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ORIGINAL ARTICLE

The use of interconnected β-tricalcium phosphate as bone substitute after curettage of benign bone tumours

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Abstract
Objective The purpose of this study was to analyse the clinical and radiological outcome in patients after implantation of β-tricalcium phosphate as a bone graft substitute to fill the defects after curettage of benign bone tumours and tumour-like lesions.
Method A total of 21 male and 26 female patients underwent the process of curettage of the tumour and filling of the bone defect with interconnected β-tricalcium phosphate in granule form. In 39 patients, β-tricalcium phosphate was exclusively used; in contrast, in 8 patients, it was combined with a cancellous autografts. The mass of implanted β-tricalcium phosphate ranged from 1.5 to 66 g (mean = 12.5 g). The clinical examination and radiographs were performed 24–96 months (50 months on average) after curettage of the tumour and implantation of the bioactive ceramics.
Results No patient complained of local pain, and all patients were satisfied with their limb function. Periodic radiographic assessments revealed that the material was incorporated in the surrounding bone without significant difference between implantation of β-tricalcium phosphate only and implantation of β-tricalcium phosphate mixed with autografts. Gradual resorption has started on the periphery and progressed centrally in both groups. Signs of the implanted β-tricalcium phosphate still remained radiographically in all 8 cases after implantation of synthetic material mixed with bone grafts and 27 of 39 cases after implantation of synthetic material only. The resorption was dependent on the mass of implanted β-tricalcium phosphate. In small defects with the mass of implanted material $\leq$3.5 g, we observed complete resorption of the material. The larger lesions with the mass of implanted material $\geq$5.5 g have healed more slowly, and β-tricalcium phosphate granules have been gradually resorbed but still remained radiographically distinct.
Conclusion According to our study, interconnected β-tricalcium phosphate is a safe and successful bone graft substitute for the treatment of benign bone tumours and tumour-like lesions because of its biocompatibility and bioresorbability.

Keywords Bone tumour · Tricalcium phosphate · Biocompatibility · Bioresorbability

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Introduction

A variety of synthetic bone graft substitutes have been developed to fill bone defects in an effort to overcome the limitations of autografts and allografts. An ideal synthetic bone substitute should be a porous matrix with

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interconnecting porosity that promotes rapid bone ingrowth, and at the same time, it should possess a sufficient strength to prevent its crushing under physiological loads during integration and healing. Hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$), β-tricalcium phosphate ($Ca_3(PO_4)_2$), their derivatives and combinations are the most commonly used ceramic materials in bone surgery. While hydroxyapatite materials provide an osteoconductive matrix for bone ingrowth and ongrowth, slow in-vivo resorption profiles can potentially limit their clinical applications [1–6]. Although β-tricalcium phosphate has been studied extensively in animal models and its biocompatibility, osteoconductivity and cell-mediated resorbability have been reported, there have been only limited data regarding long-term outcome of its clinical use in surgery for bone tumours [7–17]. The information regarding biological responses such as bone bonding and resorption of ceramics is very important in clinical applications.

The purpose of this study was to analyse the clinical and radiological outcome in patients after implantation of β-tricalcium phosphate as a bone graft substitute to fill the defects caused by curettage for benign bone tumours and tumour-like lesions.

Materials and methods

There were 47 consecutive patients who fulfilled the following inclusion criteria: (1) histologically confirmed benign bone tumour or tumour-like lesion, (2) treatment by curettage of the lesion and implantation of beta-tricalcium phosphate, (3) follow-up after at least 24 months to confirm a static radiographic outcome without recurrence of benign bone lesion. A total of 21 were men and 26 were women. Their age at the time of surgery was 5–65 years with an average age of 19 years. The benign bone tumours and tumour-like lesions were located in the humerus (11 patients), femur (10), tibia (10), phalanx (7), metacarpal bone (3), calcaneus (3) and fibula (3). Histological examinations revealed that 18 were unicameral bone cysts, 11 were enchondromas, 8 nonossifying fibromas, 5 fibrous dysplasias, 4 aneurysmal bone cysts and 1 bone cyst in neurofibromatosis.

All patients underwent the process of curettage of the tumour and filling of the bone defect with β-tricalcium phosphate (Poresorb®, Lasak Ltd., Prague, Czech Republic) in granule form with particle size of 0,6–2 mm. The porosity of the interconnected β-tricalcium phosphate scaffold was 35 ± 5%, the average macropore size was 100 μm in diameter, the size of micropores was 1–5 μm and the sintering temperature was 1180°C. The mass of implanted β-tricalcium phosphate ranged from 1.5 to 66 g (mean = 12.5 g). In 39 patients, β-tricalcium phosphate was exclusively used; in contrast, in 8 patients, it was combined with a cancellous autografts harvested from iliac crest. Internal fixation was employed in 8 patients because a pathological fracture occurred in 4 cases and an impending fracture was in 4 patients. Splints or bandages were used postoperatively for patients judged to be at risk of pathologic fracture. Full weight bearing was allowed after 8–12 weeks. The patients were scheduled for follow-up evaluations which included clinical and radiographic examinations at 4- to 6-week, 10- to 14-week, 6- and 12-month intervals. Thereafter, they were seen yearly. All patients were followed up 24–96 months (50 months on average) after curettage of the tumour and implantation of the bioactive ceramics.

The clinical findings were evaluated according to the criteria of Enneking et al. [18]. The radiographs were taken in standard projections and assessed independently by three investigators (two orthopaedic surgeons and one independent radiologist). The data were then checked for interobserver agreement. In the case of disagreement, the patient′s radiograph was re-evaluated by all three observers together. To determine changes in the radiolucent zone surrounding the bioactive ceramics and to evaluate the resorption of β-tricalcium phosphate, a radiographic analysis was performed. We also investigated whether a difference of incorporation after implantation of β-tricalcium phosphate only and β-tricalcium phosphate mixed with cancellous autografts exists.

The values were presented as mean ± SD. The Mann–Whitney U test was used to determine differences between the periods necessary for disappearance of radiolucent zones in β-tricalcium phosphate only and β-tricalcium phosphate mixed with autografts. Comparison of implanted synthetic material mass in both groups was performed using the Kolmogorov–Smirnov test. The Aspin–Welch unequal variance test was applied to determine differences between the amounts of implanted synthetic material for completely and partially resorbed cases. A P value of less than 0.05 was considered significant.

Results

Neither postoperative infection nor adverse reaction due to the material was observed. No patient complained of local pain at final examination. All patients were satisfied with their limb function; the average limb function was 100%. Radiographs obtained immediately after surgery demonstrated radiolucent zones between the implanted ceramics and the surrounding bone. Over time, radiolucent zones faded and new bone developed in all 47 patients. The mean period necessary for disappearance of these zones was 9 weeks (range 5–13 weeks) without significant difference

between implantation of β-tricalcium phosphate only and implantation of β-tricalcium phosphate mixed with cancellous autografts. Periodic radiographic assessments showed decreased radiographic density of β-tricalcium phosphate and replacement of β-tricalcium phosphate granules by newly formed bone trabeculae. These processes appear to have started on the periphery and progressed centrally in both groups. A significant difference in the mass of implanted synthetic material was observed between the group of patients who had implanted β-tricalcium phosphate only and the group of patients after implantation of β-tricalcium phosphate mixed with autografts ($P < 0.05$). In patients who had implantation of β-tricalcium phosphate mixed with cancellous autografts, mean mass of implanted synthetic material was 30.5 ± 17.8 g and the incorporated β-tricalcium phosphate still remained distinct centrally but resorbed gradually on the periphery at the final follow-up in all 8 cases (Fig. 1). In patients who had implanted β-tricalcium phosphate only, mean mass of the implanted synthetic material was 10.6 ± 9.0 g and complete resorption of β-tricalcium phosphate was observed in 12 cases. Signs of the implanted β-tricalcium phosphate still remained radiographically at the final follow-up in 27 cases, but the material was incorporated in the surrounding bone and gradually resorbed (Fig. 2). A significant difference in the mass of implanted synthetic material was documented between the patients who had completely resorbed and still remained β-tricalcium phosphate ($P < 0.05$). The amount of implanted β-tricalcium phosphate was 2.2 ± 1.3 in completely resorbed cases and 14.0 ± 8.5 in gradually resorbed cases with β-tricalcium phosphate still remained radiographically distinct.

Postoperative fractures occurred in two patients with a unicameral bone cyst in the humerus. One boy fell 3 weeks after surgery; the fracture was treated conservatively. The other patient has had a car accident 20 months after operation; the displaced diaphyseal fracture was treated with open reduction and plate osteosynthesis. In two young patients, growth arrest or deformity were seen before curettage of the lesion and implantation of β-tricalcium phosphate. Premature closure of the physeal plate with resulting shortening of the arm was found as a complication after pathological fracture of proximal humerus in one boy with unicameral bone cyst. Mild coxa vara was observed as a complication after repeated pathological fracture of proximal femur in one girl with fibrous dysplasia. Recurrences of the lesion were seen in only 4 cases (two unicameral bone cysts, two fibrous dysplasias). All patients had further curettage of recurrence in the area surrounding an incorporated ceramic material. In the skeletally mature male patient with a unicameral bone cyst, the cavity was filled with cancellous autografts; in other patients, β-tricalcium phosphate was added to the cavity at the time of repeat curettage.

Discussion

The synthetic bone graft substitutes were fabricated from a variety of materials, including calcium phosphates, calcium sulphates, bioactive glasses and glass-ceramics which appear to be the ideal substances for use as matrices because the inorganic component of bone is composed of calcium hydroxyapatite.

Bioceramics can be divided into three categories: bioinert ceramics (alumina), surface-bioactive ceramics (sintered hydroxyapatite, bioactive glasses and apatite-wollastonite glass-ceramics) and resorbable bioactive ceramics (low-crystalline hydroxyapatite and tricalcium phosphate). The ideal biodegradable substitute materials should fulfill some requirements such as biocompatibility, adequate initial strength and stiffness and retention of mechanical properties throughout sufficient time to assure its biofunctionality and nontoxicity of the degradation by-products [19–21]. The continuous degradation of a resorbable implant causes a gradual load transfer to the healing tissue, preventing stress-shielding phenomenon, and stimulates the healing and remodelling of bones [6, 22]. The surgeon should be concerned with the mechanical and biological properties of the bone substitute material as well as the handling and ability to assess healing of the grafted site. The small granules of the implanted β-tricalcium phosphate allow tight packing of irregularly shaped defects. This material can be only used in regions with intrinsic skeletal stability and the postoperative immobilization may be required due to its low mechanical properties because the synthetic filling contributes no significant structural support.

Aside from chemical composition, the microstructure (the volume, density and size of pores and interconnections, the specific surface) acts on the bone ingrowth of porous materials. An increase in porosity would make bone ingrowth inside materials easier but would decrease their biomechanical properties. The interconnections in a porous biomaterial act only as pathways for nutritional elements, vascularization and cells between the pores that are the sites for bone tissue growth proceeding from the outside to the inside. Therefore, pore size should be larger than interconnection size [23]. Macroporosity (pore size ≥50 μm), microporosity (pore size ≤10 μm) and pore wall roughness play a critical role in new bone formation [16, 24–29]. Thus, the larger surface area can contribute to higher bone inducing protein adsorption, ion exchange and bone-like apatite formation by dissolution and reprecipitation, while the surface roughness enhances attachment,

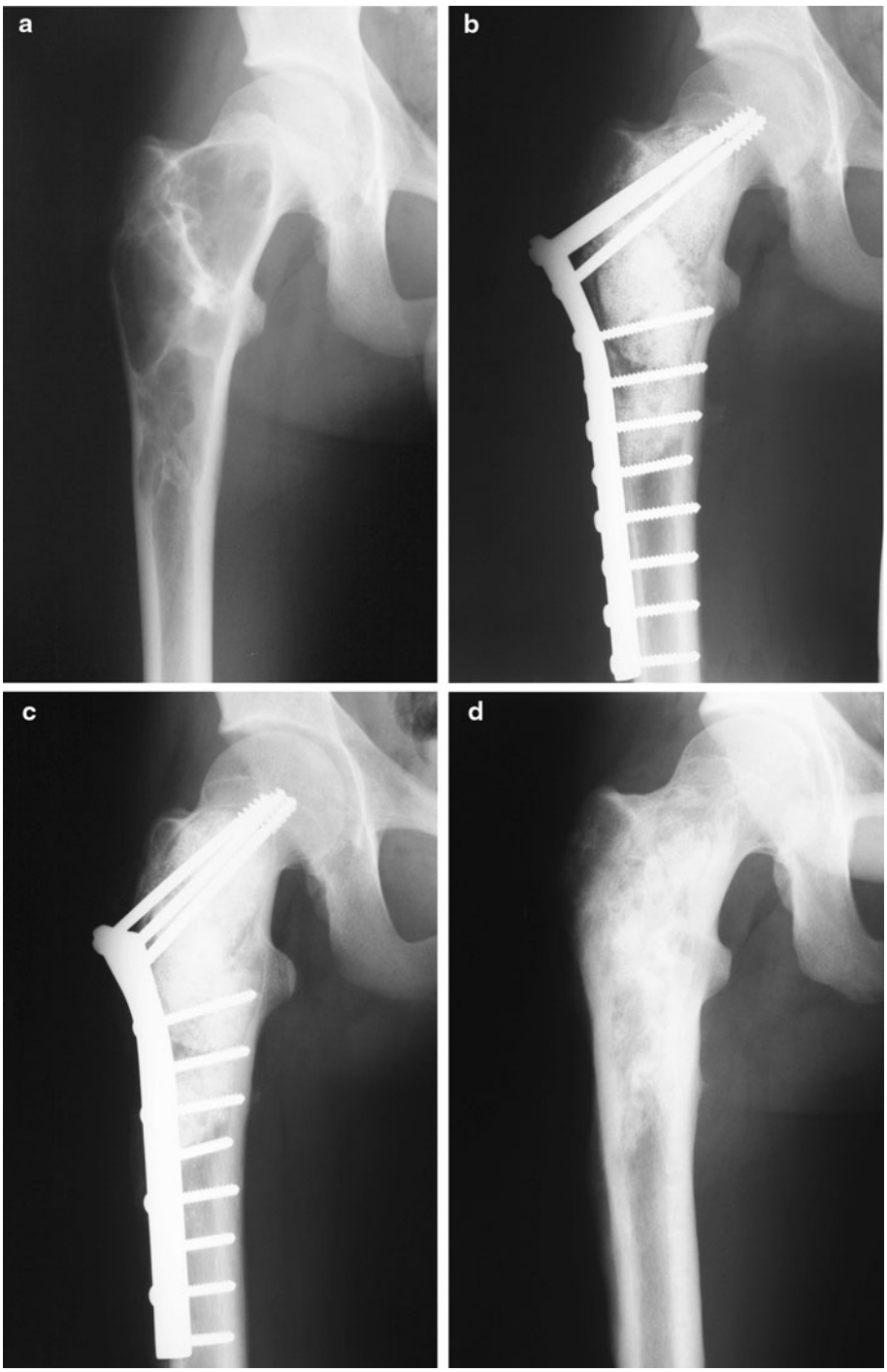

Fig. 1 Anteroposterior radiograph of the right proximal femur showing a large unicameral bone cyst in a 15-year-old boy preoperatively (**a**); radiolucent zones between the implanted material and the surrounding bone apparent 6 weeks after surgery (**b**); radiolucent zones vanished 11 weeks after curettage of the cyst and filling with ceramic granules mixed with cancellous autografts (**c**); decreased radiographic density of β-tricalcium phosphate and replacement of ceramic granules by newly formed bone have started on the periphery and progressed centrally, and remnants of the implanted material still remained distinct 3 years later (**d**)

proliferation and differentiation of bone-forming cells [28]. These data suggest that more extensive dissolution and reprecipitation of low-crystalline calcium phosphates can cause more osteoconductive and cell-mediated degradation characteristics [30].

Resorption is an important characteristic of biomaterials and can be divided in two mechanisms: solution-mediated dissolution processes and cell-mediated (phagocytic) processes. The degradation characteristics of calcium phosphates are dependent on the chemical composition, crystal structure, crystal and grain size, microporosity, neck geometry and neck dissolution rates of the materials [30]. Pore density and interconnection density that expresses the quantity of connections between pores of porous materials play a more important role than their size that is modified during degradation of resorbable bioceramics, whereas the sizes and the densities are equally important in unresorbable biomaterials [23].

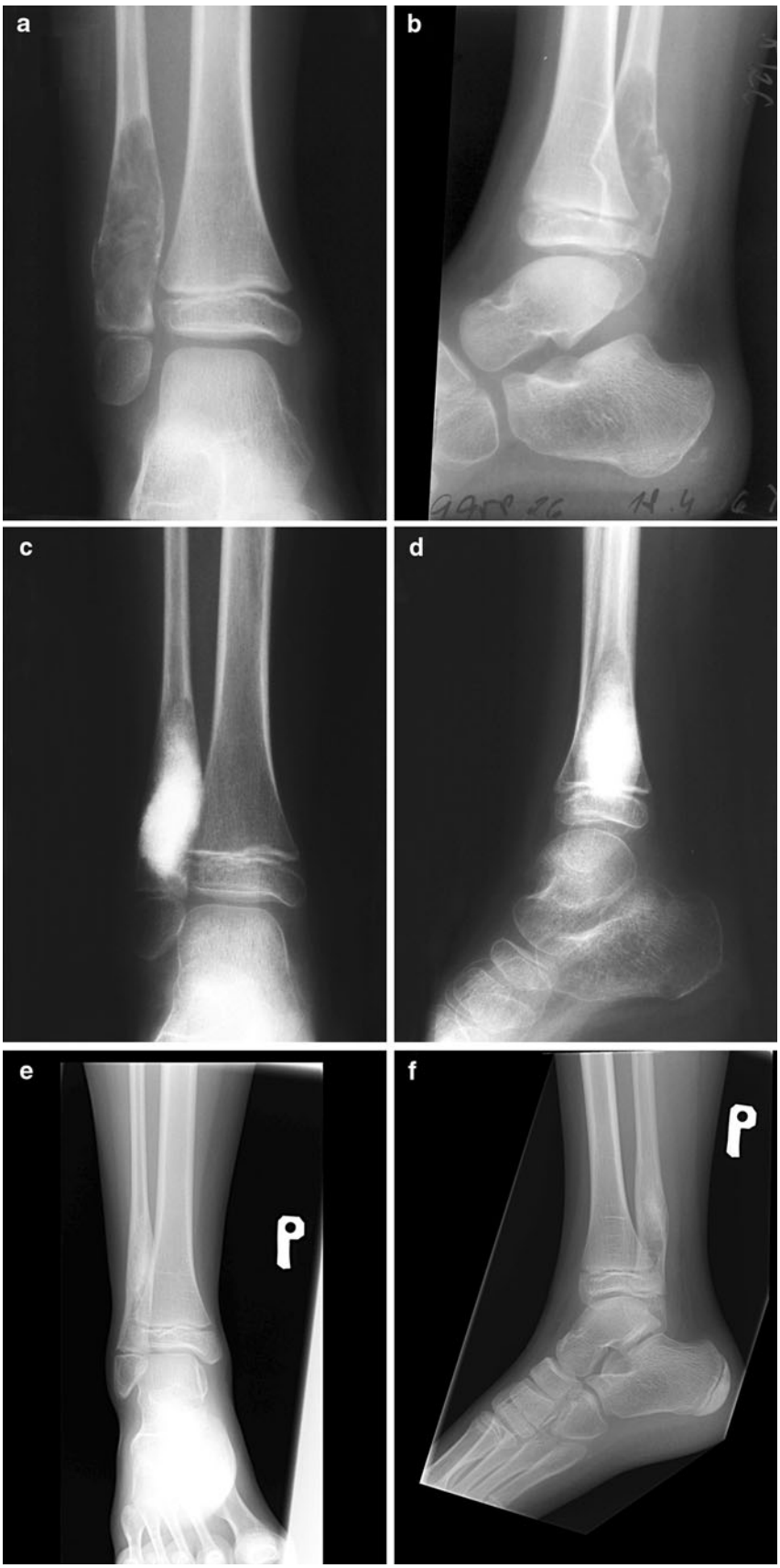

Fig. 2 Anteroposterior (**a**) and lateral (**b**) radiographs of the right distal fibula showing an active unicameral bone cyst with pathologic fracture in a 7-year-old girl preoperatively; radiolucent zones between the implanted ceramic and the surrounding bone faded 9 weeks after curettage of the cyst and packing with β-tricalcium phosphate only (**c, d**); the implanted β-tricalcium phosphate was nearly completely absorbed and replaced by newly formed bone 4 years later (**e**, **f**)

This study presents the appropriate new bone formation with incorporation of the implanted β-tricalcium phosphate. In agreement with other authors, resorption was dependent on the defect size [9, 11, 31]. In small defects with the mass of implanted β-tricalcium phosphate $\leq$3.5 g, we observed complete resorption of the material. The larger lesions with the mass of implanted β-tricalcium phosphate $\geq$5.5 g appear to heal more slowly, and the replacement of β-tricalcium phosphate granules by newly formed bone appears to have begun on the periphery and progressed centrally. Although the material was incorporated in the surrounding bone and gradually resorbed, signs of the implanted β-tricalcium phosphate still remained radiographically in 35 cases (74%). In our opinion, the implanted mass of biomaterial was higher in our patients compared to other authors [9, 10]. More experimental and clinical studies will be required in order to resolve the healing problems of large bone defects using osteoinductive factors and cell cultures. According to our study, interconnected β-tricalcium phosphate is a safe and successful bone graft substitute for the treatment of benign bone tumours and tumour-like lesions because of its biocompatibility and bioresorbability.

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