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SCIENTIFIC ARTICLE

Chronology of the radiographic appearances of the calcium sulphate–calcium phosphate synthetic bone graft composite following resection of bone tumours—a preliminary study of the normal post-operative appearances

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Abstract
Objective To describe the normal chronological radiographic appearances of the calcium sulphate–calcium phosphate ($CaSO_4/CaPO_4$) synthetic graft material following bone tumour resection during the processes of graft resorption and new bone incorporation into the post-resection defect.
Materials and methods Retrospective review of our oncology database identified patients who had undergone serial radiographic assessment after treatment with the $CaSO_4/CaPO_4$ synthetic graft following bone tumour resection. Post-operative radiographs were assessed for (1) partial resorption of graft material with partial ingrowth of new bone at the graft site and (2) complete resorption of graft material with complete incorporation of new bone into the graft site. The pattern of resorption of graft material was also documented. Any radiographic evidence of complication was recorded. Radiographs were also divided into groups according to their interval from surgery to establish a pattern of time-related changes.
Results A total of 11 patients were identified from our database. Partial resorption of graft material/partial ingrowth of new bone was seen in nine patients, initially observed at a mean of 1.4 months from surgery. Resorption commenced peripherally with gradual inward progression in 100% (9 of 9) of cases. Complete resorption of graft/complete new bone incorporation at the graft site was seen in 89% (8 of 9) of cases followed up for more than 5 months after surgery. The other patient developed recurrence of tumour at 14 months, before complete incorporation was demonstrated. The mean time to complete incorporation of new bone was 5 months. Two patients have, to date, been followed up at 2 and 3 months respectively with a pattern of peripheral graft resorption observed so far in both cases. Ten of 13 (77%) radiographs performed 1–3 months after surgery demonstrated peripheral resorption of graft material with partial osseous ingrowth into the defect. Seven of eight (88%) radiographs performed 6–12 months after surgery demonstrated complete new bone incorporation at the graft site with graft material completely resorbed. Ten of 11 (91%) radiographs performed 1 year after surgery demonstrated complete new bone incorporation, the other examination demonstrating recurrence.
Conclusion Our preliminary observations suggest a characteristic, time-related radiographic pattern during the processes of $CaSO_4/CaPO_4$ bone graft resorption and complete new bone incorporation. This pattern can be directly related to processes that occur at the molecular level. Radiographic findings that are not in keeping with this may merit closer follow-up.

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Keywords Bone · Tumour · Graft · Synthetic · Radiographs

Introduction

Surgical treatment of bone tumours commonly involves intralesional resection and reconstruction of the resulting defect with bone graft material. The three main types of bone graft used are autograft (graft from the patient's own bone stock), allograft (graft from cadaveric bone stock) or synthetic bone substitutes [1]. Successful incorporation of graft material into the defect depends on the material's ability to promote new bone formation and provide a scaffold for osteogenesis [1]. While autogenous bone grafts have the advantage of providing both bone stock and osteogenic precursor cells, they are associated with morbidity at the donor site. Allografts are also associated with complications such as infection, fracture and non-union [2–11].

Due to the disadvantages of autograft and allograft material, synthetic bone substitutes are being increasingly used in bone reconstruction techniques [12–14]. Ceramics and demineralised bone matrix make up the main subtypes of synthetic bone grafts. Various composite synthetic grafts are also used to combine the properties of different compounds to achieve an optimal environment for bone formation. One such composite is the bone graft substitute PRO-DENSE® (Wright Medical Technology). This is a fully synthetic composite comprising a $CaSO_4/CaPO_4$ matrix mixed with beta-tricalcium phosphate (β-TCP) granules. The $CaPO_4$ component of this composite provides a scaffold for osteogenesis while the relatively rapid resorption of $CaSO_4$ confers graft porosity allowing ingrowth of bone [15]. The combination of $CaSO_4$ and $CaPO_4$ has been shown to promote significantly more new bone formation compared to an autograft [15] and also when compared to TCP alone in canine studies [16].

The promising early results, in both preclinical and clinical trials, of the $CaSO_4/CaPO_4$ composite bone graft have led to an increase in its use in bone reconstruction techniques [15, 17, 18]. At our center, PRO-DENSE® is now the first choice bone graft material for reconstructing contained defects following resection of bone tumours. Familiarity with the normal radiographic evolution of this graft material, reflecting the processes of resorption and new bone formation, is essential in the serial assessment of successful graft incorporation. Knowledge of the normal pattern of time-related radiographic changes at the graft site can avoid confusion with complications such as tumour recurrence, infection and fracture. While the radiographic appearances of bone graft materials have previously been described [1], the serial appearances of the $CaSO_4/CaPO_4$ composite have yet to be documented. We present our preliminary experience of the typical pattern of time-related radiographic changes of this composite at the graft site following resection of bone tumours. We relate these findings to the biological reactions involved in achieving successful new bone incorporation into the defect.

Materials and methods

Review of our ethics-approved orthopaedic oncology database was performed to identify patients who had undergone bone reconstruction using a synthetic graft composite comprising a $CaSO_4/CaPO_4$ matrix mixed with β-TCP granules (PRO-DENSE®, Wright Medical Technology) following resection of a bone tumour, from July 2007–April 2009.

Twelve patients who had undergone reconstruction of bone defects with the $CaSO_4/CaPO_4$ composite following resection of bone tumours were identified from our oncology database. In one patient, no post-operative imaging was available for review. The study group thus comprised 11 patients. Six of the patients were male and five were female with a mean age of 28 years at the time of surgery (age range 14–64 years).

The locations and types of bone tumour are listed in Table 1. Giant-cell tumour of bone (GCT) and aneurysmal bone cyst (ABC) were the most common tumours in the study group, each making up 33% (3 of 11) of cases. The tibia and fibula were the most common locations accounting for 55% (5 of 11) of cases. The shortest period of follow-up was 2 months from surgery while the longest was 26 months from surgery.

Post-operative radiographs in these patients were retrospectively assessed by two fellowship-trained musculoskeletal radiologists. This was initially performed on an independent basis but where there was a difference in interpretation, joint review was undertaken and a consensus decision reached. All radiographs were performed using a Siemens Radiography system (Vertex and Multex model).

Radiographs were assessed for (1) partial resorption of graft material with surrounding, partial osseous ingrowth at the graft site and (2) complete resorption of graft material with complete incorporation of new bone into the defect. The pattern of resorption was documented as peripheral, central or mixed. Complete incorporation of new bone was defined as complete replacement of the radiodense graft material with new bone filling the pre-existing defect. Any radiographic evidence of complications such as tumour recurrence, infection or fracture was also noted. Where recurrence was radiographically suspected, pathological correlation was sought.

Radiographs were also divided into groups according to their interval from surgery to establish a pattern of time-

Table 1 Results of the radiographic follow-up of patients treated with $CaSO_4/CaPO_4$ composite bone graft following bone tumour excision

Patient no.	Primary tumour	Site of primary tumour	Earliest radiographic evidence of partial resorption/osseous ingrowth	Earliest radiographic evidence of complete resorption/new bone incorporation	Complications
1	UBC	Fibula	1 month	3 months	None at 2 years, 1 month
2	GCTOB with secondary ABC formation	Humerus	1 month	Not incorporated	Recurrence at 14 months
3	ABC	Patella	N/A	2 months	None at 2 years
4	ABC	Clavicle	3 months	7 months	None at 19 months
5	Enchondroma	Metatarsal	1 month	2 months	None at 19 months
6	GCTOB	Fibula	1 month	7 months	None at 14 months
7	Chondroblastoma	Humerus	3 months	6 months	None at 12 months
8	GCTOB	Tibia	1 month	9 months	None at 9 months
9	Enchondroma	Phalanx	N/A	2 months	None at 5 months
10	Chondromyxoid fibroma	Humerus	1 month	Not incorporated by 3 months	None at 3 months
11	ABC	Tibia	1 month	Not incorporated by 2 months	None at 2 months

UBC Unicameral bone cyst, *GCTOB* giant cell tumour of bone, *ABC* aneurysmal bone cyst, *N/A* not applicable

related changes. Where more than one examination was carried out on the same patient at a defined time interval, both or all radiographs were included. The time intervals from surgery to initial graft resorption and to complete bone incorporation were recorded for each case.

Results

Partial resorption of graft material was seen on radiographs in nine patients (Table 1). The earliest radiographic evidence of partial resorption was seen within 1 month of surgery and the latest was at 3 months, with a mean interval of 1.4 months. Resorption of graft material was initially peripheral with gradual progression towards the center in 100 % (9 of 9) of cases (Figs. 1, 2 and 3). In two patients, complete resorption of graft material with complete incorporation of new bone into the defect was seen at the first post-operative radiograph.

Complete resorption of graft with complete incorporation of new bone into the graft site was seen in 89% (8 of 9) of cases followed up over 5 months from surgery (Table 1; Figs. 1, 2 and 3). The other patient developed recurrence of the tumour at 14 months before complete new bone incorporation had been demonstrated (Fig. 4). Two patients have, to date, only had radiographs at 2 months and 3

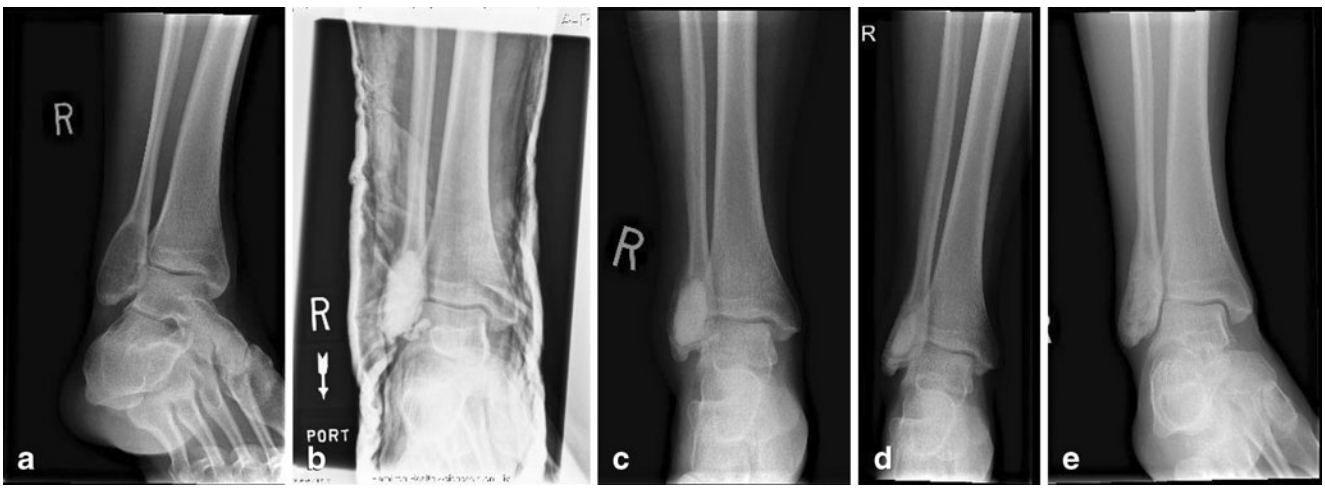

Fig. 1 **a** Radiograph of a 33-year-old male with giant-cell tumour of the distal fibula. Post-operative radiographs performed **b** immediately, **c** 1 month, **d** 3 months and **e** 5 months after surgery illustrate the characteristic time-related pattern of peripheral resorption of the $CaSO_4/CaPO_4$ graft material and replacement by new bone to fill the defect at 5 months

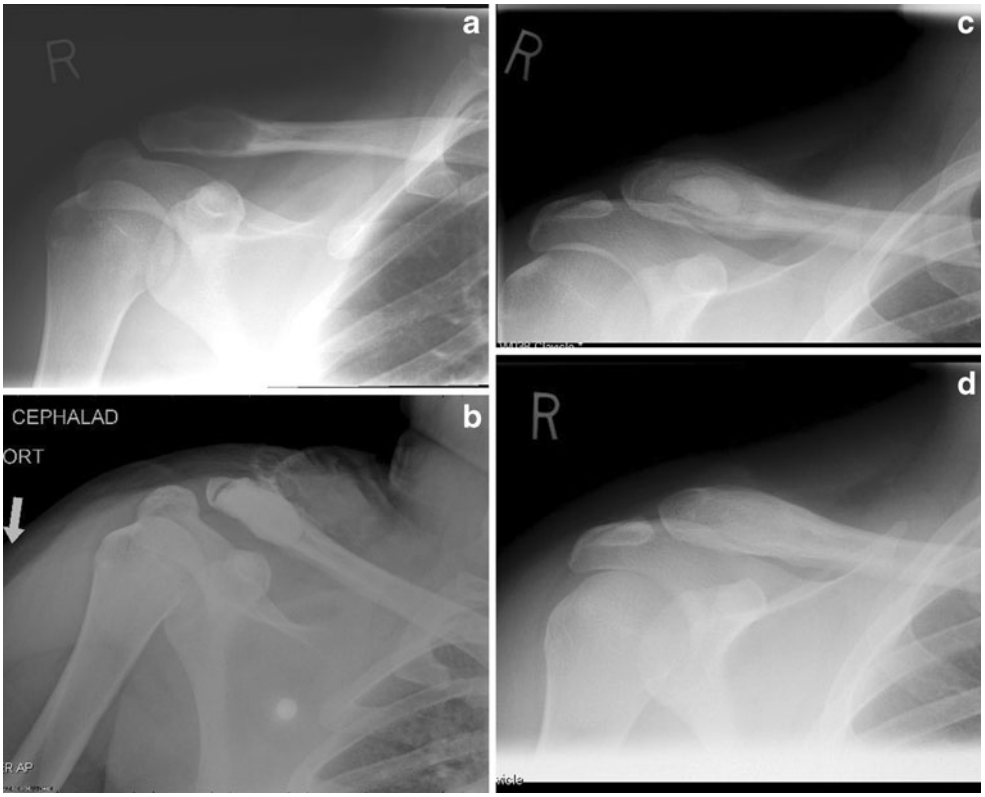

Fig. 2 **a** Radiograph of a 17-year-old male with an aneurysmal bone cyst of the distal clavicle. Post-operative examinations at **b** 6 days, **c** 2 months and **d** 7 months demonstrate the characteristic peripheral resorption of graft material and replacement with new bone at the resection site

months after surgery respectively with as yet no evidence of complete new bone incorporation. The earliest radiographic evidence of complete new bone incorporation was at 2 months from surgery and the latest was at 9 months with a mean interval of 5 months.

Of radiographs performed 1–3 months after surgery, 77% (10 of 13) showed evidence of partial resorption of graft material with partial ingrowth of bone and 23% (3 of 13) showed complete new bone incorporation (Table 2). Between 6 and 12 months, 88% (7 of 8) radiographs showed complete incorporation of new bone while 12% (1 of 8) showed partial resorption of graft material with only partial ingrowth of bone. Almost all radiographs (10 of 11) performed more than 1 year after surgery, excluding the examination which showed recurrent tumour, demonstrated complete new bone incorporation.

In one case, recurrent GCT was demonstrated centrally within an area of new bone formation in the proximal

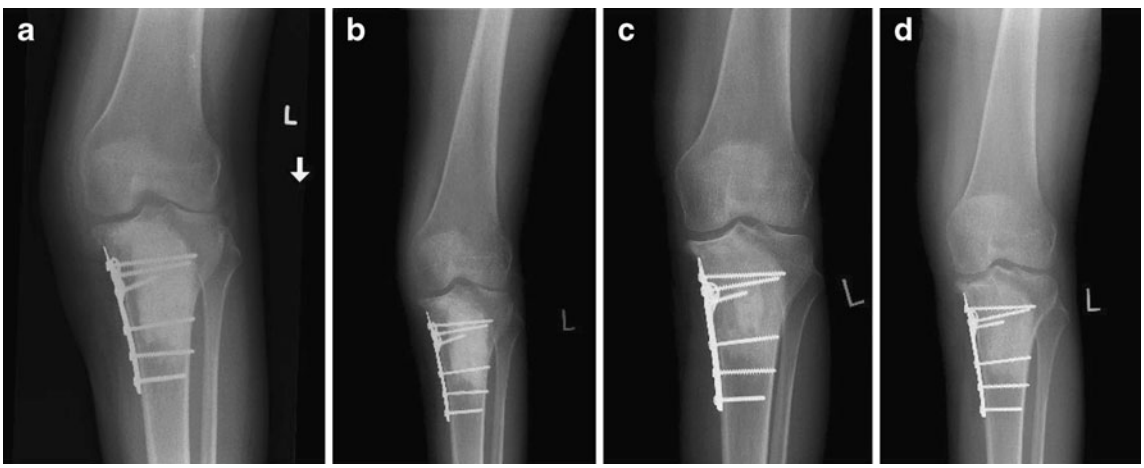

Fig. 3 Radiographs of a 32-year-old female post resection of a giant-cell tumour of the tibia at **a** 1 months, **b** 2 months, **c** 7 months and **d** 9 months showing gradual resorption of the large volume of graft material and new bone formation filling in the large defect

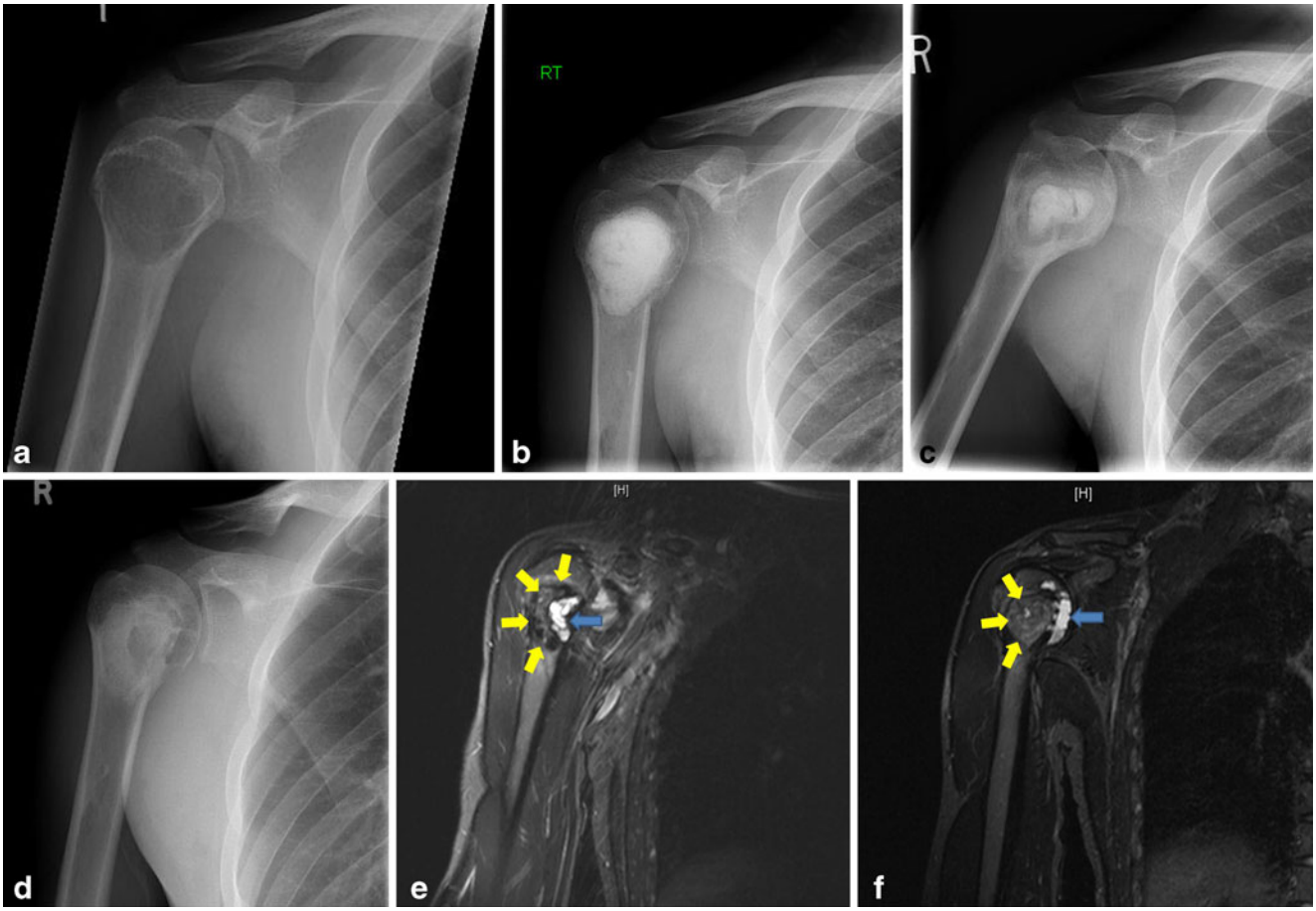

Fig. 4 **a** Pre-operative radiograph of a 26-year-old male with a giant-cell tumour of the humerus with secondary aneurysmal bone cyst formation. Post-operative radiographs at **b** 1 month and **c** 6 months demonstrate the expected pattern of peripheral graft resorption. **d** At 14 months all graft material has been resorbed but a lucent central defect has developed within new bone at the graft site. **e** and **f** Coronal T2-weighted, fat-saturated MRI of the proximal humerus at 14 months demonstrates a well-circumscribed area of low signal intensity within humeral head corresponding to new bone at the graft site (*yellow arrows*) with internal high signal intensity representing recurrent tumour (*blue arrows*)

humerus at 14 months (Fig. 4). This diagnosis was histologically confirmed after subsequent surgery with the patient ultimately undergoing further resection and endoprosthetic replacement. There were no cases of post-operative infection or fracture.

Discussion

Bone graft materials are widely used in orthopaedic reconstructive techniques. Morbidity associated with autografts and allografts has led to the increasing use of synthetic bone graft

Table 2 Time-related radiographic changes of the $CaSO_4/CaPO_4$ composite bone graft and associated complications

Time interval from surgery	Number of radiographs	Partial resorption/ osseous ingrowth	Complete resorption/ new bone incorporation	Pattern of resorption	Infection	Recurrence	Fracture (cement/ new bone)
< 5 days	10	0	0	N/A	0	0	0
1–3 months	13	10 (77%)	3 (23%)	Peripheral - 10	0	0	0
3–6 months	10	4 (40%)	6 (60%)	Peripheral - 4	0	0	0
6–12 months	8	1 (12%)	7(88%)	Peripheral - 1	0	0	0
12–24 months	11	0	10 (90%)	N/A	0	1 (10 %)	0
>2 years	3	0	3 (100%)	N/A	0	0	0

N/A Not applicable

materials [12–14]. The radiographic appearances of bone graft materials are variable and can lead to confusion with recurrent or residual disease [1]. The promising early results and more frequent use of the $CaSO_4/CaPO_4$ composite mean that this is likely to be more commonly encountered by the radiologist during the evaluation of post-operative radiographs. Knowledge of the typical radiographic appearances during the process of graft resorption and new bone incorporation along with a basic knowledge of the molecular processes behind these step-wise appearances can avoid confusion and lead to more confident assessment.

Different graft materials use different processes to achieve bone reconstruction within the host bed. Osteogenesis involves transplantation of osteogenic precursor cells into the defect allowing new bone formation, a process which is specific to cancellous, cortical or vascularised bone grafts [19, 20]. Osteoinduction involves recruitment of surrounding mesenchymal, pluripotent cells which differentiate into osteoblasts, partly mediated by growth factors within bone matrix [19, 20]. Osteoconduction occurs where graft material is gradually resorbed with the residual graft acting as a scaffold for the ingrowth of bone and vascular tissue into the defect [1].

The PRO-DENSE® injectable synthetic composite used at our center uses both osteoconduction and osteoinduction to induce new bone formation. The composite consists of a $CaSO_4$ and $CaPO_4$ (Brushite) matrix which is embedded with β-TCP granules. $CaSO_4$ has been used as a bone filler for many years, but its rapid resorption renders it ineffectual since its resorption rate is considerably faster than bone growth, resulting in an absence of the appropriate scaffold within the defect [16, 21]. $CaPO_4$ cements have a slower resorption rate than bone and are usually too dense to allow bone tissue to grow into the defect in a limited period of time [22–24]. When mixed together, the dissolution of $CaSO_4$ is slowed by the brushite crystals and the β-TCP granules remain as a scaffold allowing enough porosity for ingrowth of bone and blood vessels and time for bone formation (Fig. 5). This gives the composite prolonged osteoconductive properties. The calcium phosphate scaffold also has osteoinductive properties with in-vitro results demonstrating that proteins released by the scaffold are both active and stimulatory [25]. Local growth factors stimulate angiogenesis and recruitment of osteoblasts leading to new bone formation.

In our study partial resorption of the composite matrix was first observed at an average of 1.4 months after surgery. All radiographs performed 1–3 months after surgery demonstrated evidence of graft resorption. In a previous canine study which used serial radiographic assessment of the same graft material, partial resorption was noted as early as 2 weeks with up to 50% resorbed by 8 weeks [15]. In our study, resorption was always initially seen at the periphery of the graft, gradually progressing inwards

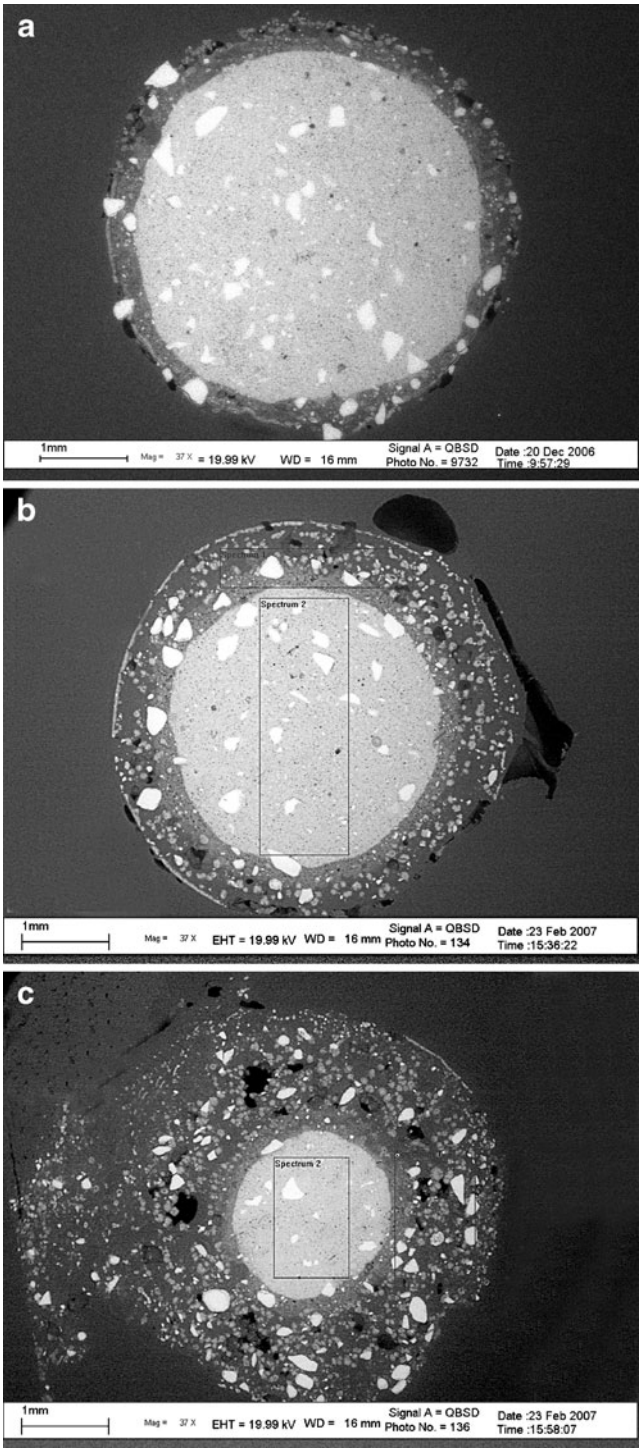

Fig. 5 Cross-section through a PRO-DENSE® pellet with scanning electron microscopy after **a** 4, **b** 8 and **c** 12 days of accelerated in vitro dissolution. **a** The darker region on the outer edge of the pellet represents the area in which $CaSO_4$ has mostly dissolved, leaving $CaPO_4$ (*brushite*) and TCP particles (*bright white*). **b** and **c** Further resorption/dissolution of $CaSO_4$ and now also $CaPO_4$ with progression inwards, diminishing the volume of intact matrix (*light grey*). The TCP particles remain (courtesy of Wright Medical Technology)

centripetally. The pattern of peripheral resorption is due to the initial burst of $CaSO_4$ dissolution on the surface of the graft material with gradual inward resorption of the $CaSO_4$/$CaPO_4$ matrix (Fig. 5). This together with formation of non-mineralised bone matrix accounts for the radiographic findings of peripheral radiolucency that progresses more centrally, a pattern which has also been observed in a previous canine study and confirmed on corresponding histological sections [15]. In only one case was central radiolucency observed at the graft site. This occurred in a patient who developed recurrence at 14 months (Fig. 4). The presence of recurrent tumour may explain why this was the only case followed up over 1 year from surgery which did not show complete resorption of graft material. The development of central radiolucency within graft material/new bone does not correspond to the known biological process of peripheral resorption with inward progression. While our study group is too small to draw a definitive conclusion, our preliminary experience suggests central radiolucency is atypical and thus may merit closer clinical and radiographic follow-up. A larger study would however be required to confirm this.

Complete resorption of graft material with complete incorporation of new bone into the defect was observed in all patients followed up over 5 months after surgery who did not develop recurrence. All cases of complete incorporation of new bone occurred within 1 year. Of radiographs performed 6–12 months after surgery, only one (14%) did not show complete resorption of graft/new bone incorporation at the defect. In a previous canine study using the same composite, almost complete resorption with extensive new bone formation was observed on histological sections at 13 weeks [15]. In a further canine study, complete healing of the defect was present by 4 months at histology [16]. The radiographic findings presented here thus correspond well to the histological findings of these previous studies. Three cases in this study demonstrated radiographic evidence of complete incorporation of new bone into the defect at 2 months. These were all in small bones (patella, metatarsal, phalanx) with only small defects, which suggests that where smaller volumes of graft are used, resorption and new bone incorporation are quicker, though a larger number of patients is needed to confirm this theory.

Of the 11 patients in the study group, only 1 developed a post-operative complication, a case of recurrent tumour. No other complications were demonstrated. Of four patients followed up for more than 18 months after surgery, no intermediate term complications have been identified. Another study of this patient group is required to assess the long-term outcome of treatment with this composite synthetic graft and possibly also to determine the histology of the remodeled bone, which would be of use if further surgery is required.

Our study was limited by its retrospective nature. This meant that patients in the study group had their post-operative radiographic assessments at slightly different time intervals. A more accurate way of establishing a chronological pattern would have been a prospective analysis with radiographs performed at pre-defined time points from surgery. Nevertheless a clear pattern of the normal time-related radiographic changes of this synthetic graft composite has been established.

In summary, our preliminary experience with the $CaSO_4$/$CaPO_4$ composite bone graft represents a baseline for the anticipated normal radiographic appearances during the processes of graft resorption and complete new bone incorporation. Our early observations suggest a characteristic, time-related radiographic pattern during these processes. This pattern can be directly related to processes that occur at the molecular level. Radiographic findings that are not in keeping with this may merit closer follow-up.

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