A prospective randomized 14-year follow-up study of bioactive glass and autogenous bone as bone graft substitutes in benign bone tumors

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Abstract: A prospective randomized long-term follow-up study of bioactive glass (BG)-S53P4 and autogenous bone (AB) used as bone graft substitutes in benign bone tumor surgery during 1993–1997 was conducted. Twenty-one patients (11 in the BG group, 10 in the AB group) participated in a 14-year follow-up. X-rays and MRI scans were obtained, and in the BG group, CT scans were also performed. In the BG group, the filled cavity had a dense appearance on X-ray. MRI showed a mainly or partly fatty bone marrow, and in the large bone tumor group, remnants of glass granules were also observed. Increased cortical thickness was seen in nonossifying fibromas and enchondromas. BG-S53P4 is a safe and well-tolerated bone substitute with good long-term results. BG-S53P4 does not disturb the growth of bone in children. © 2010 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 94B:157–164, 2010.

Key Words: bioactive glass, bone substitute, biocompatibility/hard tissue

INTRODUCTION

Autogenous bone (AB) with its osteoinductive potential has been the golden standard of graft material in bone reconstruction surgery. The limitations of AB and AB-associated morbidity at the donor site have prompted scientists in the field of orthobiology to develop bone graft substitutes for different applications. The focus in developing biomaterials to be used in bone defects has been on the ability of the material to stimulate bone formation and restore structural integrity. Many different bone substitutes are today available on the market, and physicians are able to choose between a variety of these substitutes, including ceramics, bioactive glasses (BGs), demineralized bone matrix, allograft bone and bone morphogenetic proteins. However, for a better understanding of these products, prospective randomized studies with long-term follow-ups are needed.

BGs have proven to be bone bonding, osteoconductive bone substitutes with bone-stimulative and antibacterial properties.[1–6] They elevate mRNA levels for synthesis markers, such as type I-III collagens, osteocalcin, osteonectin, and osteopontin, as well as for resorption markers, such as cathepsin K and MMP-9, and are thus known to enhance the activity of osteoblasts and to induce a high local turnover of bone formation and resorption. Molecular analysis of defects filled with BG has shown elevated mRNA levels for these bone turnover markers at 8 weeks compared with unfilled control defects, suggesting that an interaction between BGs and the surrounding tissue takes place over time.[7]

Bonding between glass and bone can be presented as a complex series of reactions among the glass and the host tissue.[8–10] As the glass is implanted in the bone, reactions start at the glass surface, with a subsequent formation of a Si-rich layer. On top of this layer, a stabilizing layer of hydroxyapatite (HA) is formed. This HA layer has been demonstrated to chemically bind to bone.[11] The initial leaching of alkali, and alkaline earth ions from the surface of the glass leading to a fast increase in pH around the glass, and the subsequent osmotic effect cased by dissolution of the glass has been suggested to partly explain the antibacterial properties observed for BGs.[12,13] The aim of this study was to evaluate the clinical long-term outcome and radiological findings of BG and AB used as bone graft materials in operative treatment of benign bone tumors. To our knowledge, this is the longest prospective randomized follow-up study of synthetic bone substitutes.

PATIENTS AND METHODS

Twenty-five patients (9 females, 16 males), who had taken part in a prospective randomized study of benign bone tumors treated with BG or AB during 1993–1997 participated in this long-term follow-up study.

The bone tumors were primarily found on X-rays taken either because of local pain or after a pathologic fracture. All pathological fractures ($n = 13$) were treated conservatively. The patients were then randomized into one of two groups, BG or AB. In the BG group (14 patients), BG-S53P4 (manufactured today as BonAlive™ by BonAlive Biomaterials, Finland) was used as bone graft substitute. In the AB group (11 patients), AB harvested from the iliac crest was used as a filling material.

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TABLE I. Type of Tumor Classified by Histopathological Examination, Location of Tumor, and Bone Graft Used

Patient Number	Tumor	Location	Size Large/Small	Bone Graft
1	Aneurysmal bone cyst	Proximal humerus	Large	BG
2	Nonossifying fibroma	Distal tibia	Large	BG
3	Enchondroma	Finger	Small	BG
4	Enchondroma	Finger	Small	BG
5	Enchondroma	Finger	Small	BG
LF				BG
7	Nonossifying fibroma	Distal tibia	Large	BG
LF				BG
9	Simple cyst	Proximal humerus	Large	BG
10	Aneurysmal bone cyst	Proximal humerus	Large	BG
LF				BG
12	Nonossifying fibroma	Distal tibia	Large	BG
13	Simple cyst	Proximal humerus	Large	BG
14	Nonossifying fibroma	Distal tibia	Large	BG
15	Enchondroma	Finger	Small	AB
16	Simple cyst	Patella	Large	AB
17	Enchodroma	Finger	Small	AB
18	Simple cyst	Proximal humerus	Large	AB
19	Simple cyst	Finger	Small	AB
20	Nonossifying fibroma	Distal tibia	Large	AB
21	Simple cyst	Distal tibia	Large	AB
22	Aneurysmal bone cyst	Talus	Large	AB
LF				AB
24	Simple cyst	Proximal humerus	Large	AB
25	Enchondroma	Finger	Small	AB

LF, lost to follow-up; BG, bioactive glass; AB, autograft bone.

The volume of the tumors was estimated on both X-rays and CT scans by measuring three orthogonal diameters. An ellipsoidal volume was used. In both groups, 64% of the bone tumors were classified as large (mean 23.4/28.8 cm^3) and 36% as small (2.3/1.1 cm^3).

The patients were operated on at the Department of Surgery, Turku University Hospital. During the operation, a cortical fenestration was performed, and a biopsy was taken to confirm the preoperative clinical and radiological diagnosis. The tumors were carefully evacuated and the inner wall of bone was refreshed using bone drills. The cavity was filled with either BG-S53P4 granules or AB, according to the randomization. In small bone tumors ($n = 5$), the size of the glass granules was 1–2 mm, and in larger tumors ($n = 9$), glass granule sizes of 1–2, 2–3, or 3.15–4 mm were used. The filled cavity was covered with a cortical fragment that had been detached to access the tumor. The mean hospital stay in both groups was 4 days. Antibiotics, anti-thromboembolic prophylaxis, and anti-inflammatory drugs were provided according to routine hospital procedures. The tumor types classified by histopathological examination and location are shown in Table I.

The follow-up comprised visits to an outpatient department over a 3-year postoperative period. X-rays and CTs were taken for evaluation of the bone lesion. Two reoperations due to growing residual cysts were performed; one in the BG group and one in the AB group.[14]

In this long-term follow-up, the patients were reexamined at an out-patient department. All patients were asked to subjectively evaluate their long-term results according to a scale; excellent, good, fair or poor. X-rays and MRI scans were taken for evaluation of the treated bone area in both groups, and in the BG group CT scans were also performed on 10 patients. MRI examinations were conducted using a 1.5-T scanner (Intera Achiera, Philips Medical Systems, Best, Netherlands). Axial and coronal T1-weighted sequences, axial proton density + T2-weighted fat suppression sequence, coronal proton density, and sagittal intermediate-weighted fat suppression sequence were included. Gadolinium was not used. Slice thicknesses were adjusted according to filled cavity size; 2- to 4-mm thicknesses were used. If needed, one axial T1 sequence of the contra lateral side was added for comparison of cortical thicknesses.

CT examinations were performed using a 4-slice helical CT-scanner (HiSpeed QX/i, General Electric, Milwaukee, WI). The treated area was scanned in the axial plane and reconstructed in three orthogonal planes on a work station (GE Advantage AW 3.06 sdc workstation). The slice widths and intervals were 2.5/1.25 mm for large-filled cavities and 1.25/0.625 mm for small-filled cavities.

BG-S53P4 gained European approval for orthopedic use as a bone graft substitute in 2006. This study was conducted in accordance with the ethics principles of the latest version of the Declaration of Helsinki, applicable regulatory requirements, including standards of the International Organization of Standardization, and adherence to Finnish laws, and regulations. The local ethics committee approved the study protocol, and patient-informed consent was obtained. The clinical study, the use of case reports, and the statistical evaluation were performed according to the Good Clinical Practice standard.

TABLE II. Radiological Data

		X-ray				MRI					CT				
Nr	Bone Graft Used	R	Area Sclerotic	BG Visible	Affected Cortex	R	BM Fatty	BM Sclerotic	Affected Cortex (mm)	Nonaffected Cortex (mm)	Affected Cortex	R	Affected Cortex (mm)	Nonaffected Cortex (mm)	Affected Cortex	Cavity Size (mm^3)
1	BG	−	+	+	−	−	++	+	2.6, 2.8	4.1, 4.6	−	−	2.8, 2.8	5.5, 5.6	−	0
2	BG	−	+	−	++	−	+	+		NA	++	−	4.4, 4.4	2.0, 2.0	++	0
3	BG	−	+	−	++	−	++	+	1.9, 2.4	1.3, 1.6	++	−	2.1, 2.4	1.3, 1.1	++	0
4	BG	−	+	−	++	−	+	++	1.7, 2.1	1.3, 1.3	++	−	3.1,2.1	1.4, 1.1	++	0
5	BG	−	+	−	++	−	++	+	1.7, 1.7	1.5, 1.8	norm	−	1.9, 1,9	1.4, 1.4	++	0
LF																
7	BG	−	+	+	++	−	−	+		NA	++	−	3.6, 1.7	2.0, 1.5	++	0
LF																
9	BG	−	+	−	−	−	++	+		NA	−	−	3.2, 3.4	5.5, 4.7	−	0
10	BG	−	+	+	norm	−	+	+		NA	NA	−	2.9, 2.1	2.8, 2.8	−	0
LF																
12	BG	−	+	+	++	−	+	+		NA	++	−	2.8, 2.2	2.2, 2.0	++	0
13	BG	−	+	+	norm	−	++	+	2.3, 2.0	3.5, 3.3	−	−	NA	NA	NA	
14	BG	−	+	+	++	−	++	+	5.5, 4.3	NA	++	−	5.2, 4.5	2.4, 2.4	++	0
15	AB	−	−		norm	−	++	−	0.8, 0.8	0.9, 0.8	norm					
16	AB	−	−		norm	−	++	−	1.7	1.5	norm					
17	AB	−	−		−	−	++	−	0.8, 1.2	0.9,1.1	norm					
18	AB	−	+		norm	−	++	+		NA	NA					
19	AB	−	−		norm	−	++	−		NA	NA					
20	AB	−	−		norm	−	++	−	4.4, 4.3	4.4, 2.7	++					
21	AB	−	+		norm	−	++	+	2.7, 2.7	2.9, 2.9	norm					
22	AB	−	−		norm	−	++	−	0.9, 0.7	1.5, 0.9	−					
LF																
24	AB	−	+		norm	+	++	+	3.0, 3.5	3.8, 5.2	−					
25	AB	−	−		norm	−	++	−	1.2, 1.3	1.5, 1.5	−					

BG, bioactive glass; R, residive; Affected cortex (++, thicker; norm, normal; −, thinner; compared to nonaffected cortex); BM, bone marrow (BM fatty ++, mainly normal fatty BM; BM fatty +, partly normal fatty BM; BM sclerotic ++, mainly sclerotic BM; BM sclerotic +, partly sclerotic BM); LF, lost to follow-up; NA, not available.

STATISTICAL ANALYSIS

The intent-to-treat populations, which included all randomized patients, were used in all tables and analyses. Descriptive statistics were calculated for all variables. Categorical variables are presented in frequency tables (PROG FREQ in SAS®) (number of cases and percentages) by treatment. The numerical variables were tabulated by treatment (PROG UNIVARIATE in SAS®).

CT and X-ray measurements were evaluated with analysis of variance for repeated measures (ANOVA) when treatment, size of the bone tumor, time, and treatment × time interaction were included in the model (PROC MIXED in SAS®). Thickness of the cortex (thick vs. normal) was analyzed by Fisher's Exact Test (PROC FREQ in SAS®).

All statistical evaluations utilized SAS Procedures in SAS® system for Windows (version 8.2)

A P-value of <0.05 was considered significant.

RESULTS

Twenty-one patients, (11 in the BG group, 10 in the AB group) completed the long-term follow-up. One patient had been lost to follow-up, and three patients lived far away and declined to participate in the study.

In the BG group, eight of the filled cavities were classified as large and three as small. In the AB group, six of the filled cavities were classified as large and four as small. The mean postoperative follow-up was 14 years. [12–16]

Recovery of limb function was normal in both groups: shoulder abduction, 180°; elevation, 180°; external rotation in abduction, 90–120°; knee extension, 0; knee flexion, 100–150°. Ankle function was normal, except for one patient who showed a plantar flexion of 60°. X-rays verified osteoarthritis in the talus. The subjective outcome of the operative treatment was graded by the patient according to the patients' subjective feeling of the treatment as follows; excellent, good, fair, or poor. The subjective outcomes in the BG group were as follows: excellent ($n = 5$), good ($n = 4$), fair ($n = 1$), and poor ($n = 1$). In the AB group, the subjective outcomes were excellent ($n = 7$) and good ($n = 3$). In both groups, the reason that the operative results were not subjectively evaluated as excellent was due to postoperative complications, including a small deviation of a finger because of a missed fracture and lack of postoperative immobilization, feeling of shoulder instability, hyperesthesia in the operated region and muscle atrophy. None of the complications were associated with the bone graft material used. In the AB group, pain at the donor site at the iliac crest was reported by three patients. The pain lasted for 6 months in two patients and for 1 month for one patient. One patient graded the pain as mild and continuous, another as mild and intermittent and the third as severe and continuous.

Radiology

The radiological data are summarized in Table II. Comparable radiological findings (X-ray, MRI, and CT) are visualized for one

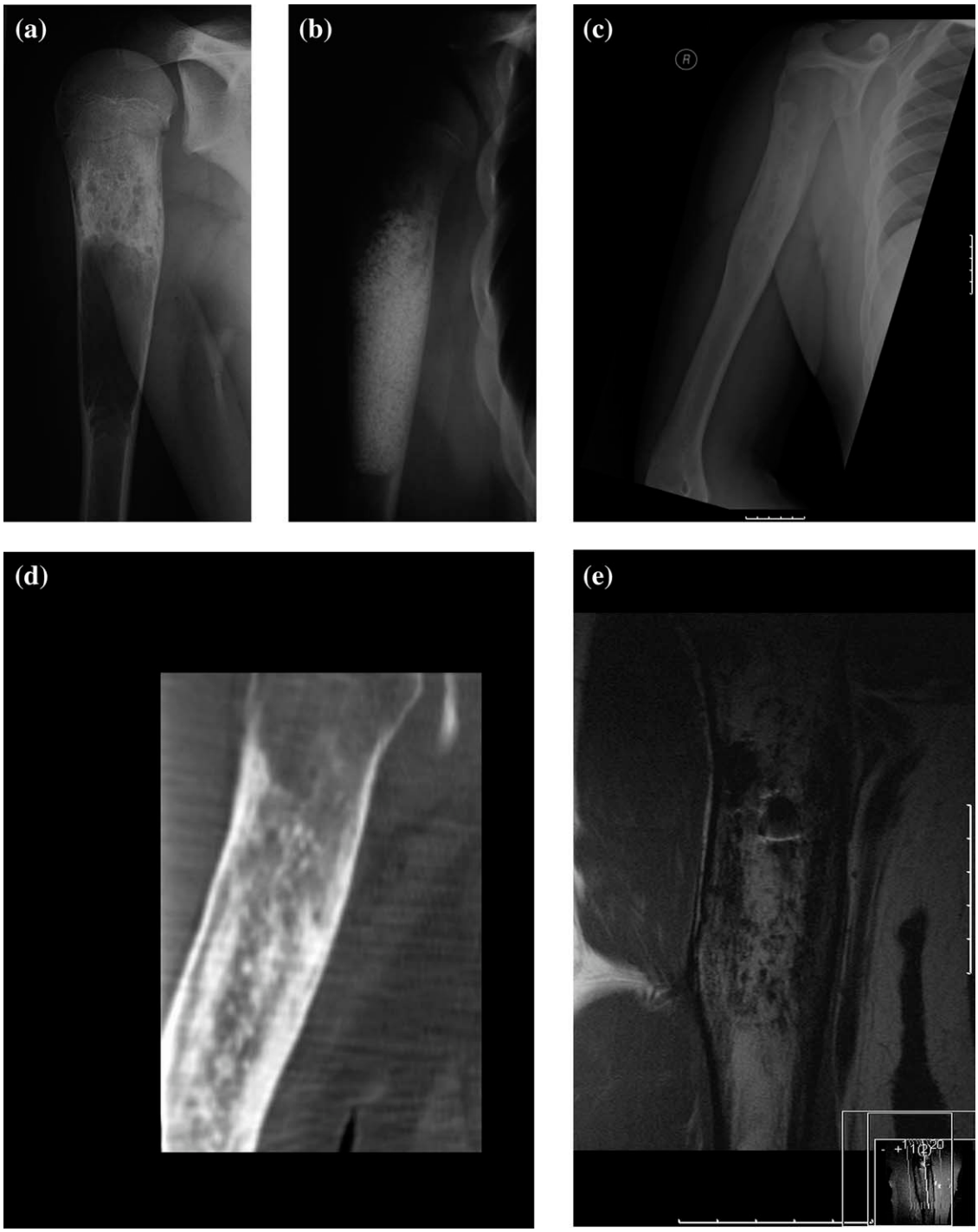

FIGURE 1. Aneurysmal bone cyst in the humerus treated with BG, (a) preoperative X-ray, (b) postoperative X-ray showing cavity filled with BG granules, (c) long-term follow-up X-ray showing the treated cavity with a dense appearance, (d) long-term follow-up coronal CT reformat of the treated cavity showing remnants of glass granules in the bone, (e) long-term follow-up coronal T1 MRI of the treated cavity showing a mainly fatty bone marrow with remnants of glass granules.

aneurysmal bone cysts (ABC) in the proximal humerus treated with BG in Figure 1(a–e), and for one simple bone cyst in the proximal humerus treated with AB in Figure 2(a–d).

X-ray findings

In the BG group, both the small- and the large-filled cavities had a dense, sclerotic appearance. Ill-defined glass granules among new bone were still visible in six of eight treated large bone tumors; but in the group of small bone tumors, no glass granules were observed. No ectopic bone was found in the surrounding soft tissue. No residives were observed.

In seven of the 11 filled cavities, the cortex appeared thicker than normal. This was observed for all small-filled cavities and for four large-filled cavities. The cortical

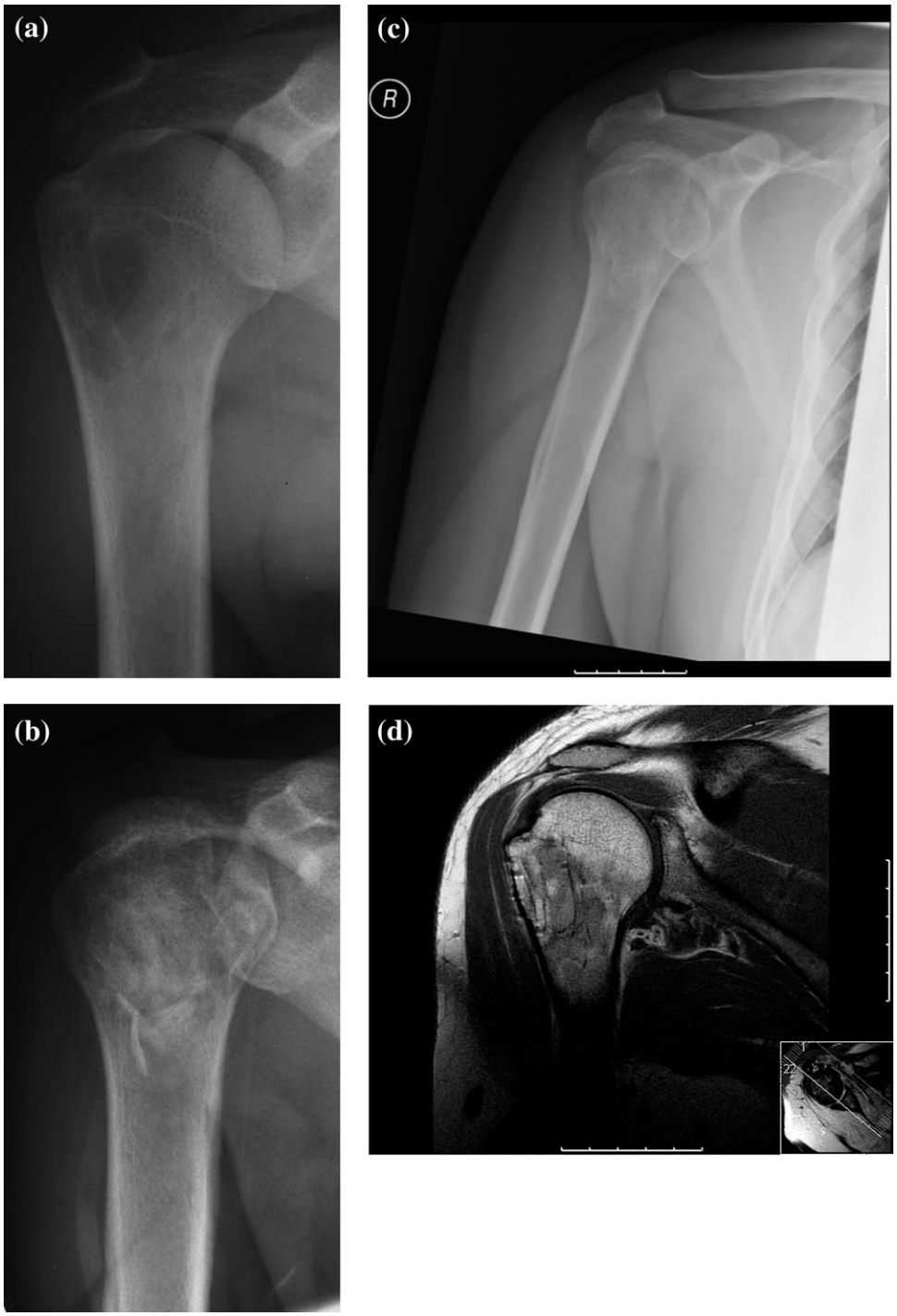

FIGURE 2. A simple bone cyst in the proximal humerus treated with AB, (a) preoperative X-ray, (b) postoperative X-ray showing cavity filled with AB, (c) long-term follow-up X-ray showing small sclerosis in the treated cavity, (d) long-term follow-up coronal T1 MRI of the treated cavity showing sclerosis and remnants of AB

thickness in the BG group compared to the AB group increased significantly with time ($P < 0.0001$). The thickening of the cortex that had been observed already at 8 months remained during the follow-up (Figure 3).

The thickening of the cortex seemed to be dependent on the type of treated tumor. The cortex appeared thickened for enchondromas and nonossified fibromas, and normal or thin for bone cysts or ABCs. According to Cochran-Mantel-Haenszel statistics based on table scores, this finding was, however, not statistically significant, due to the small number of patients.

Weight-bearing, defect dimension or previous pathological fractures did not solely affect the thickening of the cortex. All nonossified fibromas were classified as large and

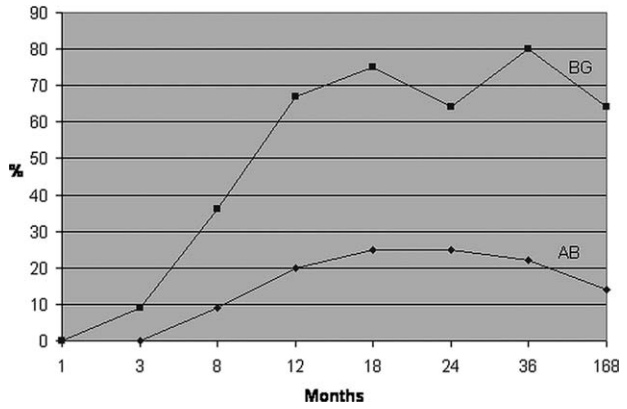

FIGURE 3. The cortical thickness in the BG group compared to the AB group increased significantly with time ($p < 0.0001$).

found in weight-bearing regions in the distal tibia. The enchondromas were classified as small and found in the fingers. The pathological fractures in the BG group were found in three enchondromas and in two simple cysts and two aneurysmal cysts in the humerus.

In the AB group, the filled area appeared normal in five cases. In three large-filled cavities, the region was visualized as a dense, slightly sclerotic area, and in one large-filled cavity, also remnants of cortical bone fragments were observed. No ectopic bone was seen. No tumor recurrences were found. The cortex appeared normal in nine of 10 cases and thin after one treated enchondroma. In one aneurysmal bone cyst, the shape of the talus remained abnormal. In one treated bone cyst in a finger, mild osteoarthritis in the adjacent distal interphalangeal joint had developed.

MRI findings

In the BG group, granules were still visible in the filled region in five of the treated large bone tumors. No connection between appearance of bone marrow and type of treated bone tumor was observed. The bone marrow appeared mainly fatty, with focal low signal areas, probably due to remnants of glass granules (four large, two small). In four cases, the bone marrow was classified as partly fatty and partly sclerotic (three large, one small). The low-signal intensity areas were mainly observed in the periphery of the treated cavity. No bone marrow edema was observed, except in one treated nonossified fibroma where the bone marrow between the glass granules was still T2-hyperdense and a "double cortex" was present (Figure 4). The cortex was thicker than normal in 55% of the cases, in four large nonossifying fibromas and in two small enchondromas and thinner than normal in two bone cysts and in one ABC. A nongrowing residual ($8 \times 4 \times 3$ mm^3), observed already at 36 months, was present in one small enchondroma.

In the AB group, the bone marrow appeared normal in seven cases. A connection between appearance of bone marrow and type of the treated bone tumor was observed in all three treated large simple bone cysts; mild or partial sclerosis was detected. The cortex, relative to a normal cortex, was graded as thicker in one case (one large treated nonossifying fibroma), normal in three cases (two large treated bone cysts, in one small enchondroma), and thinner in three cases (one large treated ABC, one large bone cyst, one small enchondroma). In one case, no normal reference was available, and in one case, surgical metal artefacts along the cortex made measurements impossible. A residive (8×8 mm^2) in one filled bone cyst in the proximal humerus that had been observed at 36 months was still present. In an aneurysmal bone cyst in the talus, bone marrow edema was observed in the subchondral bone probably due to joint shape abnormality and severe osteoarthritis.

CT findings

A CT was performed on 10 patients in the BG group. In seven cases (six large, one small), glass granules surrounded by bone were visible in the filled cavity. The cortical thicknesses, compared with a normal cortex, were graded thick in seven of 10 cases; in four treated nonossifying fibromas and in three enchondromas. The cortical thickness was thinner than normal in two treated large ABCs and in one large bone cyst. A regional "double cortex" formation was observed in two treated nonossifying fibromas in the distal tibia.

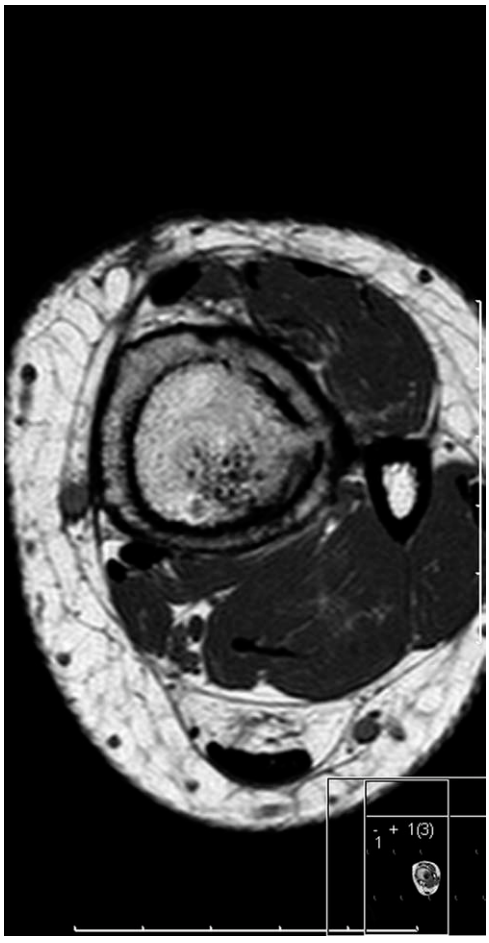

FIGURE 4. Long-term follow-up axial CT of nonossified fibroma in the distal tibia treated with BG, showing a thickened cortex with "double cortex" formation (arrow).

DISCUSSION

BGs are osteoconductive bone substitutes with documented bone bonding, antibacterial, and angiogenesis promoting properties.[1–15] BG-S53P4 has been reported to be well tolerated, with no adverse effects observed.[14] In this study, no material-dependent adverse effects were detected in the 14-year follow-up.

In our earlier 3-year follow-up study, a significant difference was demonstrated between the BG and AB groups in how the filled bone cavity disappears over time. Remodeling was slower in the BG group, but at 36 months, no statistical difference in cavity volume between the two groups could be observed. In the BG group, the filled cavities were visualized as dense on X-rays, and on CT scans glass granules were still visible.[14]

Density of bone on plain films usually mainly represents cortical thickness, not properties of cancellous bone.[16] However, in this study, the area of the filled cavity affected bone density on plain films. This is in accordance with previous observations revealing that glass granules are well incorporated in cancellous bone that appears to be harder than normal.[14] This long-term follow-up demonstrates that the filled cavity in the BG group still has a dense appearance on X-ray. MRI and CT reveal, however, that the bone marrow is mainly or partly fatty, and therefore observations made solely on X-ray may lead to an impression of a more sclerotic area than actually is the case. Interestingly, a dense appearance is also observed in some treated bone cysts in the AB group. This finding was verified on MRI, which showed mild or partly sclerosis of bone marrow.

Our study shows that remnants of glass granules, especially in large filled cavities, will remain during a long time. BGs have, in an *in-vitro* study, been reported to be resistant to osteoclastic activity. The authors concluded that the degradation of BG starts by physicochemical reaction with cell culture medium and not by osteoclastic activity. The authors did not, however, exclude the possibility that BGs could be degraded by osteoclasts *in-vivo* or in long-term cultures after separation into apatite and silica-gel compartments. In the study, it was also shown that the BG surface was fully occupied by osteoblasts.[17]

Although the remodelation of a grafted region is slow, it has been demonstrated that BG-S53P4 does not disturb the growth of bone in the hand in children. A recurrent aneurysmal bone cyst of the proximal phalanx of the index finger of a 3-year-old child was treated with BG-S53P4. At 2 years, no cavity was observed and the homogenous region resembled normal trabecular bone. The phalanx had grown in length and remodeled to an almost normal shape.[18]

Previous observations have also indicated that the remodelling process in the BG group can stimulate the cortex to grow in thickness. This has been reported to occur already at eight months.[14] In our long-term follow-up, BG was shown to stimulate the cortex to grow in thickness, and the cortex remained thickened. However, for an unknown reason, this was demonstrated only for treated enchondromas and nonossifying fibromas, not for treated bone cysts or ABCs, for which the originally thin cortex remained thin. Weight-bearing, dimension of treated region or previous pathological fracture did not affect the cortical thickening seen for enchondromas and nonossified fibromas.

In the AB group, no correlation between bone tumor etiology and cortical thickness emerged. In this group, the cortex remained thin in three of eight treated bone tumors. The bone tumors were all of different origin: one ABC, one bone cyst, and one enchondroma.

For some unknown reason, a double cortex formation was observed in the BG group, in two treated nonossifying fibromas. One of the patients had post-operatively sustained a fracture in the operated region, which may have contributed to the finding. The other patient had healed well, with no complications.

Recent studies have indicated that bone defects following curettage do not necessarily need augmentation, and that sufficient bone strength can be achieved without grafts.[19,20] However, the risk of subsequent fracture or late development of osteoarthritis has been described to be strongly related to the size of the unfilled bone tumor, with tumors more than 5 cm in diameter having a much higher complication rate.[20] A higher complication rate was also observed for high-loaded large bone tumors in the BG group. Two patients with treated nonossifying fibromas sustained fissural fractures 1 and 3 months postoperatively. The fractures could probably have been avoided with cast immobilization. BGs can, therefore, also be used in cavitary defects under high-loading conditions.

Depending on the type of bone tumor, different recurrence rates have also been noted. For example, for ABCs, the recurrence rate after curettage and bone grafting has been reported to range from 30 to 66%, and recurrences are most likely within 2 years of primary treatment.[21] During this long-term follow-up, no recurrences after 3 years were observed in either of the groups, and earlier detected recurrences did not grow.

It is well known that autograft bone is superior to osteoconductive bone substitutes in the aspect of how fast the bone graft area will remodel to bone. Some small bone tumors can apparently also successfully be treated without bone grafting. Bone graft materials are, however, needed for many reasons in orthopedic surgery. Therefore, prospective, randomized, long-term follow-up studies on bone substitutes are needed to evaluate bone remodeling. The aim of this study was to evaluate the clinical and radiological outcome of a grafted region over a long period of time, as this is not well known for bone substitutes. Our findings demonstrate that BG-S53P4 is a safe and well-tolerated bone substitute with good long-term results. BG-S53P4 does not disturb the growth of bone in children, and it has proven osteoconductive, bone bonding, and antibacterial properties. We, therefore, find BG-S53P4 to be a good material of choice in benign bone tumor surgery both in children and adults.

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