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Review

Clinical Application of Beta-Tricalcium Phosphate in Human Bone Defects

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ABSTRACT

We report the results of treatment with the ceramic bone graft substitute beta-tricalcium phosphate (β-TCP) in 304 patients. All patients were followed up for at least 2 years (range, 26 to 113 months) with physical and radiological examinations. Resorption of TCP and replacement by new bone were observed in 299 patients. Three patients with recurrence of bone cysts and two patients with recurrence of osteomyelitis showed β-TCP resorption but no bone formation. Two to three weeks after implantation, resorption of β-TCP occurred from the periphery of the defects, then continued toward the center over time. Complete or nearly complete bone healing was achieved in most cases within a few years and was dependent upon the amount of implanted material, the patient's age, and the type of bone (cortical or cancellous). The larger the implant was and the older the patient was, the longer the healing time was. Similarly, healing time was prolonged if the defect involved cortical bone rather than cancellous bone. No adverse reactions were attributable to the grafted material. Thus, β-TCP is clinically useful, particularly in young patients. (Jikeikai Med J 2006 ; 53 : 45-53)

Key words : bone substitute, tricalcium phosphate, bone defect, remodeling, bone formation

INTRODUCTION

Autologous bone is the preferred graft material for treating skeletal defects and repairing fractures. However, disadvantages of autografting are significant and include procurement morbidities, increased operative time, and limited availability. In addition, autologous bone is difficult to obtain when the patient is a child. Allografts have commonly been used as substitutes for autogenous bone grafts in Europe and the United States but not in Japan. Significant problems associated with allograft introduction include a low bone-fusion rate and disease transmission[1,2]. Recently, bone substitute materials have been advocated as alternatives to autografts and allografts. Hydroxyapatite is widely used as a bone substitute because of its excellent biocompatibility and osteoconductive properties[3]. However, hydroxyapaptite has several disadvantages, such as slow biodegradation and no progressive bone formation during the repair of bone[4]. Beta-tricalcium phosphate (β-TCP) has recently received considerable attention as a bone graft substitute because of its biocompatibility and biodegradability[5-8]. In animal experiments, β-TCP is gradually degraded during bone remodeling and is finally replaced by mature new bone[5,8]. In this study, we report the clinical results of β-TCP implantation in 304 patients.

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MATERIALS AND METHODS

From 1989 to 2002 the subjects were 304 patients who had bone defects due to curettage of benign bone tumors (146 cases), trauma (93 cases), osteotomies (64 cases), or osteomyelitis (10 cases). In one case, β-TCP was placed on the periosteum after fibula harvest for scoliosis surgery. Patients ranged in age from 2 to 82 years at the time of surgery. Since 1989 β-TCP was used mostly as a composite graft in combination with autologous bone to increase graft volume. As successful results accumulated, β-TCP was used exclusively. Overall, 196 of 304 patients were treated with β-TCP alone. All patients were followed up at regular intervals in our outpatient clinic and underwent radiographic examination.

The β-TCP used in all patients was obtained in block form (Olympus Co., Tokyo, Japan). Beta-TCP was synthesized with a mechanochemical method (wet milling). Briefly, $CaHPO_4/H_2O$ and $CaCO_3$ at a molar ratio of 2 : 1 were mixed into a slurry with pure water and particles of zirconium in a pot mill for 24 hours and dried at 80°C. The calcium-deficient hydroxyapatite was converted to β-TCP by calcinations at 750°C for 1 hour. After the β-TCP powder was sintered at 1,050°C for 1 hour, a porous β-TCP block with a mean pore size of 200 μm and a porosity of 75% was obtained.

RESULTS

Case 1. A 16-year-old girl with a giant cell tumor in the distal part of the femur. Curretage of the tumor was performed, and 8 mm^3 of β-TCP was implanted. Nine years after surgery, most of the β-TCP had been resorbed and replaced by bone (Fig. 1).

Case 2. A 67-year-old man with a giant cell tumor of the right humeral neck. Curretage of the tumor was performed, and an 8-mm^3 block of β-TCP was implanted. Resorption of β-TCP was noted at the circumference 2 months after surgery. However, 9 years later, more β-TCP was present in this case than in case 1 (Fig. 2).

Case 3. A 2-year-old boy with osteomyelitis due to tuberculosis of the talus. Ten months after surgery, most of β-TCP had been resorbed. Restoration of trabecular bone with complete resorption of β-TCP was noted 18 months after surgery (Fig. 3).

Case 4. A 3-year-old boy with a benign bone tumor of the tibia. Curretage of the lesion was performed, and β-TCP was implanted. Partial resorption of β-TCP was observed 10 months after surgery. Most of the β-TCP had been resorbed and replaced by bone 18 months after surgery (Fig. 4).

Case 5. A 53-year-old woman with a shaft and comminuted depressed fracture of the lateral tibia plateau. Four weeks after open reduction and internal fixation, the resulting defect was filled with an 8-

A B C D

Fig. 1. Radiographs of a giant cell tumor in the distal part of the femur in a 16-year-old girl. One month (A) and 18 months (B) postoperatively. Nine years after surgery, most of the β-TCP had been resorbed and replaced by bone (C, D). The arrow indicates remaining TCP on a T1-weighted MR image (D).

A B C D

Fig. 2. A 67-year-old man with a giant cell tumor of the right humeral neck (A). Curettage of the tumor was performed, and β-TCP was implanted. Resorption of β-TCP is noted at the circumference 2 months postoperatively (B). However, 9 years later, more TCP remained (C) than in the 16-year-old girl in Figure 1. A T1-weighted MR image 9 years after surgery shows the remaining TCP as an area of low signal intensity and resorbed TCP as an area of high signal intensity (D).

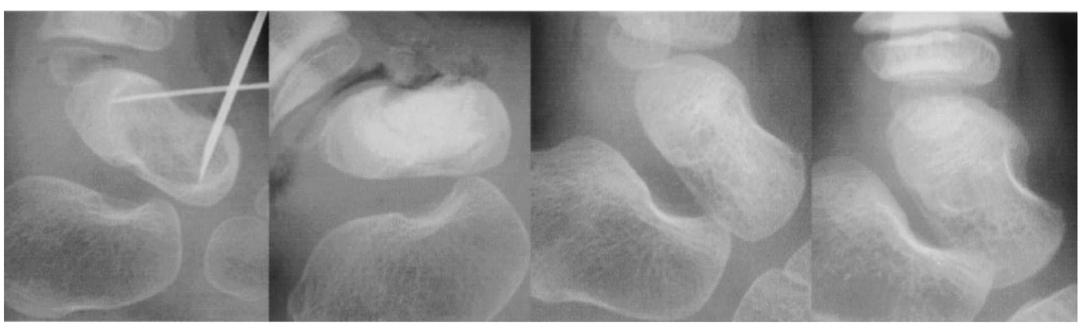

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Fig. 3. Radiographs of a 2-year-old boy with osteomyelitis due to tuberculosis in the talus, during surgery (A) and after surgery (B). Ten months after surgery, most of the β-TCP has been resorbed (C). Restoration of trabecular bone with complete resorption of β-TCP is noted 18 months after surgery (D).

cm^3 block of β-TCP. Eighteen months later, additional TCP was implanted into defects left by the removal of internal fixation devices. Three years after surgery, osteoarthritic changes of the knee were minimal (Fig. 5).

Case 6. A 48-year-old man with a comminuted fracture of the proximal part of the right tibia. Open reduction and internal fixation were performed, and a 4-cm^3 block of β-TCP was implanted in the cortical bone defects in the posterolateral side of the tibia. Eighteen months after surgery, healing with graft incorporation was radiographically confirmed. However, resorption of TCP was less than in the metaphysis of the tibia. Complete resorption was confirmed 5 years after surgery (Fig. 6).

Case 7. A 13-year-old girl. An 18-cm-long fibula graft was obtained for spinal fusion, and β-TCP blocks were placed on the remaining periosteum. Resorption of β-TCP and formation of cortical bone were observed over time. Nine years after implantation, the fibula had been almost completely reconstructed. In addition, magnetic resonance (MR)

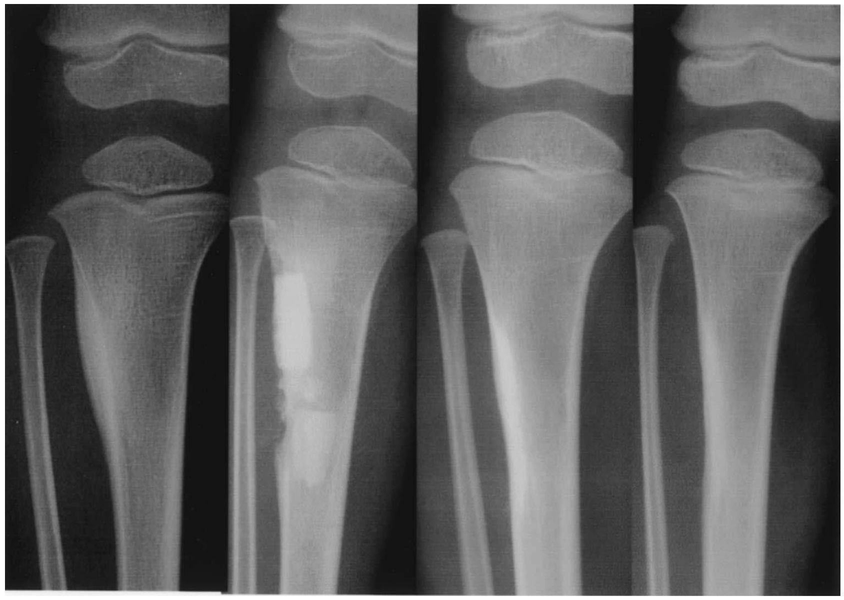


Fig. 4. Radiographs of a 3-year-old boy with a benign tumor of the tibia (A). Curettage of the lesion was performed, and β-TCP was implanted (B). Partial resorption of β-TCP is observed 10 months after surgery (C). Eighteen months after surgery most of the β-TCP has been resorbed and replaced by bone.

Fig. 5. Radiographs of a 53-year-old woman with a shaft and comminuted depressed fracture of the lateral tibia plateau (A). Four weeks after open reduction and internal fixation with filling of the resultant defect with an 8-cm^3 block of β-TCP (B). Eighteen months later, additional TCP was implanted into defects left by the removal of the internal-fixation devices (C). Three years after surgery, osteoarthritic changes of the knee were minimal (D).

showed that the bone marrow had been also reconstructed (Fig. 7).

Case 8. A 40-year-old woman with enchondroma of the phalanx with expansion of the cortex. Curettage of the bone tumor was performed, followed by β-TCP implantation. Resorption of β-TCP and remodeling was observed 2 years after implantation (Fig. 8).

Case 9. A 68-year-old woman with medial compartmental knee osteoarthritis. The mechanical axis was corrected from varus to valgus after opening osteotomy. Resorption of an 8-cm^3 block of β-TCP with 75% porosity implanted in the defect was found 2 years postoperatively (Fig. 9).

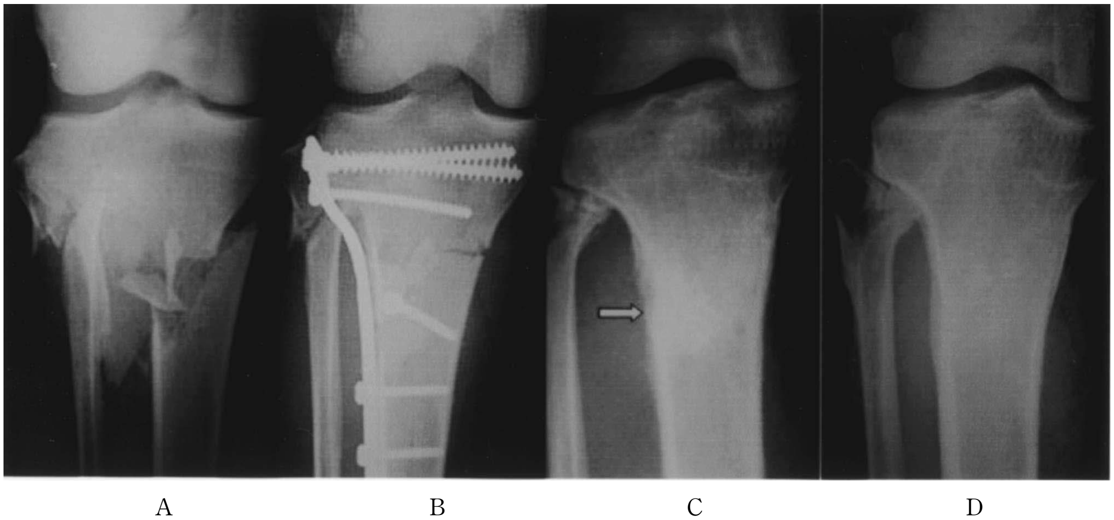


Fig. 6. Radiographs of a 48-year-old man with a comminuted fracture of the proximal part of the right tibia (A). Open reduction and internal fixation were performed, and a 4-cm^3 block of β-TCP was implanted in the cortical bone defects of the posterolateral side of the tibia (B). Eighteen months after surgery, healing with graft incorporation was radiographically confirmed (C). However, resorption of β-TCP was less than in the metaphysis of tibia. Complete resorption was observed 5 years after surgery (D). The arrow indicates remaining TCP.

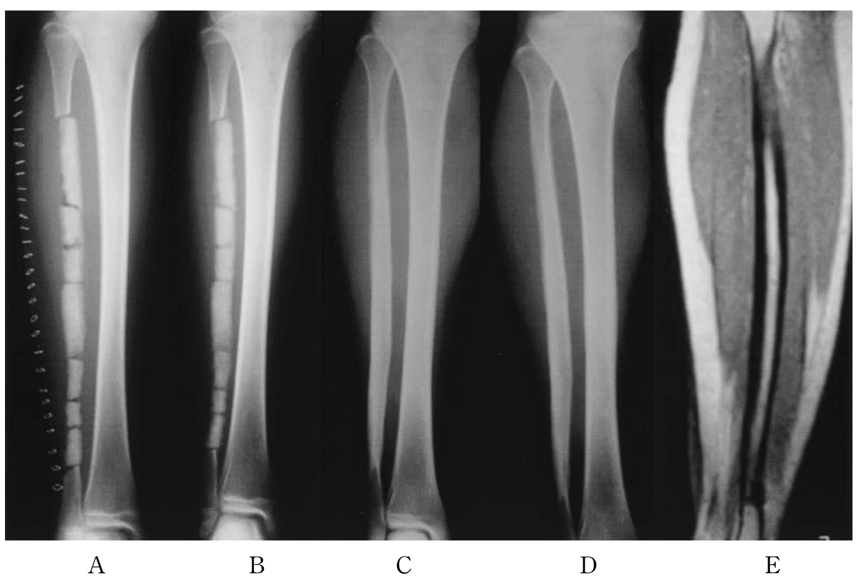


Fig. 7. Radiographs of a 13-year-old girl. An 18-cm-long section of the fibula was obtained for spinal fusion, and β-TCP blocks were placed on the remaining periosteum (A). Resorption of β-TCP and formation of cortical bone can be observed 6 weeks (B) and 18 months (C) after surgery. Nine years after implantation, the fibula is almost fully reconstructed (D). In addition, MR shows reconstruction of the bone marrow (E).

Case 10. A 51-year-old woman with medial compartmental knee osteoarthritis. Opening high tibial osteotomy (HTO) was performed using β-TCP blocks with 60% and 75% porosity without autogenous bone grafting. A wedge-shaped TCP block with 60% porosity, which was slightly larger than the protruding part of the Puddu plate, was implanted in the medial cortical defect in front and in back of the plate, and a second TCP block with 75% porosity was implanted in the remainder of the defect

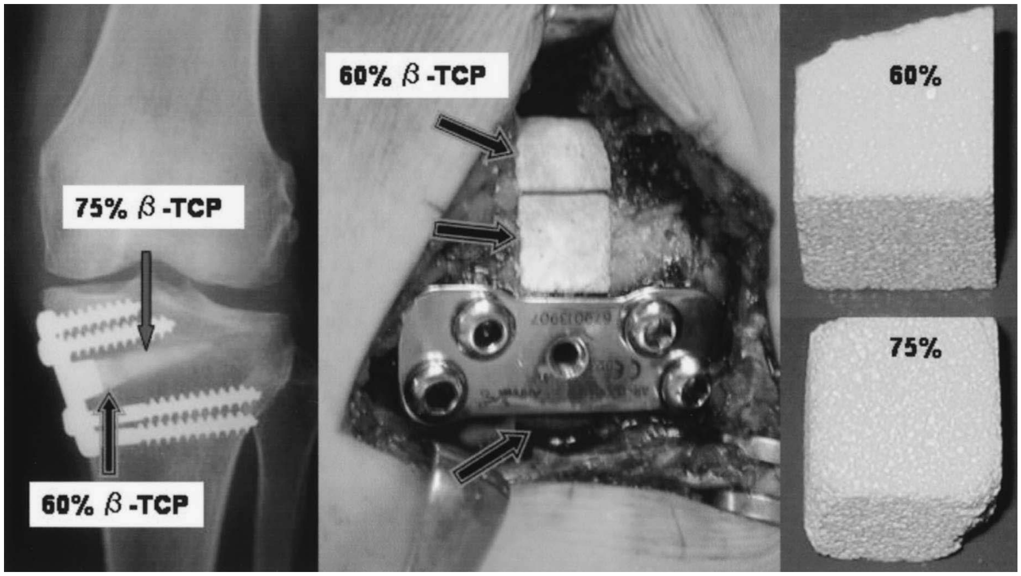
Fig. 8. A 40-year-old woman with enchondroma of the phalanx and expansion of the cortex (A). Bone tumor curettage was followed by β-TCP implantation (B). Resorption of TCP and remodeling are observed 2 years after implantation (C).

(Fig. 10).

No adverse reactions to β-TCP or disturbances of wound healing were observed in the postoperative period. Bone formation was observed in 299 cases. Three patients with recurrence of a bone cyst showed β-TCP resorption but no bone formation. A similar phenomenon was observed in two patients with postoperative recurrence of osteomyelitis. Resorption of β-TCP occurred from the periphery of the β-TCP implant at 2 to 3 weeks and then continued toward the center over time. In most adult patients, complete or nearly complete healing of bone defects had occurred within several years. All four patients younger than 10 years showed complete resorption of β-TCP within 2 years after surgery. On the other hand, all 5 patients older than 80 years showed partial resorption of β-TCP, but none showed complete resorption. Resorption of β-TCP was dependent upon the amount implanted, the patient's age, and the type of bone (cortical or cancellous bone). The larger the implant was and the older the patient was, the slower the healing was (Figs. 1, 2, 3, and 4); similarly, cortical bone defects healed more slowly than cancellous bone

A B C D

Fig. 9. Radiographs of a 68-year-old woman with medial compartmental knee osteoarthritis (A). The mechanical axis is corrected from varus to valgus after opening osteotomy (B). Resorption of an 8-cm^3 block of β-TCP with 75% porosity implanted in the defect can be seen 10 months (C) and 2 years postoperatively (D).



A B C

Fig. 10. A 51-year-old woman with medial compartmental knee osteoarthritis. Opening HTO is performed with 60% and 75% porosity β-TCP blocks without autogenous bone grafting (A). A wedge-shaped TCP block with 60% porosity, which is slightly larger than the protruding part of the Puddu plate, is implanted in the medial cortical defect in front and back of the plate (B), and another TCP block with 75% porosity is implanted into the rest of the defect. The macroscopic appearance of the two types of β-TCP block (C). The compression strengths of β-TCP blocks with 60% and 75% porosity are 20 and 3 MPa, respectively. The arrows indicate β-TCP blocks.

defects (Figs. 3, 4, 5, and 6). MR showed the remaining β-TCP as low-intensity signals on T1- and T2-weighted images. Areas in which TCP was resorbed were visualized as high-intensity signals, indicative of bone marrow formation (Figs. 1D and 2D).

In the case of the 13-year-old girl, β-TCP blocks were placed in the remaining periosteum after 18 cm of the fibula had been obtained for scoliosis surgery (Fig. 7A). New bone formation and TCP resorption were observed after 6 weeks, and the original shape of the fibula was reconstructed (Figs. 7B and C). At the most recent follow-up examination, 9 years after surgery, X-ray and MR images showed bone marrow formation (Figs. 7D and E). In all patients with enchondroma showing expansion of the cortex, remodeling of the deformity was observed after curettage and β-TCP implantation (Fig. 8). When β-TCP was implanted into defects of load-bearing sites, mostly caused by trauma, partial-weight bearing was possible after 5 to 6 weeks, and total-weight bearing was possible after 2 to 3 months. None of the patients with fractures showed postoperative fractures or deformities (Figs. 5 and 6).

Discussion

Hydroxyapatite has been widely used to repair bone defects due to tumor and trauma surgery. Recently, Matsumine et al.[9] have reported long-term results of calcium hydroxyapatite ceramic implantation in bone tumor surgery. In their report, hydroxyapatite was incorporated well into host bone, but none of the patients showed complete resorption. Thus, hydroxyapatite might interfere with remodeling and create a locus of increased stress owing to its slow resorption. In contrast, in the present study β-TCP was resorbed and replaced by bone. Thus, sites where β-TCP was implanted were amenable to remodeling. Moreover, bone reconstructed (Fig. 7) after implantation of β-TCP may be reusable for bone grafting. This advantage does not appear with hydroxyapatite-implanted bone.

The mechanism of bioceramic resorption involves two processes: solution-mediated disintegration and cell-mediated disintegration[10]. An example of the first process is calcium sulfate resorption. The β-TCP resorption is thought to involve both solution- and cell-mediated disintegration[11,12]. In contrast, poor resorption of β-TCP has been reported. A possible reason for differences in β-TCP resorbability is differences in pore structure. Handschel et al.[13] have reported that β-TCP is poorly resorbed after being implanted in a non-load-bearing environment. However, the β-TCP granules (Cerasorb, Curasan, Kleinostheim, Germany) used in their study differed in pore structure from the β-TCP used in our study. Altermatt et al.[14] have reported that most implanted β-TCP remains in calcaneal defects even after 7 years. They used highly purified β-TCP but with 60% porosity. They did not discuss pore structure in detail. We speculate that the number and size of macropores and micropores and the communications between pores were inadequate for TCP resorption and bone formation. Although implant purity and surface area are important, β-TCP resorption appears to depend on pore structure. The β-TCP used in our study had both macropores and micropores, most of which were interconnected. This structure facilitates the entry of proteins and cells for bone formation and resorption. De Groot[15] has suggested that the rate of degradation is determined by implant microporosity. Macroporous materials without microporosity allow only bone ingrowth, whereas dense materials without pores of either type show little degradation. The highly pure β-TCP used in the present study contained numerous micropores. In previous animal experiments, we have found numerous multinucleated giant cells on the surface of β-TCP upon hematoxylin-eosin staining; most of these cells were positively stained for tartrate-resistant acid phosphatase on serial sections[5]. This result was obtained 2 weeks after implantation and is consistent with the present clinical results in which the outer margin of the implanted β-TCP was unclear 2 to 3 weeks after implantation. We also found clusters of multinucleated giant cells and osteoblasts at the boundary between new bone and ceramic 2 to 4 weeks after surgery in a rabbit model. Ogose et al.[16] have reported a lining of osteoblastic cells on the surface of β-TCP and new bone, and a considerable number of osteoclast-like giant cells surrounding β-TCP in a human specimen 4 weeks after surgery.

Resorption of β-TCP and replacement by bone are influenced by the host environment as well as by the internal structure of TCP. Both β-TCP resorption and bone formation 9 years after surgery were good in a 16-year-old girl (Fig. 1). In contrast, a 67-year-old man who was treated at the same time showed less resorption of β-TCP (Fig. 2). Despite a similar amount of β-TCP having been implanted and a similar interval after surgery the younger patient showed greater resorption of β-TCP. A 2-year-old boy and a 3-year-old boy showed even greater resorption (Fig. 3 and 4). These results suggest that β-TCP resorption and replacement by bone are dependent on age.

We also found that the type of bone affected β-TCP resorption. The rates of β-TCP resorption and bone formation were greater in cancellous bone defects than in cortical bone defects (Figs. 3-6). This difference in resorption may be due to differences in blood flow between cancellous bone and cortical bone. Bone substitutes have been used to fill original bone defects. However, as better bone substitutes have been developed, they have also been used for newly created bone defects, such as in opening osteotomies. Recently, opening HTO has become popular because of its several advantages. Koshino et al.[17] have reported good long-term results after opening HTO using hydroxyapatite as a bone filler; no correction loss was reported. However, if severe varus or valgus knee deformity were to occur, fixing a component in the tibia during total knee arthroplasty might be difficult. In contrast, most of the porous β-TCP can be resorbed within a few years (Fig. 9). The TCP used in this study had a compression strength of only 3 megapascals (MPa), which is inadequate for weight-bearing sites until bone incorporation occurs. Initially during HTO, we implanted autogenous iliac bone on the medial side of the tibia to support compression and filled the remainder of the defect with TCP having 75% porosity (Fig. 9). Compression strength can be increased by reducing porosity. Thus, we have recently developed wedge-shaped β-

TCP with 60% porosity exclusively for opening HTO. This TCP has a compression strength of 20 MPa, which is approximately seven-fold greater than that of TCP with 75% porosity. During opening HTO, the opened defect was fixed with a Puddu plate, after which TCP with 75% porosity was used to fill the defect, except the medial side where a wedge-shaped TCP block with 60% porosity was implanted in front and back of the plate (Fig. 10). The use of a β-TCP block with 60% porosity avoided autogenous bone grafting and shortened the surgical time. We have used this technique in 40 patients and have observed no correction loss or nonunion. However, because the longest follow-up period has been only 22 months, these cases were not included in the present study. Resorption of β-TCP with 60% porosity occurred but required more time than that of β-TCP with 75% porosity.

Our present results indicate that, among calcium phosphate ceramics, β-TCP is an excellent bone substitute. In addition, the β-TCP block contains pore structures that can retain both cells and proteins. Thus, some growth factors can be retained to promote bone formation and β-TCP resorption.

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