J Mater Sci: Mater Med (2011) 22:1073–1080
DOI 10.1007/s10856-011-4272-0

Bioactive glass granules: a suitable bone substitute material in the operative treatment of depressed lateral tibial plateau fractures: a prospective, randomized 1 year follow-up study

Jouni T. Heikkilä · Juha Kukkonen · Allan J. Aho · Susanna Moisander · Timo Kyyrönen · Kimmo Mattila

Received: 9 August 2010 / Accepted: 19 February 2011 / Published online: 23 March 2011

Abstract Purpose of this study was to compare bioactive glass and autogenous bone as a bone substitute material in tibial plateau fractures. We designed a prospective, randomized study consisting of 25 consecutive operatively treated patients with depressed unilateral tibial comminuted plateau fracture (AO classification 41 B2 and B3).14 patients (7 females, 7 males, mean age 57 years, range 25–82) were randomized in the bioglass group (BG) and 11 patients (6 females, 5 males, mean age 50 years, range 31–82) served as autogenous bone control group (AB). Clinical examination of the patients was performed at 3 and 12 months, patients' subjective and functional results were evaluated at 12 months. Radiological analysis was performed preoperatively, immediately postoperatively and at 3 and 12 months. The postoperative redepression for both studied groups was 1 mm until 3 months and remained unchanged at 12 months. No differences were identified in the subjective evaluation, functional tests and clinical examination between the two groups during 1 year follow-up. We conclude that bioactive glass granules can be clinically used as filler material instead of autogenous bone in the lateral tibial plateau compression fractures.

Paper selected for publication from the 23rd European Conference on Biomaterials, Tampere, Finland, September 2010.

J. T. Heikkilä
Sports Clinic Mehiläinen, Turku, Finland
e-mail: jouni.heikkila@mehilainen.fi

J. Kukkonen (✉) · A. J. Aho · S. Moisander
Department of Traumatology, Turku University Hospital, P.O. Box 28, 20701 Turku, Finland
e-mail: jupeku@utu.fi

A. J. Aho
e-mail: allan.aho@fimnet.fi

S. Moisander
e-mail: susanna.moisander@tyks.fi

T. Kyyrönen
Medical Imaging Centre of Southwest Finland, Salo District Hospital, University of Turku, Turku, Finland
e-mail: timo.kyyronen@tyks.fi

T. Kyyrönen · K. Mattila
Department of Diagnostic Radiology, University of Turku, Turku, Finland
e-mail: kimmo.mattila@tyks.fi

K. Mattila
Medical Imaging Centre of Southwest Finland, Turku University Hospital, Turku, Finland

1 Introduction

In the proximal tibial plateau fractures direct trauma causes in addition to the depression of the joint line, disruption and compression of the trabecular bone structure. This may cause bony defect and fragmentation of the articular surface above it. An intra-articular lateral tibial plateau fracture with a depression of more than 3 mm, valgus deformation of more than 5° and widening of the proximal tibia of more than 5 mm is routinely treated operatively to minimize posttraumatic osteoarthrosis [1–3]. The reconstruction of the articular surface includes autogenous bone grafting to fill the fracture gap of the compressed cancellous bone and to support the joint surface after the elevation. The autogenous bone graft is a golden standard in filling the fracture defect. Harvesting autogenous bone necessitates a second operation and lengthens operation time. It also may cause donor site morbidity, pain and hemorrhage [4, 5]. Occasional difficulties in harvesting sufficient amount of good quality autogenous filler bone has led to necessity for biomaterial to replace bone. In metaphyseal areas synthetic calcium phosphate bone substitute materials e.g.

tricalcium phosphate and hydroxylapatite are used to replace autogenous bone. In the literature, good results have been presented using calcium phosphate substitutes also in fracture treatment [6–10]. However, some material related problems remain. The negative feature of these substitutes is brittleness. In fracture treatment the resorption of tricalcium phosphate can be too fast while that of hydroxylapatite is very slow. The slow resorption rate can be a problem if later arthroplasty is needed. For these reasons, there is a need for other bone bonding bioactive bone substitute materials.

Bioactive glasses are silicate glasses containing sodium, calcium and phosphate as main components. Bioactive glasses have earlier been reported to be bone bonding and osteoconductive [11–13]; i.e. they have ability to form chemical binding with living tissues and the osteocytes can proliferate on their surface. Bioactive glass has also shown to have angiogenic capacity when combined with vascular endothelial growth factors [14]. The chemical bonding of bioactive glass to bone is due to complex series of reactions on and in the glass surface [15]. It has been verified histologically and using push-out tests and scanning electron microscopy [16, 17]. Silica based bioactive glasses form carbonated hydroxylapatite inside and on its surface due to a bioactive reaction between the host bone and the glass surface. This in the body formed hydroxylapatite resembles closely that of human bone making bioactive glass an attractive alternative for autogenous bone [18–20].

Bioactive glasses offer a wider spectrum of possibilities to adjust the properties of given glass by changing the glass composition, i.e. the material can be adjusted for different clinical demands [11, 21]. Furthermore, the granule size affects the dissolving time. Continuous proceeding of the reaction layer and ingrowth of new bone in between the granules leads to replacement of the glass granules and eventual remodelling of the bone graft area to bone over time [22]. Additionally the bioactive glass has proven to be antibacterial [18, 23]. This bioactive glass (S53P4) is composed of 53% SiO_2, 23% Na_2O, 20% CaO, and 4% P_2O_5 given as weight percentages. S53P4 has been earlier studied in animals and maxillofacial, oral, dental and bone tumour surgery with good results [18–20, 23–28]. So far there are no randomized studies concerning the use of bioactive glass granules as a bone substitute material in fresh fractures.

Knowing the advantages of bioactive glass we designed a prospective, randomized study in clinical traumatology using bioactive glass as a bone substitute material in tibial plateau fractures. Our hypothesis was, that bioactive glass is a suitable bone substitute material with good bone bonding ability, and will be in due time replaced by host bone. Our aims were to analyze the fracture anatomy pre- and postoperatively and at follow-up using both plain films and computed tomography (CT) scans and to evaluate the patients' subjective and functional results.

2 Patients and methods

This study was conducted between 1995 and 1999 at the Orthopaedic Division in the Department of Surgery, Turku University Hospital. The study protocol was approved by the local ethics committee and written informed consent was obtained from the patients. The randomization was performed using closed envelopes. The study groups consisted of 25 consecutive patients with depressed unilateral tibial comminuted plateau fracture (AO classification 41 B2 and B3). 14 patients (7 females, 7 males, mean age 57 years, range 25–82) were randomized in the bioglass group (BG) and 11 patients (6 females, 5 males, mean age 50 years, range 31–82) served as autogenous bone control group (AB). All patients were healthy, without systemic diseases, with normal bone structure. The two groups were statistically identical with regard to demographic factors of the patients, fracture anatomy and degree of the joint line depression. The fractures were closed and resulted from either road-traffic accident or falling.

The composition of bioactive glasses was studied earlier. The glass (S53P4) with best properties for clinical purposes was chosen to our study [11]. The bioactive glass (S53P4) was composed of 53% SiO_2, 23% Na_2O, 20% CaO, and 4% P_2O_5 given as weight percentages. The glass was produced by melting the oxides at high temperatures and dissolving the silica into the melt. The bulk glass was crushed into particulate and sieved, the size of the granules used in this study were 0.83–3,15 mm. The granules were sterilized using ethylen oxide.

Joint line depression of more than 3 mm was indication for operative treatment. The injured legs were preoperatively immobilized with a posterior splint during admission at the hospital. The operation was performed by experienced orthopaedic surgeons on the first or second post-trauma day using spinal anaesthesia and tourniquet. Routine antibiotic and antithromboembolic prophylaxis were used. The lateral condyle was exposed through an anterolateral posteriorly curved incision. Intact lateral meniscus and anterior cruciate ligament were observed in all knees. Lateral meniscus was detached at its tibial insertion to be able to visualize the joint line. After lateral cortical fenestration the articular surface was elevated under direct visual control. The fracture was then temporarily fixed using K-wires and the elevation of articular surface was confirmed by preoperative plain films. Thereafter in the BG group, the granules were packed manually to quantitatively fill the defect caused by the fracture and the elevation. Precaution was used to prevent the granules from intruding into the knee joint. Moisturising the granules with saline made them to adhere together and easier to pack into the defect. The amount of the filler granules, S53P4, ranged from 20 to 35 g, mean 27 g. Finally the fracture was fixed with an anatomical condylar plate (Kerboul, Howmedica inc. Rutherford, NJ, USA). In the AB group, the same surgical procedure was performed but the defect was filled with autogenous bone harvested from anterior iliac crest. The iliac crest was exposed using an incision along the superior iliac crest, which was chiseled temporarily aside and medial lamina and cortico-cancellous bone chips were used as filler material. The raw bone surface was left uncovered. All surgical wounds were closed in layers and drained. The drain was removed after the first postoperative day. The amount of drainage bleeding was measured. After the operation the leg was supported with a knee orthosis for 6 weeks and the patients were verticalized at the second postoperative day without weight bearing. Partial weight bearing and active knee mobilization and muscle strengthening exercises were started under physiotherapeutic control after two weeks. Full weight bearing was allowed after 6 weeks.

2.1 Radiological analysis

Plain AP and lateral radiographs were obtained in all patients preoperatively, immediately postoperatively and at 3 and 12 months. CT was taken at same time points, with an exception, no CT was obtained at 3 months in the AB group. CT was performed using Picker PQ 2000 scanner (Picker Medical Systems, Cleveland, Ohio, USA). Spiral protocols were used, and images with 1.5–4 mm slice thicknesses and 1.5–3 mm increments were used for analysis. Additionally, weight bearing radiographs of both lower limbs were obtained at 1 year to assess alignment of the injured leg.

Radiological analysis was carried out by an independent radiologist (T.K.) after follow-up. The images were initially printed out, and hard copies were used for analysis. The joint line depression was measured on both plain films and CT hard copies. Tibio-femoral angles (TF) and deviation of mechanical axes (DMA) were measured in both injured and contralateral uninjured legs.

Evaluation of the incorporation of the bioactive glass granules was made visually by analyzing morphological changes of the granules, especially the definition of their outlines on plain films and CT slices.

2.2 Clinical evaluation

Clinical evaluation of the injured legs was performed by one of the orthopaedic surgeons (J.H.) at 3 and 12 months postoperatively. It included examination of affected and contralateral knees. The knees were tested for range of motion (hyperextension, flexion and extension), measurement of circumference of thigh 15 cm proximal to the joint line, palpation of the knee and assessment of patellar crepitation, drawer and lachman tests, evaluation of collateral stability in full extension and 15 and 30° flexion, McMurray and pivot shift tests. The range of motion was measured in degrees, thigh circumference in centimeters, palpation and crepitation as normal or abnormal, drawer and lachman as negative or positive, collateral stability normal, less than 5°, 5–10°, and over 10° and pivot shift tests as positive or negative.

The patients' subjective and functional results were evaluated at 12 months by the same orthopaedic surgeon in all patients. The functional evaluation included testing of walking, jumping, duck-walking, stair climbing and squatting ability of patients. They were graded as excellent, good, fair and poor. The ability was excellent, if the patient was able to perform the test fully normally without any complaints; good, if they were able to perform the test normally, but had slight complains or discomfort or pain; fair, if they were not able to perform the test normally, were limping or were not able to squat or duck-walk normally and poor if they were not able to perform the test at all.

2.3 Statistical analysis

The statistical analysis of associations between the patients' age, gender, the fracture anatomy, the depression (mm) and area of the fracture (mm^2) and the filler type (bioactive glass/autogenous bone) were cross-tabulated with Cochran-Mantel-Haenszel statistics. Rank scores were used. Statistical significance was calculated using Mantel-Haenszel statistics. P value of < 0.05 was used as the cutoff point of significance. Statistical computing was performed with SAS System for Windows, release 8 january 1999.

3 Results

3.1 Patients

There were no statistical differences between the BG and AB groups with regard to the fracture anatomy, surface area of the fracture or the degree of depression on condyle surface. The demographic data was statistically similar in both groups.

The postoperative course and the wound healing of the patients were uneventful. However, there was one patient with superficial wound infection in the BG group, which was treated by debridement, the radiological results remained unchanged, however. The mean drain bleeding from the operation area of the tibia in the BG group was 195 ml (0–010) and 180 ml (0–1390) in the AB group. The mean bleeding from iliac crest was 215 ml (0–960) in the AB group.

3.2 Clinical results

In the clinical examination, the groups were also similar with regard to muscle atrophy, stability, meniscal tests, range of movement and patellar crepitation.

There were no differences between the groups regarding the functional tests either. The patients' ability to walk was excellent or good in 13 of 14 patients in the BG group and 10 of 11 patients in the AB group. The corresponding numbers for stair climbing were 11 of 14 and 10 of 11, squatting 12 of 14 and 9 of 11, jumping 6 of 14 and 4 of 11 and duck-walking 6 of 14 and 3 of 11, respectively.

Subjective evaluation revealed no differences between the groups; 6 of 14 of the patients graded the result excellent in the BG group and 5 of 11 in the AB group.

3.3 Radiological results

Plain films showed adequately reconstructed articular plateau surface of the lateral condyles (Fig. 1). As shown in Fig. 2, the mean preoperative articular depression in the BG group was 9 ± 4 mm and in the AB group 7 ± 4 mm. Postoperatively the mean remained depression was 2 mm (±3 mm) in the BG group and 2 mm (±2 mm) in the AB group. The difference between the pre- and postoperative depression values was statistically significant in both groups ($P < 0.05$). Thereafter, there was a slight subsidence of the joint line in both groups. The mean depression increased 1 mm until 3 months, but remained unchanged at 12 months (Fig. 2). Similar results were obtained using measurements on CT (Fig. 3). In injured extremities there was 1.8 (SD 4.2) degrees more valgus than in uninjured ones in the BG group, and respectively 3.1 (SD 4.7) in the AB group. More valgus alignment was also detected in the injured extremities using DMA measurements [BG 0.9 (SD 4.4), AB 2.2 (SD 4.7)] when compared to the uninjured extremities. There was no statistically significant difference in TF angles and DMA between the two groups at 1 year follow-up (TF angles $P = 0.461$; DMA $P = 0.488$).

According to the visual analysis on plain films the bioactive glass granules started to incorporate with the surrounding bone during the first 3 months. The substitute remodellation was observed as a disappearance of the originally sharp shape and boundaries of the granules. This phenomenon was seen more detailed on repeated CT examinations, and it progressed gradually until 12 months (Figs. 1, 4).

4 Discussion

No significant differences were observed between the two demographically identical groups with regard to clinical results, redepression of articular surface measured by plain films and CT, valgus alignment, TF angle, DMA and patients' subjective results. Bioactive glass granules act as a suitable bone substitute material in the operative treatment of lateral tibial plateau fractures evaluated both

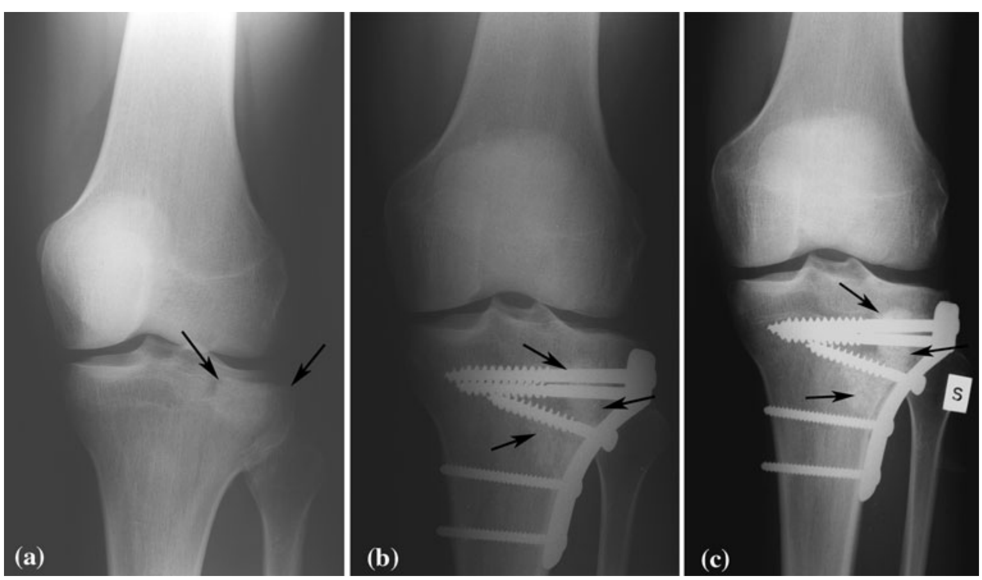

Fig. 1 Ap view of lateral condyle fracture of a 25-year-old male patient with compression fracture (*arrows*) caused by a falling injury (**a**). During the operation the impressed joint surface was elevated to it's anatomical level and the defect filled with bioactive glass (**b**, *arrows*). The fracture was secured with a Kerboul plate (**b**). In late X-rays 103 months after the injury the joint line has retained the postoperative elevated position (**c**). The implanted bioactive glass is still clearly visible (**c**, *arrows*). However, the still dense area is partly explained by sclerotic new bone ingrowth. It is difficult to differentiate between sclerotic bone and resorbing glass filler using plain films only

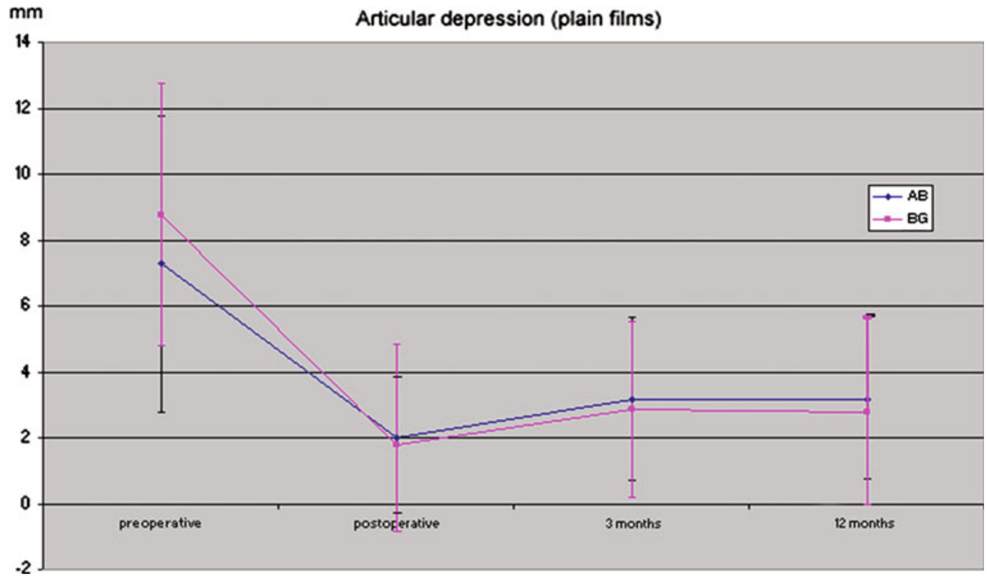

Fig. 2 The joint-line depression evaluated in plain films. In the BG group the mean depression has been reduced from preoperative 9 to postoperative 2 mm and it was increased with 1 mm until 3 months, but remained unchanged thereafter. In the AB group the mean depression was reduced from preoperative 7 to postoperative 2 mm and increased thereafter similarly with 1 mm until 3 months, and remained unchanged at 12 months

clinically and radiologically. Power analysis was not done prior this study. However, we consider that homogeneous group of patients enrolled in this study allows to make conclusions despite the small group of patients.

Autogenous bone, allograft bone and synthetic bone materials are options to fill fracture defects. The golden standard is the application of autogenous bone grafts for filling in the defect in the cancellous bone of the tibial plateau fractures. Good results have been reported in several studies using autogenous bone as a bone graft in tibial plateau fractures [3, 29–31]. In general, allograft bone grafts have also been successfully used in these fractures with low complication rates [32, 33]. However, there is lack of bone graft control group of all these studies. In the literature there are several studies of synthetic bone materials in tibial plateau fracture treatment. Itokazu et al. studied interporous hydroxyapatite as a bone graft substitute in tibial plateau fractures without a control group [34]. They reported fracture union in all patients without osteoarthrosis on plain films and computed tomograms in 2.5 years follow-up. Bucholz et al. [8] compared coral derived hydroxylapatite and cancellous autograft while treating proximal tibia fractures. They found no significant differences between the groups in radiological and clinical assessments at follow-up periods. There are several studies with good results while calcium phosphate cement was used as a bone-graft substitute material in the treatment of lateral tibial plateau fractures [35–39]. However, only one cadaver and one animal study had autogenous bone control group. As autogenous bone is the golden standard treatment, the new methods should be compared with it. In a multicenter, prospective, randomized study Russell and Leighton reported less subsidence of the articular surface when the tibial plateau fractures were augmented with calcium phosphate cement compared to autogenous bone [40].

There are only few clinical fracture studies using bioactive glass in the fracture treatment. The preliminary clinical results in this kind of application were reported earlier [41]. There is, however, no prospective, randomized study about bioactive glass as a bone substitute material in lateral tibial plateau fractures.

New bone substitute materials are expected to make the operation easier and less invasive for the patient and more convenient for the operator. It is also expected to shorten the operation time. In our study, we could not observe reduction of the operation time. Harvesting bone from iliac crest lengthens the operation time about 20–30 min. We avoided it using another surgeon harvesting autogenous bone simultaneously. The harvesting of bone grafts is nevertheless associated with morbidity and complications [4] and occasionally bleeding from the raw surface of the iliac crest necessitates blood transfusion. In our study the mean bleeding from iliac crest was 215 ml (0–960). Only two patients in the AB group and one in the BG group received blood transfusion due to bleeding over 500 ml. Preoperatively it was subjectively noted that bioglass granules reduced the bleeding from the cancellous bone. Also during the operation, the use of bone substitute material made the procedure easier both for the surgeon and the patient as well. It is obvious that postoperative pain is less intense and mobilization of the patients easier, because of the lack of iliac crest wound and drain.

The proven bacteriostatic properties of the bioactive glass (S53P4) [23] might be advantageous in patients with behavioral habits supposed to deteriorate the outcome, such as smoking and alcoholism, though in our study we could not differentiate this effect between the two groups. In the

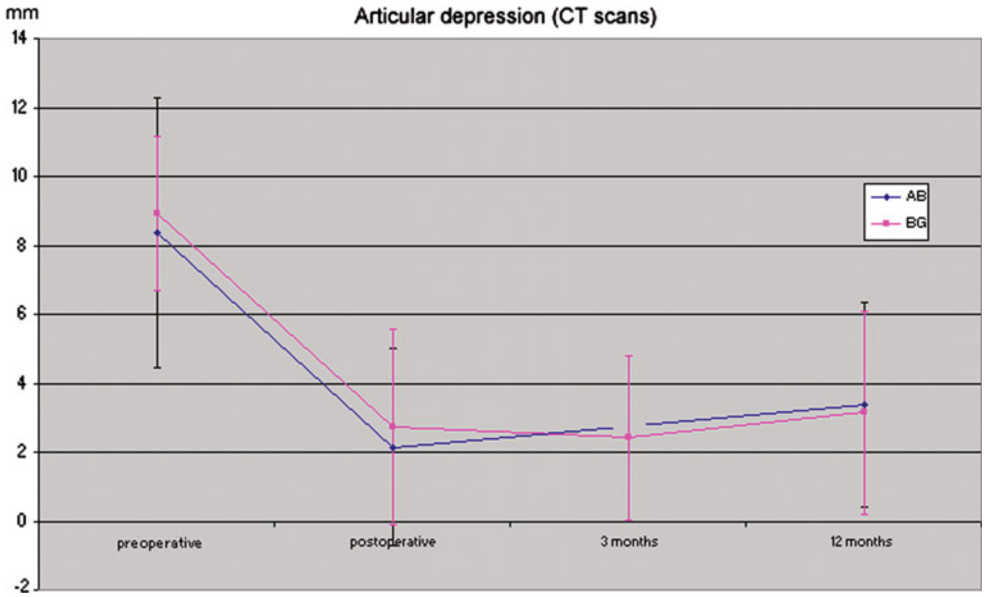

Fig. 3 The joint-line depression evaluated by CT. In BG group the depression has been reduced from preoperative 9 to postoperative 3 mm and remained unchanged thereafter until 3 months. In the AB group the mean depression was reduced from preoperative 8 to postoperative 2 mm and increased thereafter with 1 mm until 12 months (AB line is broken at 3 months because of no data at that time point)

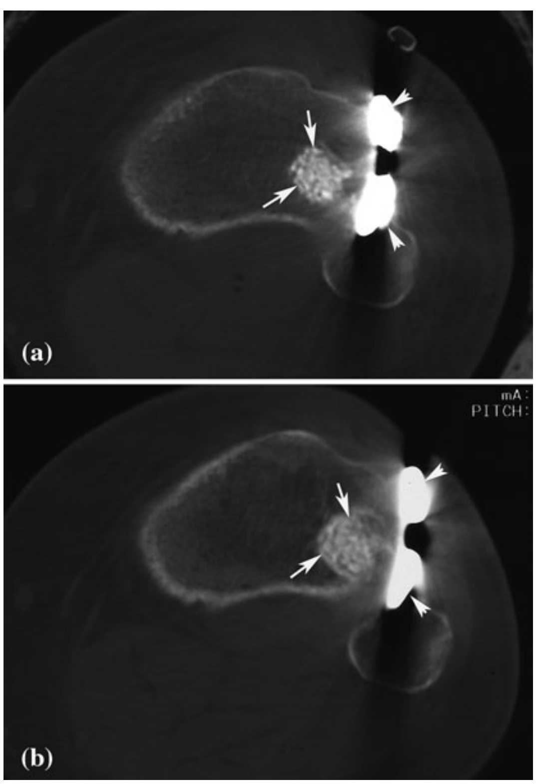

Fig. 4 Axial CT images. Same patient postoperatively (**a**) and at 12 months (**b**). Images at the level of bioactive glass filling (*arrows*). Metal implant indicated with arrowheads. Blurring of the interface between glass and surrounding host bone is clearly demonstrated, as originally sharp boundaries of the glass granules become gradually smoother with time. This is supposed to demonstrate growth of new bone in between the incorporating granules

BG group there was, however, one smoker with alcohol abuse, who developed a superficial wound infection. This complication was treated by debriding only and removing the superficial layer of the granules and closing the wound. The patient needed no further surgery due to infection.

The radiological analysis in this study was performed using both plain films and CT scans. The pre- and post-operative depression in plain films correlated well with those obtained using CT scans. The slight postoperative redepression of the fractured joint surface was similarly evident using both methods. In this study the preoperative CT helped planning of the operation, as also reported by Chan et al. [42]. The advantages of CT slices over plain films are lack of superimposing structures on the graft enabling more accurate visualization of small details. Evolving modern CT technology (multislice scanners and 3D technology) allows detailed visualization of fragment alignment and graft as well as diminishes metal implant artefacts degrading image quality.

On plain films and CT we could observe a constant finding that the interface between the granules and the host bone disappeared and the contour of the originally sharp granules became rounder with time, probably due to formation of the surface reaction layer and later, the subsequent bone formation on the granule surfaces similarly to that observed in experimental animal studies [13]. We are well aware that at least plain films are poor tools to evaluate the bonding and bone formation of the host bone on the biomaterials [43]. Nevertheless we have earlier examined the growth of vascularity and osteogenic activity in clinical tumor induced bone defects. The results in that study suggested that the host bone grows centripetally together with the granules of bioactive glass [41]. Leach et al. [14] have shown promising results on promoting vascularisation by adding vascular growth factors on the surface of bioactive glass.

In future it is important to evaluate the economical costs caused by operation theatre time, the hospital stay and the costs caused by the bone graft substitute. We believe that the use of bone substitute materials will become more popular when the cost of the bone substitute material is less than the costs caused by the additional operative theatre time and hospital stay together with the costs for the iliac crest drainage and blood transfusions. However, attention must also be paid on the patients' pain, comfort and complications caused by bone harvesting.

For the bone substitute material implanted in the defect it is favourable that it will not resorb faster than the new bone is formed. However the implanted material should resorb in proper time. This is especially important in locations where future surgery, e.g. arthroplasty, might be needed. Based on previous studies it was clear that the bioactive glass (S53P4) is bioactive, osteoconductive and bone bonding. It does resorb slowly also in human bone after implantation. The resorption time is depending on the size of the granules and amount of the glass used [27].

The present results show that bioactive glass (S53P4) can be used as a bone substiute material in this kind of acute metaphyseal defects. We believe that bone substitute materials will become more popular as filling material in the future. It remains to be seen which one of the several existing bone substitute materials will in the future be most suitable for this purpose. The major advantages of bioactive glass are good bone bonding, its bacteriostatic properties and probable gradual complete resorption.

Acknowledgments Sincere thanks to Biostatistician Hans Helenius, MSc., Head of the Department of Biostatistics, University of Turku, for his valuable help in organizing the statistical analysis of the data.

References

1. Honkonen SE. Indications for surgical treatment of tibial condyle fractures. Clin Orthop Relat Res. 1994;302:199–205.
2. Tscherne H, Lobenhoffer P. Tibial plateau fractures. Management and expected results. Clin Orthop Relat Res. 1993;292:87–100.
3. Waddell JP, Johnston DW. Fractures of the tibial plateau: a review of ninety-five patients and comparison of treatment methods. J Trauma. 1981;21(5):376–81.
4. Cockin J. Autologous bone crafting-complications at the donor site. J Bone Joint Surg. 1971;53B(1):153.
5. Burri C, Bartzke G, Goldewey J, Muggler E. Fractures of the tibial plateau. Clin Orthop Relat Res. 1979;138:84–93.
6. Jupiter JB, Winters S, Sigman S, Lowe C, Pappas C, Ladd AL, Van Wagoner M, Smith ST. Repair of five distal radius fractures with an investigational cancellous bone cement: a preliminary report. J Orthop Trauma. 1997;11(2):110–6.
7. Kopylov P, Runnqvist K, Jonsson K, Aspenberg P. Norian SRS versus external fixation in redisplaced distal radial fractures. A randomized study in 40 patients. Acta Orthop Scand. 1999;70(1): 1–5.
8. Bucholz RW, Carlton A, Holmes R. Interporous hydroxyapatite as a bone graft substitute in tibial plateau fractures. Clin Orthop Relat Res. 1989;240:53–62.
9. Suzuki K, Kurabayashi H. Efficiency of hydroxyapatite-tricalcium phosphate-composite (HAP–TCP) for bone defect of tibia fracture—comparison between HAP–TCP and autogenous iliac bone. In: Andersson ÖH, Happonen RP, Yli-Urpo A, editors. Bioceramics, vol. 7. Oxford: Butterworth-Heinemann Ltd; 1994. p. 435–40.
10. Stankewich CJ, Swiontkowski MF, Tencer AF, Yetkinler DN, Poser RD. Augmentation of femoral neck fracture fixation with an injectable calcium–phosphate bone mineral cement. J Orthop Res. 1996;14(5):786–93.
11. Andersson ÖH, Liu G, Karlsson KH, Niemi L, Miettinen J, Juhanoja J. In vivo behaviour of glasses in the SiO_2–Na_2O–CaO–P_2O_5–Al_2O_3–B_2O_3 system. J Mater Sci Mater Med. 1990;1: 219–27.
12. Hench LL, Splinter RJ, Allen WC, et al. Bonding mechanism at the interface of ceramic prosthetic materials. J Biomed Mat Res Symp. 1971;N2(Part-1):117–43.
13. Heikkilä JT, Aho HJ, Yli-Urpo A, Happonen RP, Aho AJ. Bone formation in rabbit cancellous bone defects filled with bioactive glass granules. Acta Orthop Scand. 1995;66(5):463–7.
14. Leach JK, Kaigler D, Wang Z, Krebsbach PH, Mooney DJ. Coating of VEGF-releasing scaffolds with bioactive glass for angiogenesis and bone regeneration. Biomaterials. 2006;27(17): 3249–55.
15. 15. Hench LL, Andersson ÖH. Bioactive glasses. In: Hench LL, Wilson J, editors. An introduction to bioceramics. Singapore: Reed Healthcare Communications; 1993. pp. 41–62.
16. Heikkilä JT, Aho AJ, Yli-Urpo A, Andersson OH, Aho HJ, Happonen RP. Bioactive glass versus hydroxylapatite in reconstruction of osteochondral defects in the rabbit. Acta Orthop Scand. 1993;64(6):678–82.
17. Andersson ÖH, Liu G, Kangasniemi K, et al. Evaluation of the acceptance of glass in bone. J Mater Sci Mater Med. 1992;3: 145–50.
18. Lindfors NC, Hyvönen P, Nyyssönen M, Kirjavainen M, Kankare J, Gullichsen E, Salo J. Bioactive glass S53P4 as bone graft substitute in treatment of osteomyelitis. Bone. 2010;47:212–8.
19. Turunen T, Peltola J, Yli-Urpo A, Happonen RP. Bioactive glass granules as a bone adjunctive material in maxillary sinus floor augmentation. Clin Oral Implant Res. 2004;15(2):135–41.
20. Lindfors NC, Koski I, Heikkilä JT, Mattila K, Aho AJ. A prospective randomized 14-year follow-up study of bioactive glass and autogenous bone as bone graft substitutes in benign bone tumors. J Biomed Mater Res Appl Biomater. 2010;94:157–64.
21. Jallot E, Benhayoune H, Kilian L, Irigaray JL, Barbotteau Y, Balossier G, Bonhomme P. Dissolution kinetics, selective leaching, and interfacial reactions of a bioglass coating enriched in alumina. J Colloid Interface Sci. 2001;233(1):83–90.
22. Lindfors NC. Treatment of a recurrent aneurysmal bone cyst with bioactive glass in a child allows for good bone remodelling and growth. Bone. 2009;45(2):398–400.
23. Stoor P, Söderling E, Salonen JI. Antibacterial effects of a bioactive glass paste on oral micro organisms. Acta Odontol Scand. 1998;56(3):161–5.
24. Peltola M, Suonpää J, Aitasalo K, Varpula M, Yli-Urpo A, Happonen RP. Obliteration of the frontal sinus cavity with bioactive glass. Head Neck. 1998;20(4):315–9.

25. Aitasalo K, Suonpää J, Peltola M, et al. Behaviour of bioactive glass (S53P4) in human frontal sinus obliteration. In: Sedel L, Rey C, editors. Bioceramics, vol. 10. Cambridge: Elsevier Science Ltd; 1997. p. 429–32.
26. Wilson J, Clark AE, Douek E, et al. Clinical applications of Bioglass implants. In: Andersson ÖH, Happonen RP, Yli-Urpo A, editors. Bioceramics, vol. 7. Oxford: Butterworth-Heinemann Ltd; 1994. p. 415–22.
27. Aho AJ, Suominen E, Alanen A, Yli-Urpo A, Knuuti J, Aho HJ. Remodelling of the tibia after grafting of a large cavity with particulate bioactive glass–hydroxylapatite-case report on treatment of fibrous dysplasia with 13 years follow-up. Acta Orthop Scand. 2003;74(6):766–70.
28. Lindfors NC, Heikkilä JT, Koski I, Mattila K, Aho AJ. Bioactive glass and autogenous bone as bone graft substitutes in benign bone tumors. J Biomed Mater Res Appl Biomater. 2009;90:131–6.
29. Schatzker J, McBroom R, Bruce D. The tibial plateau fracture. The Toronto experience 1968–1975. Clin Orthop Relat Res. 1979;138:94–104.
30. Holzach P, Matter P, Minter J. Arthroscopically assisted treatment of lateral tibial plateau fractures in skiers: use of a cannulated reduction system. J Orthop Trauma. 1994;8(4):273–81.
31. Asik M, Cetik O, Talu U, Sozen YV. Arthroscopy-assisted operative management of tibial plateau fractures. Knee Surg Sports Traumatol Arthrosc. 2002;10(6):364–70.
32. Segur JM, Torner P, Garcia S, Combalia A, Ramon R. Use of bone allograft in tibial plateau fractures. Arch Orthop Trauma Surg. 1998;117(6-7):357–9.
33. Lasanianos N, Mouzopoulos G, Garnavos C. The use of freeze-dried cancelous allograft in the management of impacted tibial plateau fractures. Injury. 2008;39(10):1106–12.
34. Itokazu M, Matsunaga T, Ishii M, Kusakabe H, Wyni Y. Use of arthroscopy and interporous hydroxyapatite as a bone graft substitute in tibial plateau fractures. Arch Orthop Trauma Surg. 1996;115(1):45–8.
35. Lobenhoffer P, Gerich T, Witte F, Tscherne H. Use of an injectable calcium phosphate bone cement in the treatment of tibial plateau fractures: a prospective study of twenty-six cases with twenty-month mean follow-up. J Orthop Trauma. 2002;16(3):143–9.
36. Trenholm A, Landry S, McLaughlin K, Deluzio KJ, Leighton J, Trask K, Leighton RK. Comparative fixation of tibial plateau fractures using alpha-BSM, a calcium phosphate cement, versus cancellous bone graft. J Orthop Trauma. 2005;19(10):698–702.
37. Horstmann WG, Verheyen CC, Leemans R. An injectable calcium phosphate cement as a bone-graft substitute in the treatment of displaced lateral tibial plateau fractures. Injury. 2003;34(2):141–4.
38. Simpson D, Keating JF. Outcome of tibial plateau fractures managed with calcium phosphate cement. Injury. 2004;35(9):913–8.
39. Welch RD, Zhang H, Bronson DG. Experimental tibial plateau fractures augmented with calcium phosphate cement or autologous bone graft. J Bone Joint Surg Am. 2003;85-A(2):222–31.
40. Russell TA, Leighton RK. Alpha-BSM Tibial Plateau Fracture Study Group. Comparison of autogenous bone graft and endothermic calcium phosphate cement for defect augmentation in tibial plateau fractures. A multicenter, prospective, randomized study. J Bone Joint Surg Am. 2008;90(10):2057–61.
41. Aho AJ, Heikkilä JT. Bone substitutes and related materials in clinical orthopaedics. In: Phillips GO, von Versen R, editors. Advances in Tissue Banking, vol. 1. Singapore: World Scientific; 1997. p. 73–108.
42. Chan PS, Klimkiewicz JJ, Luchetti WT, Esterhai JL, Kneeland JB, Dalinka MK, Heppenstall RB. Impact of CT scan on treatment plan and fracture classification of tibial plateau fractures. J Orthop Trauma. 1997;11(7):484–9.
43. Morii T, Koshino T, Odaka T, et al. Roentgenological and histological observations of bone reaction of glass–ceramic beads in tibial metaphysis and fibular diaphysis of man. In: Vincenzini P, editor. Ceramics in Clinical Applications. Amsterdam: Elsevier; 1987. p. 361–8.