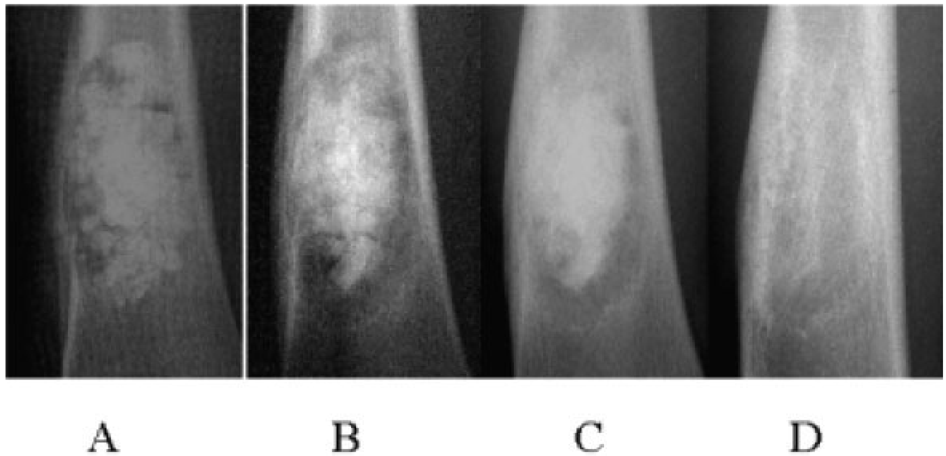

Figure 5. Radiographs of a simple bone cyst in a 5-year-old girl (Case 2-14). (A) Immediate postoperative radiograph exhibiting granules and blocks of β-TCP and surrounding radiolucent zone. (B) The periphery of the β-TCP has been absorbed. The radiolucent zone was present after 4 weeks. (C) The radiolucent zone vanished after 8 weeks. The periphery of the β-TCP has been absorbed and replaced by new bone. (D) One year later, the β-TCP is characterized by nearly total absorption and replacement by newly formed bone trabeculae.

β-TCP Group

Neither postoperative infection nor toxic complications were observed. Postoperative radiographs demonstrated radiolucent zones between implanted β-TCP and the surrounding bone immediately after surgery, which was similar to that of the HA cases. Over time, radiolucent zones disappeared and new bone developed in all 30 patients. The mean period required for disappearance of the zones was nine weeks (range 4–16 weeks).

Periodic radiographic assessment revealed decreased roentgen density of β-TCP and replacement of β-TCP by newly formed bone. These processes appear to have begun on the periphery and progressed centrally. After 12 months postimplantation, nearly all c-TCP was replaced by newly formed bone in 13 cases. However, exact evaluation of the ratio of residual β-TCP and newly formed bone was impossible by radiograph (Figures 5–7).

Postoperative MR imaging was performed in six patients. Duration of MR evaluation and surgery ranged from 8 to 18 months (mean = 12 months). On both T1- and T2-weighted images, all areas of implanted β-TCP exhibited intensity that was nearly identical to surrounding cancellous bone with a scattered low-intensity area, which probably represented small amounts of residual β-TCP [Figure 7(C,D)].

One patient presenting with a simple bone cyst of the humerus developed local recurrence 12 months after surgery. However, this subject displayed no symptoms. Postoperative fracture occurred in two individuals within four weeks postsurgery. One patient exhibiting fibrous dysplasia of the proximal femur fell four weeks after the procedure; the nondisplaced fracture united as a result of conservative treatment. A second patient with fibrous dysplasia of the distal femur fell two weeks after surgery; subsequently, the displaced fracture was treated successfully with intramedullary nailing.

No patient complained of local pain at final follow-up (Table II).

DISCUSSION

Numerous experimental studies regarding the use of biomaterials for bone graft appear in the literature of the past 30

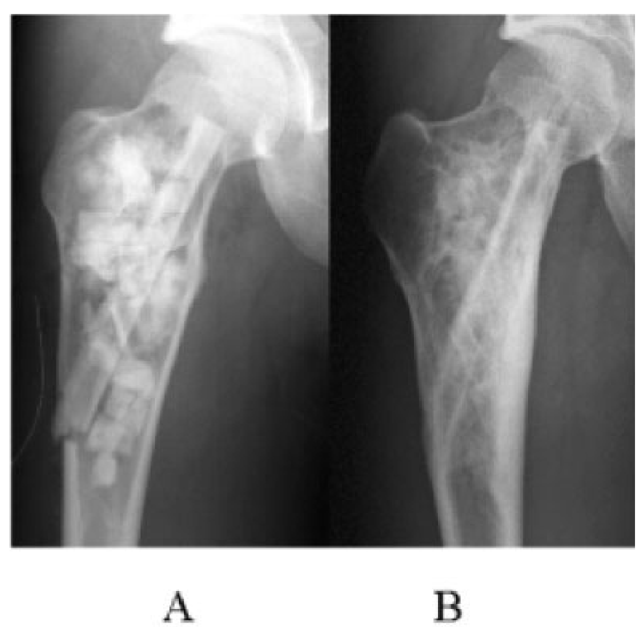

Figure 6. Radiographs of a simple bone cyst in a 17-year-old male (Case 2-6). (A) Immediate postoperative radiograph displaying the free autologous fibula and blocks of β-TCP and surrounding radiolucent zone. (B) The radiolucent zone has vanished and the periphery of the β-TCP was absorbed after 36 months. Residual β-TCP remained at the center of the grafted area.

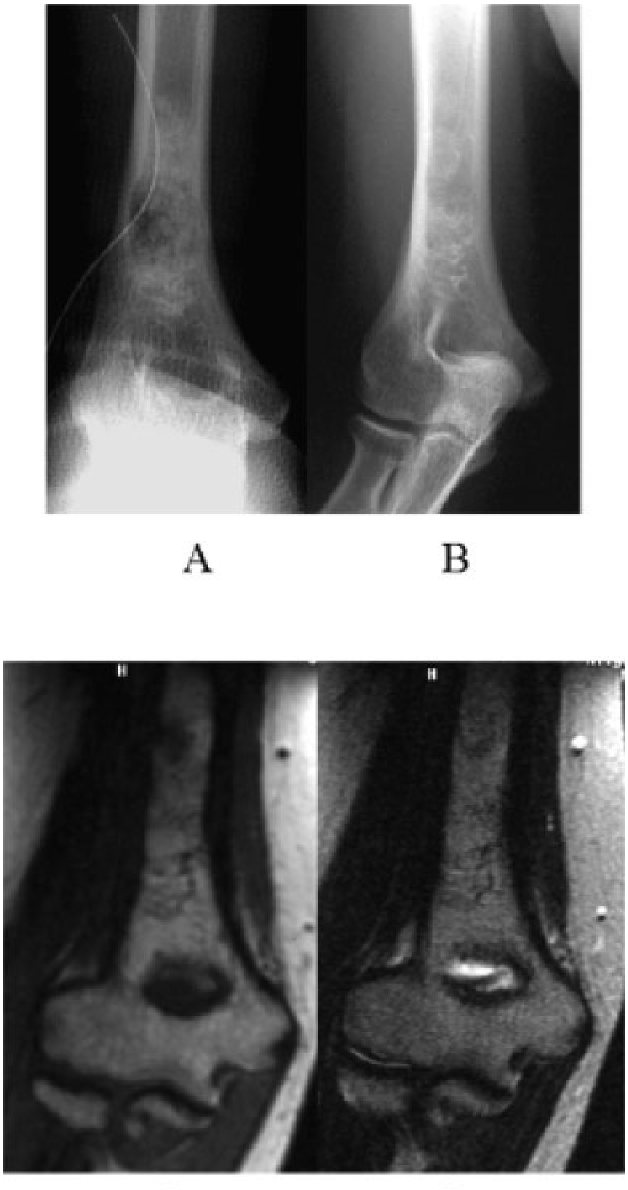

Figure 7. Radiograph and MR images of fibrous dysplasia in a 28-year-old female (Case 2-12). (A) Immediate postoperative radiograph exhibiting granules and blocks of β-TCP and surrounding radiolucent zone. (B) One year later, the β-TCP is characterized by nearly total absorption and replacement by new bone. (C) T1-weighted and (D) T2-weighted MR images showing an area nearly identical to surrounding cancellous bone with scattered signal voids.

years; however, few clinical findings pertaining to these materials have been published with respect to surgery involving bone tumors.[1–18] Long-term results of ceramic graft for bone tumors have been documented scarcely. In our institution, two types of calcium phosphate ceramics have been used in the roles of graft substitute and graft extender. Apparently, addition of autograft did not affect the quality or the speed of ceramic integration.

In the present patient series, no adverse reactions to either ceramic, such as excessive postoperative drainage, dermatitis, allergic reaction, or other local complications, were observed. Postoperative early fracture (within 4 weeks after surgery) occurred in two patients receiving HA and in two patients receiving β-TCP. These fractures appear to be attributable to faulty postoperative care as evidenced in a previous report.[9,16]

Radiographic observations indicate the distinct nature of these ceramics in human bone. While no obvious evidence of HA biodegradation was detected, all β-TCP was absorbed and replaced by normal bone trabeculae. Previous short-term clinical results and animal experiments involving HA described the nonabsorbed nature of this osteoconductive biomaterial.[6,8–12] Our results demonstrated the absence of any evidence of HA biodegradation even after 130 months postimplantation.

On the other hand, all β-TCP was, at least partially, absorbed and replaced by newly formed bone. Thirteen of 30 cases displayed nearly total resorption of β-TCP on radiograph. Postoperative MRI revealed the replacement of the grafted areas by surrounding normal bone of nearly identical signal intensity. The osteoconductive, bioresorbable nature may be advantageous relative to HA, which remains unremodeled despite long periods following implantation.

In fact, one patient in this series exhibited varus deformity of the tibia two years after implantation of HA. Hibi et al. also demonstrated late deformity of the femur following implantation of HA.[12] HA cannot be replaced by newly formed bone; consequently, a minor fracture might occur either in the HA itself or at the interface with host bone. A minor fracture may be the cause of these late deformities. No such complications were observed in the patients with β-TCP. Ozawa et al. documented 167 patients receiving β-TCP implantation identical to that used in the current investigation, none of whom developed fractures or deformities.[20] Hirata et al. reported that β-TCP displayed earlier incorporation into surrounding bone than did HA.[17] Galois et al. also noted that β-TCP was a valuable substitute for the filling of defects in cases of benign bone tumor. In their report, implant fragmentation, migration, and poor results were not evident in 110 patients.[18]

In the present investigation, grafted ceramics were well incorporated into surrounding host bone in 21 of 23 cases involving HA and in all cases involving β-TCP. Radiographs revealed radiolucent zones between the implanted ceramics and the surrounding bone immediately after surgery. Over time, the radiolucent zones disappeared. These radiographic changes are believed to represent direct bone apposition on the ceramics, which is referred to as osteoconduction.[9,16] The mean period required for disappearance of the zones was 17 weeks in HA and nine weeks in β-TCP. Ozawa et al. reported that radiographs of all but three of 167 cases characterized by identical β-TCP implantation exhibited new bone formation around the ceramics. The three exceptions demonstrated postoperative complications including two instances of infection and one example of tumor recurrence.[20] Highly purified β-TCP appears to possess superior osteoconductivity in comparison to HA in this series. Important features of osteoconductivity are appropriate chemical composition and appropriate architectural geometry.[1–3]

The purity of ceramics also influences bone formation and biocompatibility.[21] Highly purified β-TCP utilized in this investigation possesses macropores that average 200–400 μm in diameter and micropores of 1 μm. Nearly all macropores were interconnected via a 100–200-μm path.[21] Prominent bioresorbability and osteoconductivity of this β-TCP have been documented in both animal experiments and clinical studies.[19–22] The histological features of β-TCP four weeks after surgery of the femur in a human adult was reported. The histological specimens of β-TCP revealed abundant, direct new bone apposition and proliferation of osteoclast-like cells on the ceramics.[22] These observations underscored the superior osteoconductivity and biodegenerative nature of this highly purified β-TCP.

In conclusion, although HA was typically incorporated into host human bone, no obvious evidence of biodegradation was detected even after long periods following implantation. Highly purified β-TCP was, at least partially, absorbed and replaced by newly formed bone in clinical use. Highly purified β-TCP appears to be advantageous in comparison to HA for surgery involving bone tumors consequent to the nature of remodeling and superior osteoconductivity.

REFERENCES

1. Bucholz RW. Nonallograft osteoconductive bone graft substitutes. Clin Orthop 2002;395:44–52.
2. LeGeros RZ. Properties of osteoconductive biomaterials: calcium phosphates. Clin Orthop 2002;395:81–98.
3. Vaccaro AR. The role of osteoconductive scaffold in synthetic bone graft. Orthopedics 2002;25:S571–S578.
4. Albee FH, Morrison HF. Studies in bone growth: tricalcium phosphate as a stimulus to osteogenesis. Ann Surg 1920;71:32–39.
5. Metsger DS, Driskell TD, Paulsrud JR. Tricalcium phosphate ceramic, a resorbable bone implant: revise and current status. J Am Dent Assoc 1982;105:1035–1038.
6. Renooji W, Hoogendoorn A, Visser WJ, Lentferkink RHF, Schimitz MGJ, Ieperen HV, Oldenburg SJ. Janssen WM, Akkermans LMA, Wittebol P. Bioresorption of ceramic strontium-85-labelde calcium phosphate implants in dog femora. Clin Orthop 1985;197:272–285.
7. Passuti N, Daculsi G, Rogez JM, Martin S, Bainvel JV. Macroporous calcium phosphate ceramic performance in human spine fusion. Clin Orthop 1989;248:1169–1176.
8. Daculsi G, Passuti N, Martin S, Deudon C, Legeros RZ, Raher S. Macroporous calcium phosphate ceramic for long bone surgery in human and dogs. Clinical and histological study. J Biomed Mater Res 1990;24:379–396.
9. Uchida A, Araki N, Shinto Y, Yoshikawa H, Kurisaki E, Ono K. The use of calcium hydroxyapatite ceramic in bone tumour surgery. J Bone J Surg Br 1990;72-B:298–302.
10. Giannini S, Moroni A, Pompili M, Ceccarelli F, Cantagalli S, Pezzuto V, Trinchese L, Zaffe D, Venturini A, Pitagato M. Bioceramics in orthopaedic surgery: state of art and preliminary results. Ital J Orthop Traumatol 1992;18:431–441.
11. Inoue O, Ibaraki K, Shimabukuro H, Shingaki Y. Packing with high-porosity hydroxyapatite cubes alone for the treatment of simple bone cyst. Clin Orthop 1993;293:287–292.
12. Hibi A, Ishikawa T, Asano M, Ohsawa S, Tsuge K, Iyoda K. A study of failed implantation of hydroxyapatite for benign bone tumor. Orthoped Surg (Sekiekgeka) 1994;45:1423–1428.
13. Nicholas RW, Lange TA. Granular tricalcium phosphate grafting of cavitary lesions in human bone. Clin Orthop 1994;306: 197–203.
14. Gouin F, Delecrin J, Passuti N, Touchais S, Poirier P, Bainvel JV. Biphasic macroporous calcium phosphate ceramic bone substitute for filling bone defects: a report of 23 cases. Rev Chir Orthop 1995;81:59–65.
15. Shinjo K, Asai T, Kondou K, Tsukamoto M, Anma H, Hirashima Y, Kanou T. The longterm results of treatment with hydroxyapatite implants: more than 10 years of follow-up cases. Orthop Ceramic Imp 1998;17:77–82.
16. Yamamoto T, Onga T, Mizuno K. Use of hydroxyapatite to fill cavities after excision of benign bone tumors. Clinical results. J Bone Joint Surg Br 2000;82:1117–1120.
17. Hirata M, Kusuzaki K, Takeshita H, Nakamura S, Hashiguchi S, Murata H. Comparative study on beta-TCP and HA as artificial bone filler after curettage of benign bone neoplasms. Orthop Ceramic Imp 2002;21:99–101.
18. Galois L, Mainard D, Delagoutte JP. Beta-tricalcium phosphate ceramics as a bone substitute in orthopedic surgery. Int Orthop 2002;26:109–115.
19. Ozawa M. Experimental study on bone conductivity and absorbability of the pure β-TCP. J Jap Soc Biomat 1995;13:17–25.
20. Ozawa M, Tanaka K, Morikawa S, Chazono M, Fujii K. Clinical study of the pure β-tricalcium phosphate: reports of 167 cases. J East Jpn Orthop Traumatol 2000;12:409–413.
21. Dong J, Uemura T, Shirasaki Y, Tateishi T. Promotion of bone formation using highly pure porous β-TCP combined with bone marrow-derived osteoprogenitor cells. Biomaterials 2002;23: 4493–4502.
22. Ogose A, Hotta T, Hatano H, Kawashima H, Tokunaga K, Endo N, Umezu H. Histological examination of beta-tricalcium phosphate graft in human femur. J Biomed Mater Res (Appl Biomater) 2002;63:610–604.