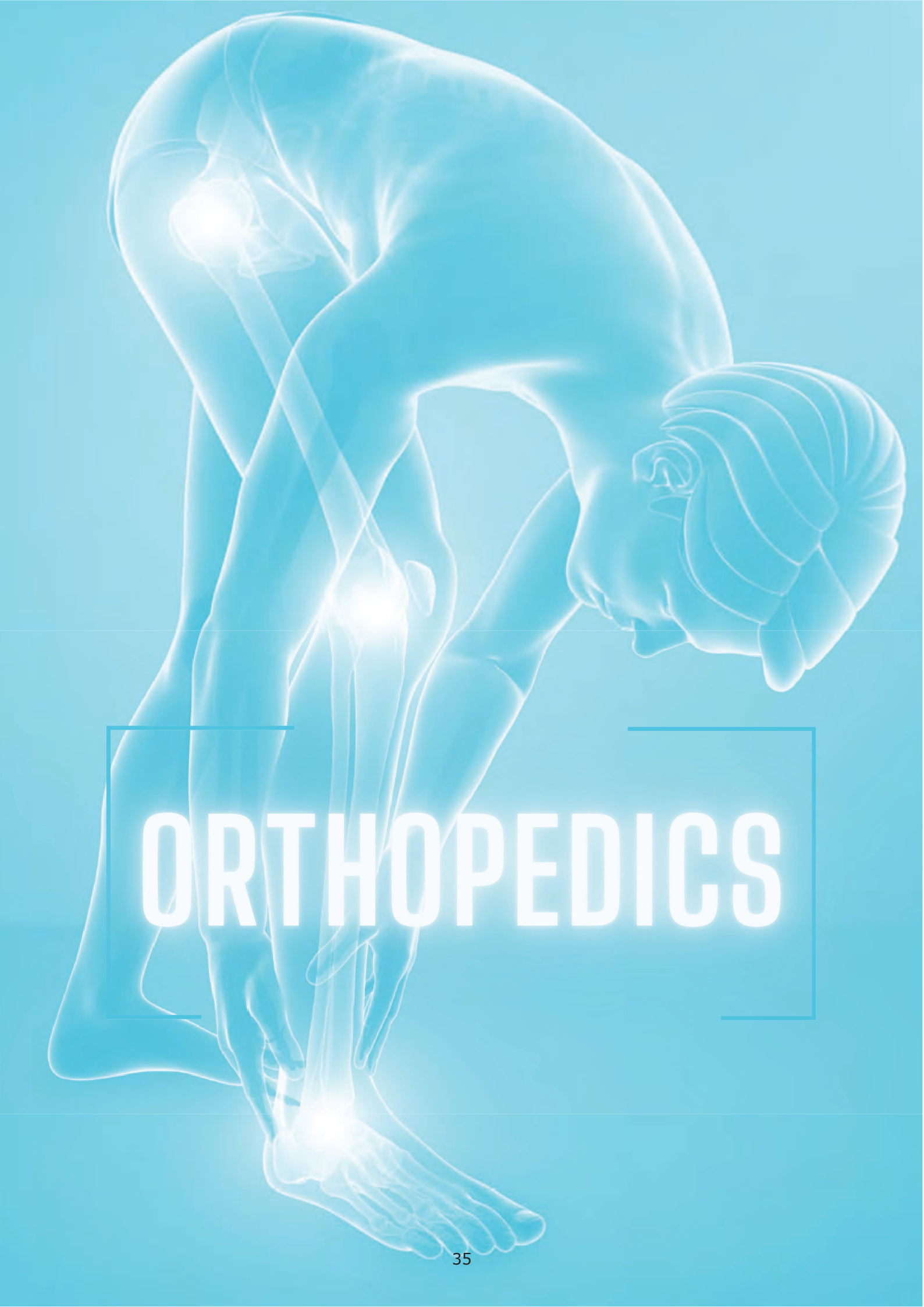

ORTHOPEDICS

SPINE

ORTHOPEDICS

CRANIO MAXILLO FACIAL - EAR NOSE THROAT

DENTAL

Orthopedic surgeries are performed daily to repair bone tissue due to traumatic injuries, disease as ntumors, deformity, and degeneration. It is intended to correct the osteoarticular deformations and to treat the painful joints/defect mainly due to the cysts, the tumors of the limbs and, finally, to correct the after-effects of the traumatisms (Andreasson et al., 2020; D'Elia et al., 2010; Dhanakodi et al., 2019; Dragosloveanu et al., 2020; Ferguson et al., 2019; Gaiarsa et al., 2019; Heikkila et al., 2011; Lindfors et al., 2009; Lindfors et al., 2010; Loveland et al., 2021; Pan et al., 2018; Pernaa et al., 2011; Shrouder-Henry et al., 2019; Thordarson & Kuehn, 2003; Wang & Yeung, 2017; Zhao et al., 2020) with or without infections.

Bone is one of the most common organs affected by metastases. Metastatic bone disease (MBD) can be caused by different primary tumors, with the highest prevalence being from breast and prostate cancer (Phull et al., 2021; Sebghati et al., 2021). Also, bone loss can be caused by the presence of a cyst or bone tumour that enlarge over time, resulting in thinning of the bone. Cysts are described as cavities filled with a benign fluid. Usually, these cysts are reported in the metaphyseal regions of long bones (50-70%) and 85% of unicameral bone cysts occur almost exclusively in children and adolescents (Dong et al., 2020; Noordin et al. 2018).

The treatment of tumors, cysts or even treatment-resistant infections often requires removing bone fragments that are too large for the natural self-repair process to be effective. Currently recommended treatment options include:

- curettage and bone-grafting
- intralesional injections with corticosteroids, bone marrow, demineralized bone matrix
- or bone ceramic filling, PMMA bone cement, decompression, not filling
- internal fixation
- and also combinations of these (Dong et al., 2020; Deventer et al., 2021; Gava & Engel, 2021).

After a fracture, the dead bone must be resorbed, and the new bone reformed. Bone resorption is performed mainly by osteoclasts and new bone formation is performed by osteoblasts. Osteoblasts line the outer surface of bones and are also present in most bone cavities. These cells secrete a very strong protein matrix, consisting mainly of collagen fibres. The matrix is then mineralized, and the osteoblasts become osteocytes. Blood vessels containing mineral elements are key contributors to the process of osteogenesis. Most bone fractures occur as a result of inconvenient or incompetent bone regeneration.

But sometimes segmental bone fractures did not repair instinctively and require orthopedic
operation (Ansari, 2019). Depending on the case, a repair of the fracture (osteosynthesis) by nail, plate, screw will be carried out with or without graft. In some cases (complex fracture of the elderly, risk of bone necrosis of the head, etc.) replacement by partial or total shoulder prosthesis will be chosen (Marongiu et al., 2020; Martin et al., 2021).

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ORIGINAL ARTICLE

The impact of bone graft type used to fill bone defects in patients undergoing ACL reconstruction with bone–patellar tendon–bone (BPTB) autograft on kneeling, anterior knee pain and knee functional outcomes

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Abstract

Purpose Multiple different materials are used for filling bone defects following bone–patellar tendon–bone (BPTB) graft ACL reconstruction surgery. The theoretical objective being to minimize kneeling pain, improve clinical outcomes and reduce anterior knee pain following surgery. The impact of these materials is assessed in this study.

Methods A prospective monocentric cohort study was conducted from January 2018 to March 2020. There were 128 skeletally mature athletic patients who underwent ACL reconstruction using the same arthroscopic-assisted BPTB technique, with a minimum follow-up of two years identified in our database. After obtaining approval from the local ethics committee, 102 patients were included in the study. Patients were divided into three groups based on type of bone substitute. The Bioactive glass 45S5 ceramic Glassbone™ (GB), collagen and hydroxyapatite bone void filler in sponge form Collapat® II (CP), and treated human bone graft Osteopure®(OP) bone substitutes were used according to availability. Clinical evaluation of patients at follow-up was performed using the WebSurvey software. A questionnaire completed in the 2nd post-operative year included three items: The ability to kneel, the presence of donor site pain, and the palpation of a defect. Another assessment tool included the IKDC subjective score and Lysholm score. These two tools were completed by patients preoperatively, and postoperatively on three occasions (6 months, 1 year, and 2 years).

Results A total of 102 patients were included in this study. In terms of Kneeling pain, the percentage of GB and CP patients' who kneel with ease were much higher than that of OP patients (77.78%, 76.5% vs 65.6%, respectively). All three groups experienced an important increase in IKDC and Lysholm scores. There was no difference in anterior knee pain between the groups.

Conclusion The use of Glassbone® and Collapat II® bone substitutes reduced the incidence of kneeling pain compared to Osteopure®. There was no influence of the bone substitute type on the functional outcome of the knee or on the anterior knee pain at two years of follow.

Keywords BTPT graft · ACL · Glassbone · Collapat · Osteopure · Kneeling pain

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Introduction

Anterior cruciate ligament (ACL) injuries are among the most common knee injuries, and ACL reconstruction (ACLR) is a widely performed operation [1, 2]. The bone–patellar tendon–bone (BPTB) and hamstring tendon autografts are two of the most commonly used autografts for ACLR [3, 4]. Furthermore, BPTB autograft has long been the gold standard for treatment, as its bone blocks at both ends of the graft provide high fixation strength [5, 6]. Nevertheless, 15–60% of patients may complain of long-term post-operative anterior knee pain during daily living or physical activities. Kneeling pain and donor site defects are also frequently observed [7–12].

It has been argued that patellar and tibial bone defects following graft harvesting are a risk factor impacting anterior knee pain in BPTB patients. Other claims are that infrapatellar nerve damage during graft harvesting is responsible for this morbidity [13, 14]. Recently, a systematic review showed that BTBP ACLR patients, whose bone defects were filled, have fewer post-operative knee complaints and better knee functional outcomes than patients treated without defect filling [8]. The most common bone grafts used are either autologous bone grafts, allogeneic bone grafts or synthetic substitutes [15–17]. Nonetheless, no study has compared the outcomes of different types of bone graft in terms of kneeling and functional outcomes in BTBP ACLR patients.

Such bone grafting options include the Bioactive glass 45S5 ceramic, such as Glassbone® (GB); collagen and hydroxyapatite bone void filler in sponge form, such as Collapat II® (CP), and treated human bone graft, such as Osteopure® (OP).

This cohort study aimed to investigate the influence of these bone graft types on kneeling and knee functional outcomes. The hypothesis was that there was no superiority of one substitute over another.

Materials and methods

A prospective single-center cohort study of the French prospective ACL Study [FAST] (NCT02511158) was performed, including all patients who performed ACLR using BPTB autograft between 2018 and 2020 by 4 senior surgeons. The study was approved by the local ethics committee (Comité de Protection des Personnes IDF VI), and informed consent was obtained from all patients. A retrospective analysis of the prospectively filled data, with a minimum follow-up of two years was performed. One hundred and two patients undergoing ACL reconstruction using BPTB autograft were assessed. Clinical evaluation of patients at follow-up was performed by the surgeons and data was entered in the WebSurvey software. The inclusion criteria were ACL reconstruction using the BTBP technique, athletes, a minimum of two years of post-operative follow-up and an age over 18 years. Exclusion criteria were associated knee ligament injury requiring surgical treatment, chondropathy of grade III or higher involving the trochlea or the patella, immune rheumatologic pathologies, preexisting anterior knee pain, and prior surgery on the same knee. Patients were divided into three groups according to bone substitute type. Three different bone substitutes were used according to availability at the time of surgery: Glassbone™, Collapat® II, and Osteopure®. The timeline is detailed in Fig. 1.

Bone substitutes

Osteopure® is a bone allograft harvested from a resected live human femoral head, and treated by sterilization at 25 kGy.

Glassbone® is a bioactive glass which is 100% synthetic, biocompatible, and osteoconductive and can integrate with the bone and soft tissue as a defect filler (Fig. 2). It is composed of a mixture of oxides (45% SiO_2, 24.5% CaO, 25.5%, Na_2O, and 6% P_2O_5 in weight %) [18–25].

Collapat® II is a bone void filler presented in spongy form. It is composed of a collagen structure in which hydroxyapatite granules are dispersed. The granules of hydroxyapatite give the material its osteoconductive properties [23].

Patient follow-up and data collection

Three tools were used for data collection at various time points. First, a questionnaire assessed the international knee documentation committee (IKDC) [24] subjective score and Lysholm score [25]. These two tools were completed by patients at four time points: first pre-operatively, and at 6 months, one year and two years postoperatively. Another standardized questionnaire was sent by email to the participants 4 months postoperatively. This was repeated at the 6 months, one year and two years marks following surgery. This questionnaire was made available online via a link to the WebSurvey software (websurvey.fr). If patients failed to answer, a first reminder was made via email, and a second by telephone call. Finally, a questionnaire was sent at the second post-operative year. It evaluated 3 items: The ability to kneel assessed by the subsection of Hacken's questionnaire [26], the presence of donor site pain during sports or daily activities assessed by the Numerical Rating Scales (NRS) [27], and the sensation of a defect at the donor site.

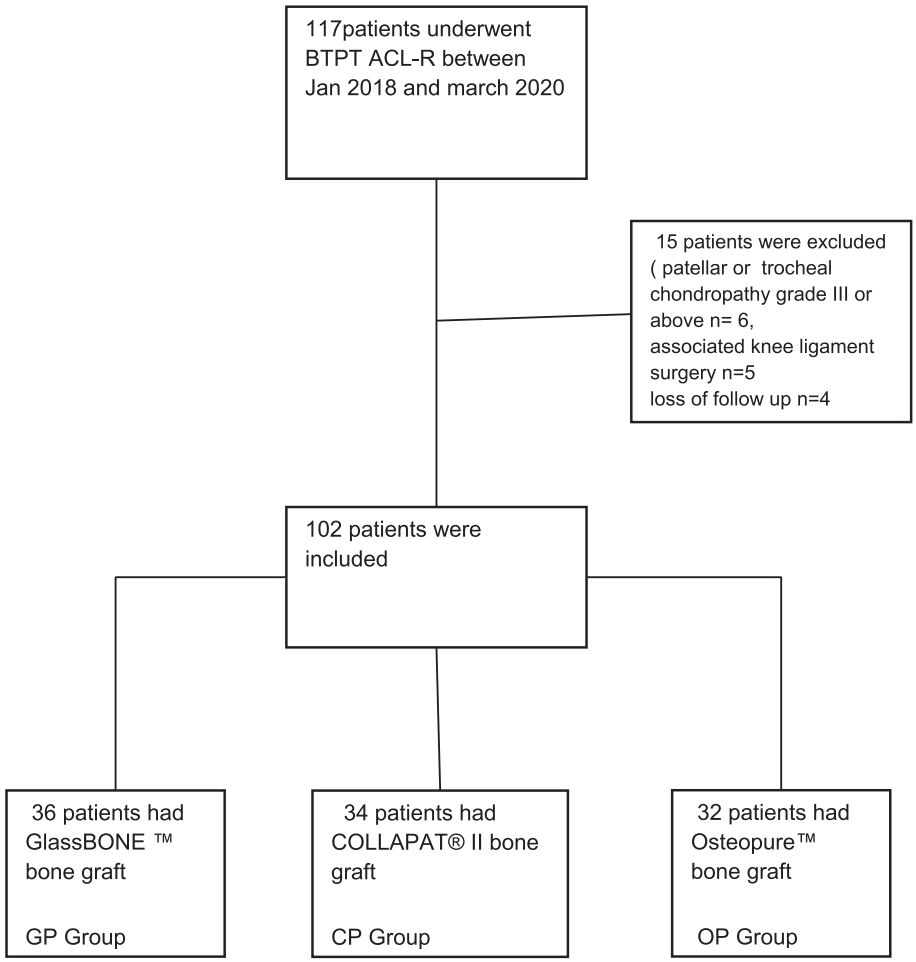

Fig. 1 Flowchart showing the distribution of patients into three groups

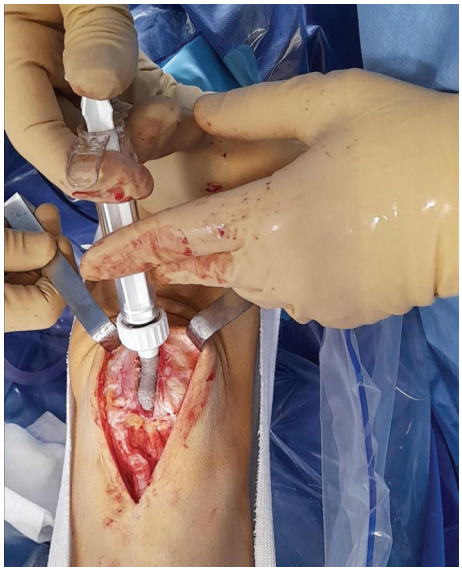

Fig. 2 Intra-operative photograph showing the patellar defect being filled with Glassbone allograft

No formal sample size calculation was done. All eligible patients who underwent ACLR BPTB graft between 2018 and 2020 at our institution were included in the study.

Surgical protocol

Under spinal anesthesia, BPTB autografts were used to reconstruct the ACL. A 9 cm para median incision was performed, the paratenon was dissected carefully, and the a middle third of the patellar tendon was harvested with approximately 10 × 10 × 20 mm bone blocks from the patella and tibia. The ACL remnant was preserved. The tibial bone tunnel was prepared to be 10 mm in diameter. The tibial tunnel was created with a specific guide (*Acufex; Smith & Nephew*). The femoral tunnel was 10 mm in diameter and placed at the origin of the native ACL, on the medial surface of the lateral femoral condyle using an inside-out technique. The BTB autograft was fixed in the femoral tunnel with a non-absorbable interference screw (*Softsilk; Smith & Nephew*) or absorbable pins using the RigidFix system (*DePuy Synthes, Mitek rigid fix*), depending on surgeon preference. After tensioning the graft, the patellar bone block

was stabilized in the tibial tunnel with another interference bioabsorbable screw (*Smith & Nephew*). Finally, the bony defects were filled with the corresponding bone graft and the paratenon was sutured over the bone substitutes.

Post-operative rehabilitation protocol

All patients underwent the same rehabilitation protocol. Immediate full weight-bearing with an articulated brace was allowed using crutches for the first 3 weeks to avoid unexpected falls. Physiotherapy for analgesia, patella mobilization, progressive full range-of-motion exercises, and isometric quadriceps contraction exercises were allowed, with the expectation that at one-month postoperatively, the patient would have a normal gait, full extension and 110° of flexion. In the case of meniscal suture, knee flexion while weight-bearing was limited to 120° for two months postoperatively.

Statistical analysis

All statistical analyses were performed using the IBM SPSS statistics software. Categorical variables were summarized as frequencies and percentages. Continuous variables were presented as means, standard deviations and ranges. One-way ANOVA was used to compare the mean IKDC and Lysholm scores, as well as the change in these scores between the three groups. Repeated measures ANOVA was used to compare the IKDC and Lysholm scores at different time points within each group. Pearson's Chi-square test or Fisher exact test were used to assess the association of gender, ability to kneel, and internal pain between the three groups. All tests were two-sided and a $p < 0.05$ was considered statistically significant.

Results

One hundred and seventeen patients underwent ACLR using BPTB autograft. Of those, 102 (87.17%) were included in this study, and 15 (12.83%) were excluded. Among the 102 patients, 36 (35.29%) patients were placed in the Glassbone® group (group 1), 34 (33.33%) in the Collapat II® group (group 2), and the remaining 32 (31.37%) in the Osteopure® group (group 3). The three groups had no significant differences in terms of age ($p = 0.127$) and gender ($p = 0.511$). The mean age was 32.17 ± 8.20 years. Men represented 78.43% of the studied population. Detailed demographic characteristics are described in Table 1.

Among the 102 patients studied, 27 (26.47%) complained of Kneeling pain. There was a significant difference between the three groups ($p = 0.045$), the percentage of Glassbone and Collapat patients' who kneel comfortably was significantly higher than that of osteobank patients (77.78%, 76,5% vs 65.6%, respectively). Moreover, the percentage of osteobank patients who were unable to kneel on hard surfaces was higher than that of Glassbone and Collapat patients (8% vs 2,78; 2.94%, respectively).

In the study population, 31 (30.39%) patients had anterior knee pain with an average of 3.77 ± 1.50 on the NRS scale. The percentage of patients experiencing anterior knee pain was 30.56% (mean 3.64 ± 1.03), 29.41% (mean 3.80 ± 1.69), and 31.25% (mean 3.90 ± 1.85) in groups 1, 2 and 3, respectively (p value 0.987).

The clinical characteristics are described in Table 2.

The IKDC score was significantly improved in the three groups compared to the pre-operative status ($P < 0.01$), as detailed in Table 3.

In group 1, the mean IKDC score increased from 56.67 ± 14.43 (range 26–84) pre-operatively to 69.22 ± 9.54 (range 36–86), 76.42 ± 9.26 (range 54–89) and 81.17 ± 10.61 (range 55–97) at 6 months, 1 year and 2 years postoperatively respectively, with a statistically significant mean change of 24.50 ± 15.64 (range (-4)–60) ($p < 0.001$).

In group 2, the mean IKDC score increased from 60.35 ± 15.28 (range 32–90) at pre-operative to 66.65 ± 14.14 (range 20–83), 74.82 ± 16.58 (range 26–99) and 81.18 ± 15.97 (range 26–100) at 6 months, 1 year and 2 years post-operative respectively, with a statistically significant mean change of 20.52 ± 15.55 (range (-8)–55) ($p < 0.001$).

In group 3, the mean IKDC score increased from 53.63 ± 18.38 (range 13–84) at pre-operative to 66.31 ± 16.15 (range 33–95), 74.16 ± 15.89 (range 39–98) and 77.69 ± 16.79 (range 40–98) at 6 months, 1 year and

Table 1 Patients demographic characteristics

		Overall ($n = 102$)	GlassBone Group ($n = 36$)	Collapat II Group ($n = 34$)	Osteobank Group ($n = 32$)	P value
Age (years)	Mean ± SD (range)	32.17 ± 8.20 (18–56)	30.36 ± 8.38 (18–48)	34.32 ± 7.57 (21–54)	31.91 ± 8.36 (20–56)	0.127*
Gender *n* (%)	Male	80 (78.43)	30 (83.33)	27 (79.41)	23 (71.88)	0.511‡
	Female	22 (21.57)	6 (16.67)	7 (20.59)	9 (28.13)	

SD: Standard deviation. *p value was calculated using one-way ANOVA. ‡p value was calculated using Chi-square test or Fisher exact test. $P < 0.05$ was considered as statistically significant

Table 2 Patient clinical characteristics

		Overall ($n=102$)	GlassBone group ($n=36$)	Collapat II group ($n=34$)	Osteobank group ($n=32$)	P value
Kneeling n (%)	No pain with kneeling	75 (73.53)	28 (77.78)	26 (76.5)	21 (65.63)	0.045‡
	Mild pain with kneeling	13 (12.75)	6 (16.66)	5 (14.71)	2 (6.25)	
	Inability to kneel on hard surfaces	10 (9.80)	1 (2.78)	1 (2.94)	8 (25.0)	
	Completely, unable to kneel	4 (3.92)	1 (2.78)	2 (5.88)	1 (3.12)	
Anterior knee pain n (%)	No	71 (69.61)	25 (69.44)	24 (70.59)	22 (68.75)	0.987‡
	Yes	31 (30.39)	11 (30.56)	10 (29.41)	10 (31.25)	
If yes, NRS score ($n=31$)	Mean ± SD (range)	3.77 ± 1.50 (1–7)	3.64 ± 1.03 (2–5)	3.80 ± 1.69 (2–7)	3.90 ± 1.85 (1–6)	0.925*
Defect sensation	Yes	0	0	0	0	NA
	No	102 (100%)	36 (100%)	34 (100%)	32 (100%)	

SD: Standard deviation. *p value was calculated using one-way ANOVA. ‡p value was calculated using Chi-square test or Fisher exact test. $P<0.05$ was considered as statistically significant

Table 3 IKDC score at each time point by type of the bone substitute groups

	Overall ($n=102$)	GlassBone group ($n=36$)	Collapat II group ($n=34$)	Osteobank group ($n=32$)	P value*
Pre-operative	56.94 ± 16.11 (13–90)	56.67 ± 14.43 (26–84)	60.35 ± 15.28 (32–90)	53.63 ± 18.38 (13–84)	0.238
6 months post-op	67.45 ± 13.37 (20–95)	69.22 ± 9.54 (36–86)	66.65 ± 14.14 (20–83)	66.31 ± 16.15 (33–95)	0.615
1 year post-op	75.18 ± 14.07 (26–99)	76.42 ± 9.26 (54–89)	74.82 ± 16.58 (26–99)	74.16 ± 15.89 (39–98)	0.794
2 years post-op	80.08 ± 14.54 (26–100)	81.17 ± 10.61 (55–97)	81.18 ± 15.97 (26–100)	77.69 ± 16.79 (40–98)	0.537
Pre-op to 2-year post-op change	23.14 ± 16.99 (− 15–73)	24.50 ± 15.64 ((− 4)–60)	20.52 ± 15.55 ((− 8)–55)	24.06 ± 19.94 ((− 15.0)–73)	0.624
P value†		< 0.001			

SD: Standard Deviation; IKDC: International Knee Documentation Committee. Data were expressed as mean ± SD (range). *P value was calculated using one-way ANOVA. †P value was calculated using repeated measure ANOVA. $P<0.05$ was considered as statistically significant

2 years post-operative respectively, with a statistically significant mean change of 24.06 ± 19.94 (range (− 15.0)–73) ($p<0.001$).

There was no statistically significant difference in the mean IKDC score between the three groups ($p>0.05$).

The evolution of IKDC score by time in the three groups is shown in Fig. 3.

The Lysholm score was significantly improved in the three groups compared to the pre-operative status ($p<0.01$) as detailed in Table 4.

In group 1, the mean Lysholm score increased from 67.53 ± 15.18 (range 28–95) at pre-operative to 81.33 ± 11.26 (range 44–95), 86.53 ± 10.24 (range 60–99) and 89.78 ± 9.90 (range 52–100) at 6 months, 1 year and 2 years post-operative respectively, with a statistically significant mean change of 22.25 ± 15.21 (range (− 6)–66) ($p<0.001$).

In group 2, the mean Lysholm score increased from 67.88 ± 18.06 (range 15–95) at pre-operative to 81.41 ± 16.02 (range 22–99), 85.68 ± 13.43 (31–100) and 87.18 ± 13.78 (range 30–100) at 6 months, 1 year and 2 years post-operative respectively, with a statistically significant mean change of 19.29 ± 14.18 (range (− 1)–80.0) ($p<0.001$).

In group 3, the mean Lysholm score increased from 60.84 ± 20.61 (range 2–99) at pre-operative to 76.09 ± 13.32 (range 49–100), 80.78 ± 11.82 (range 56–98) and 85.16 ± 12.37 (range 56–100) at 6 months, 1 year and 2 years post-operative respectively, with a statistically significant mean change of 24.31 ± 21.93 (range (− 11)–80) ($p<0.001$).

Similarly, to the IKDC score, no statistically significant difference in the mean Lysholm score between the three groups was detected ($p>0.05$).

The evolution of Lysholm score by time in the three groups is shown in Fig. 4.

All patients in the study, having subjectively assessed their knees, found no sensation of a bony defect at 2 years

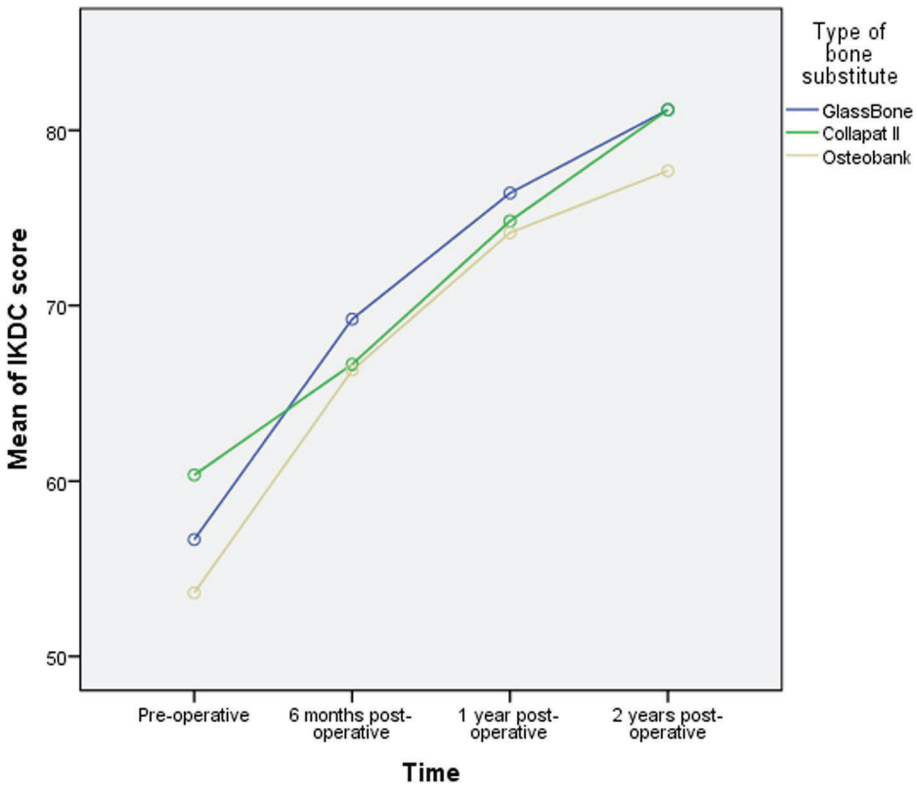

Fig. 3 Evolution of the IKDC score over time

Table 4 Lysholm score at each time point by type of the bone substitute groups

	Overall ($n=102$)	GlassBone group ($n=36$)	Collapat II group ($n=34$)	Osteobank group ($n=32$)	*P* value*
Pre-operative	65.55 ± 18.09 (2–99)	67.53 ± 15.18 (28–95)	67.88 ± 18.06 (15–95)	60.84 ± 20.61 (2–99)	0.207
6 months postoperative	79.72 ± 13.72 (22–100)	81.33 ± 11.26 (44–95)	81.41 ± 16.02 (22–99)	76.09 ± 13.32 (49–100)	0.198
1 year postoperative	84.44 ± 12.02 (31–100)	86.53 ± 10.24 (60–99)	85.68 ± 13.43 (31–100)	80.78 ± 11.82 (56–98)	0.110
2 years postoperative	87.46 ± 12.11 (30–100)	89.78 ± 9.90 (52–100)	87.18 ± 13.78 (30–100)	85.16 ± 12.37 (56–100)	0.290
Pre-operative to 2-year change	21.91 ± 17.26 (− 11–80)	22.25 ± 15.21 ((− 6)–66)	19.29 ± 14.18 ((− 1)–80.0)	24.31 ± 21.93 ((− 11)–80)	0.497
P value†		< 0.001			

Data were expressed as mean ± SD (range). *p value was calculated using one-way ANOVA. †p value was calculated using repeated measure ANOVA. $P < 0.05$ was considered as statistically significant

follow-up (Table 2). One incidence of a superficial abscess at the surgical site was observed in group 2. In this patient, the substitute was excized and an extra-articular debridement was needed to manage the complication.

Discussion

This study was designed to compare outcomes of ACL reconstruction with a BPTB autograft using one of three bone substitutes to fill the harvested zone. The primary finding was that the patients who received synthetic bone grafts, (Glassbone or Collapat II) had a higher percentage of painless kneeling compared to those who had Osteopure allograft filling. However, there was no significant difference between the three groups in terms of IKDC, Lysholm, and anterior knee pain.

Kneeling pain was evaluated using one item of Hacken's questionnaire [26]. The higher incidence of kneeling pain of patients of group 3 compared to patients from other groups might be due to the persistent inflammatory response or suboptimal bone consolidation caused by the Osteopure allograft [28]. The incidence of painless kneeling in this study was 73.53% overall, with 77.78% of the Glassbone patients reporting no pain. After reviewing the literature, it was found that this was higher than the study by Taylor et al. (62%) [29] and lower than the study by Hacken et al. (90.4%) [26]. In both of those studies, cancellous autograft

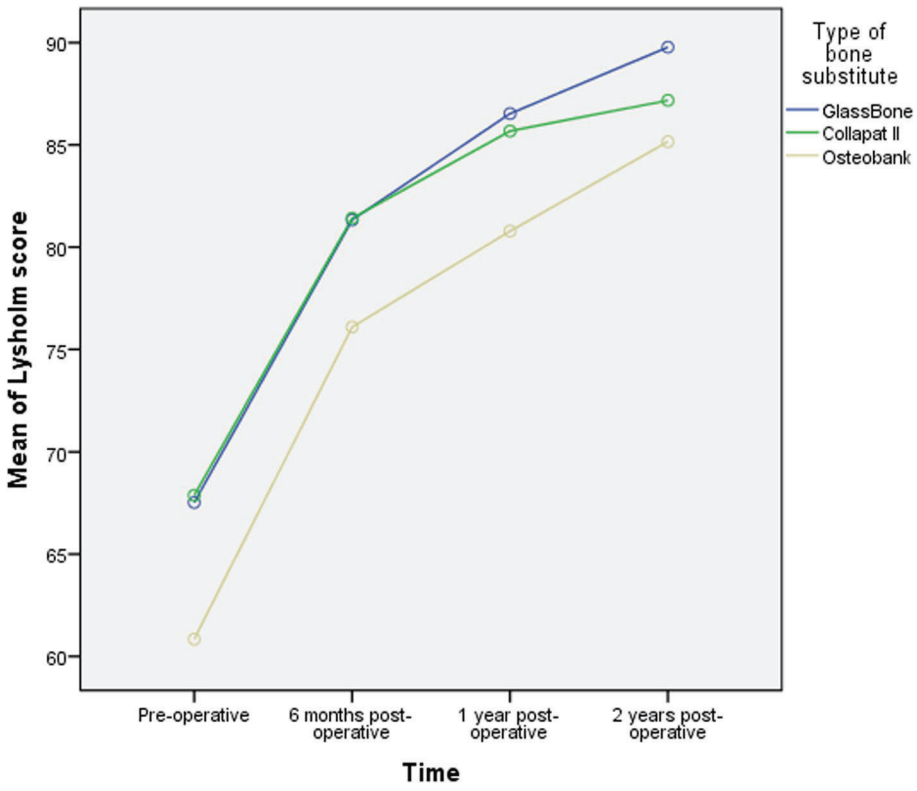

Fig. 4 Evolution of the Lysholm score over time

had been used for filling the bone defects. On the other hand Barrenius [30], Leitge [31] and Liden [32] who did not fill the bone defects registered a higher incidence of kneeling pain than the findings of the present study.

From a cosmetic standpoint, filling the defect with allograft improves appearance, a common patient concern, and abolishes the sensation of a bone gap or defect at the donor site. This allows avoidance of a further patient complaint during follow-up visits [33].

A major concern with using BPTB autograft for ACLR is donor site morbidity, specifically anterior knee pain [26]. Surgeons have attempted to change the harvesting technique in order to decrease this complication [12, 34], others have elected to change the graft type, like Schande et al. who used serum albumin-coated bone allograft [35]. Cervelline et al. filled the donor sites with PRP gel [36]. Nelson et al. also described a new technique for filling the defect [37]. Naresh et al. elected to fill the defects with ceramic bone graft but the results were non-satisfactory [38]. Our study aimed to identify the influence of different types of bone substitutes on anterior knee pain and found similar results in all three groups. The results are comparable to the findings of a systematic review by Lameire et al. who showed that filling defects decreased anterior knee pain, kneeling pain and extension loss [8].

No study evaluated and compared the functional outcome and donor site morbidity between Glassbone, Collapat II, or Osteopure bone substitutes in the BPTB ACLR population. Although there are numerous scoring tools to quantify ACLR patients' results [39], IKDC and Lysholm scores were chosen for this study, as they are standard instruments for evaluating patients postoperatively and two of the most commonly reported functional outcome scores [8, 26, 40]. Both scores in the present study showed satisfactory recovery in all three groups without significant difference between groups. Subjective IKDC ranged from 77 to 81 after two years following ACLR, and the Lysholm score ranged from 85 to 90. Comparing our results to the systematic review by Lameire et al., it is observed that the IKDC scores are similar, but the Lysholm scores are inferior [8]. Overall, however, it was determined that the type of bone substitute did not affect the functional knee outcome.

There was no complication reported in terms of wound healing except for a patient from group 2 who exhibited an extrusion of part of the bone substitute and needed surgical intervention. This case might be a coincidence, and conclusions cannot be drawn based on a single exceptional case. It is important to mention that this is the first study that showed the tolerance of donor sites to Glassbone in BPTB ACLR patients. There were no complications detected which might be due to its bacteriostatic activity [22]. No patellar fracture occurred in any patient of the three groups. This is similar to the results of Alexander et al. [41].

This study shows that the kneeling pain was higher in Osteopure group. We can only speculate about this discrepancy. Osteopure is a natural bone block which needs to be cut into shape to fill a defect. As a rigid substitute, it is more difficult to fully fill the defect with it compared to the other softer substitutes (Glassbone and Collapat). Furthermore, it is composed of cancellous bone. Perhaps the replacement of cortical bone from the patella and tibia with spongy bone from the bone substitute affects rigidity and therefore leads to more pain in this patient population. Bone graft healing is a sequential process involving inflammation revascularization, osteogenesis remodeling, and incorporation into the host skeleton to form a mechanically efficient structure so this process might be different between the three allograft types. Further studies would be needed to possibly give a more accurate response in the future.

The strengths of this study were the high response rate, the 2-year follow-up period and the prospective administration of questionnaires.

There were, however, several limitations. First, this was not a randomized trial, and it was not a blinded study. Although patients may have been blinded, the surgeons would not have been. Furthermore, the bone substitute used was done so based on availability, rather than random assignment. Secondly, although the operations were all performed in the same institution, different surgeons participated in the study and performed surgery. Moreover, concomitant meniscus injury was not part of the exclusion criteria. This likely affects standardization of the procedure and may cause variability in patient outcomes.

Conclusion

This study finds that there is a reduced incidence of kneeling pain and discomfort when using bone substitutes such as Glassbone® and Collapat II® compared to allografts such as Osteopure® at a 2-year follow-up. However, the choice of bone-filling material influences neither functional knee outcomes, nor anterior knee pain at 2 years postoperatively.

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Declarations

Conflict of interests All authors have declared and signed that they have no conflict of interests.

Ethical approval Animals are not involved.

Informed consent Humans were involved, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The Institutional review board CPP (comité pour la protection des personnes) CPP-Ile-de-France VI reviewed and approved the study protocol on 07/02/2013, see the certificate in the supplemental materials.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

Is a Bioceramic Glass Bone Graft Superior to Spongious Allografts in Femoral and Tibial Benign Bone Lesions?

Femoral ve Tibial Benign Kemik Lezyonlarında Biyoseramik Cam Greftler Spongioz Allogreftlerden Üstün müdür?

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Abstract

Objective: this study aimed to examine the results of spongious and bioceramic bone graft applications in benign lesions of the lower extremity long bones.

Methods: Forty-seven patients, who applied to our hospital between the years 2007 and 2013; who received curettage-grafting for benign bone lesions in the long bones carrying lower extremity weight were examined retrospectively.

Results: In the bioceramic glass bone graft group, an increased average consolidation ratio, which is statistically significant compared to the spongious allograft group (p=0.002), was observed. When the fibrous dysplasia patients were considered a subgroup, the consolidation ratio in the bioceramic glass bone graft group was found to be significantly high compared to the spongious allograft group (p=0.029).

Conclusion: Bioceramic glass bone grafts are bone filler materials that hold radiologically superior and clinically similar results compared to spongious allografts. Having a statistically significant radiological consolidation success in fibrous dysplasia, which is a benign aggressive tumor, bioceramic glass bone grafts may be thought to be capable of being an advantage option for benign aggressive tumors.

Keywords: Bioceramic glass bone graft, spongious allograft, femur, tibia, benign bone lesion

Öz

Amaç: Bu çalışmanın amacı, alt ekstremite uzun kemiklerindeki benign lezyonlarda uygulanmış spongioz ve biyoseramik cam greftin sonuçlarının incelenmesidir.

Yöntem: 2007 ile 2013 yılları arasında hastanemize başvuru yapmış, alt ekstremite yük taşıyan uzun kemiklerindeki iyi huylu kemik lezyonlarına yönelik küretaj-greftleme operasyonu yapılan kırk-yedi hasta retrospektif olarak incelendi.

Bulgular: Biyoseramik cam greft grubunda, insan kaynaklı spongioz allogreft grubuna kıyasla, istatistiksel olarak anlamlı, artmış ortalama konsolidasyon oranı görülmüştür (p=0,002). Fibröz displazi hastaları sub-grup olarak değerlendirildiğinde; biyoseramik cam greft grubundaki konsolidasyon oranı, insan kaynaklı spongioz allogreft grubuna kıyasla anlamlı olarak yüksek bulunmuştur (p=0,029).

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Öz

Sonuç: Biyoseramik cam greftler, insan kaynaklı spongioz allogreftlerle karşılaştırıldığında radyolojik olarak üstün, klinik olarak benzer sonuçlara sahip kemik dolgu materyalleridir. Biyoseramik cam greftlerin; benign agresif tümör olan fibröz displazideki radyolojik konsolidasyon başarısının istatistiksel olarak anlamlı olmasından dolayı, benign agresif tümörlerde avantajlı bir seçenek olarak düşünülebilir.

Anahtar Kelimeler: Biyoseramik cam greft, spongioz allogreft, femur, tibia, benign kemik lezyonları

Introduction

The gold standard is autogenous bone graft applications while there are several graft material usages for treating bone defects resulting from congenital anomalies, diseases, tumoral lesions, atrophy, or surgical excisions. An autogenous graft holds some difficulties such as generating a second surgery region, risk of having a tumor, increase in patient morbidity, and the possibility of being incapable of obtaining the desired amount of bone graft. These situations led researchers to seek an ideal bone graft material that can substitute autogenous bone grafts. MacEwen first implemented allograft in humans with the purpose of child humerus reconstruction in 1881[1]. Until quite recently, orthopedic surgeons possessed only autologous bones and allografts as bone resources. Today, several different options have been improved using tissue engineering applications. Bioactive glass grafts are the products of this technology. The recent research has served for increasing the osteo-conductive, osteo-inductive, and osteogenic features of bone grafts obtained via synthetic ways.

The aim of treatment in benign bone lesions is to provide an osteo-conductive effect rather than a biological effect. Therefore, autograft or bioceramic grafts can be used for these lesions. The current study seeks a solution to partial healing on spongious allografts and to shed light on the literature. There is no previous study on this issue in our knowledge.

Materials and Methods

In this study, patients, who applied to our hospital between the years 2007 and 2013 and who were given curettage-grafting for benign bone lesions in their long bones carrying lower extremity weight were examined retrospectively after the approval of the İzmir Tepecik Education and Research Hospital Research Ethics Committee (date: 24.11.2015, decision no: 22).

Inclusion criteria were that the tumor was located in the femur or tibia and was treated with curettage and grafting using a bioceramic glass bone graft or spongious allograft. The criteria of exclusion from the study have been determined as lesions located were not femur and tibia; malign bone tumor, non-ossifying fibroma (NOF), fibrous cortical defect (FCD), and osteoid osteoma cases, severe systematic diseases, nonattendance for follow-up.

During this period, 123 patients underwent curettage and grafting operations. Seventy-six (62%) patients were excluded because the tumor was outside the femur or tibia (n=63), two patients had malignant bone tumors, eight patients had NOF-FCD or osteoid osteoma, one patient had advanced systemic disease, and two patients had nonattendance for follow-up.

Forty-seven (38%) patients who did not meet the exclusion criteria were included in the study. There were 29 patients (62%) treated with spongious allograft in group 1, and 18 patients (38%) treated with bioceramic glass bone grafts in group 2.

Physical examination findings, surgery records, and radiological findings were evaluated.

X-rays of affected bones were taken preoperatively; and the second week, the first month, the third month, the sixth month, the first year, and following years postoperatively for a checkup, and their visual analogue scale (VAS)[2] and lower extremity functional scale (LEFS)[3] scores were calculated and evaluated.

Preoperative lesion volume and the amount of graft used in the operation were calculated in cm^3. The lesion volume was calculated in a computer environment on magnetic resonance images. Additionally, patients with fibrous dysplasia were evaluated as a subgroup.

The groups were evaluated among each other following the staging of the tumors[4].

All patients in the study received the same surgical technique, opening a cap on the bone, curettage of the mass, the application of chemical cauterization with 1% formaldehyde and 70% alcohol, respectively, each for five minutes, a lot

of irrigation with physiological saline solution and filling with bone graft materials. The operation was performed by a single surgeon.

Cefazolin was given to all patients on the day of the operation and the day after the operation in 3 equal doses of 50 mg/kg for 2 days with the purpose of prophylaxis.

The spongious bone graft used in this study has crushed and freeze-dried primer form (Tranzgraft by Aziyo Biologics) while bioceramic glass bone graft has granule and bioglass primer form. A bioceramic glass bone graft is composed of silicon dioxide (45%), calcium oxide (24.5%), disodium oxide (24.5%) and pyrophosphate (6%) (GlassBoneR by Noraker).

Statistical Analysis

Statistical Package for Social Sciences version 17 was used for statistical analysis. The normality of continuous data was evaluated with the Shapiro-Wilk test. If the distribution of data was evaluated as normal, a t-test was used for statistical comparison. In the case of non-normally distribution, the Mann-Whitney U test was used. Categorical data were compared with the Fisher exact test. A p-value <0.05 was set as statistically significant.

Results

The study included 47 patients, 19 (40%) of whom were males. The average age was found to be 23.08 (7-57) (Table 1). Twenty-three of the patients had lesions located on femurs and twenty-four located on tibias. No statistically significant differences were found between the graft materials used when considered in terms of age, gender, and location (p>0.05).

Radiological consolidation success is achieved by proportioning the volume of the consolidated region on average 16.36 months (6-48) after curettage and grafting was evaluated.

The average pain score (out of 10, according to VAS) at the end of the follow-up period in the spongious graft group was 1.07±0.96 (0-3) while it was 1.0±0.84 (0-3) in the bioceramic glass bone graft group (p=0.898).

The average lower extremity function score percentage (out of 100, according to LEFS) at the end of the follow-up period in the spongious graft group was 93.75±3.67% (86.25-100) whereas it was 94.51±3% (88.75-100) in the bioceramic glass bone graft group (p=0.581).

The preoperative volume of tumors of the 47 patients was 43.15 (7-150) cm^3 on average and the average amount of graft applied to all the patients was 58.21 (8-180) cm^3 (Table 2). The average tumor volume was 45.79 cm^3 and the average amount of graft used was 67.93 cm^3 in the spongious allograft group, whereas the average tumor volume was 38.89 cm^3 and the average amount of graft used was 42.55 cm^3 in the bioceramic glass bone graft group (Figure 1). The rate of average tumor volume and the average amount of grafts used were calculated as 62.14±17.38% (33-92) in the spongious allograft group while they were calculated as 89.11±7.07% (70-100) in the bioceramic glass bone graft group (p<0.001).

When we examine the consolidation ratio according to the graft material used, 15 (52%) of the patients who received spongious bone graft were greater than 90%; 7 (24%) were between 80 and 90; 7 (24%) were below 80% [2 (7%) were 50%>], and 15 (83%) of the patients who received bioceramic glass bone graft were above 90%, and 3 (17%) were between 80 and 90% (Figure 2). The average consolidation ratio at the end of the follow-up period was 82.58±15.55% (35-98) in the spongious graft group while it was 93.78±3.67% (87-99) in the bioceramic glass bone group (p=0.002).

The average consolidation ratio in fibrous dysplasia, which is a tumoral lesion with a benign aggressive course, was identified as 71.5±7.76% (62-81) in the spongious allograft group (n=4) whereas it was found to be 96.75±1.50% (95-98) in the bioceramic glass bone graft group (n=4) (p=0.029).

Ten of the tumors were interpreted as stage 1; 29 were stage 2, and eight were stage 3 according to Enneking benign tumor staging (Figure 3). In the spongious allograft group, the statistical results between stage 1 and stage 2 were non-significant (p=0.097); the statistical result was significant between stages 1 and 3 (p=0.032); the statistical result was non-significant between stages 2 and 3 (p=0.129). In the bioceramic glass bone graft group, the statistical result was significant between stages 1 and 2 (p=0.01); the statistical result was non-significant between stages 1 and 3 (p=0.167), the statistical result was significant between stages 2 and 3 (p=0.009) (Table 3).

Examples from several cases in the study are shown in Figures 4, 5.

The graphics of the patients with the lowest consolidation ratio identified in both groups are demonstrated in Figures 6, 7.

Table 1. Demografic characteristics and scoring

Case	Age	Sex	Pathology	Stage	Follow-up (month)	LEFS %	VAS
1	8	M	FD	2	24	95.0	0
2	7	F	FD	3	12	92.5	1
3	20	M	SBC	1	6	93.75	1
4	28	F	GSBT	2	6	88.75	3
5	51	F	PS	3	6	91.25	2
6	56	F	SBC	1	7	92.5	1
7	15	F	FD	1	11	95.0	1
8	20	F	KB	2	36	95.0	0
9	14	F	ABC	3	36	91.25	2
10	47	F	FD	2	6	95.0	1
11	9	M	ABC	1	36	98.75	0
12	28	F	SBC	2	6	93.75	1
13	18	F	SBC	1	12	97.5	0
14	26	M	SBC	1	11	93.75	1
15	16	F	ABC	2	12	97.5	0
16	9	F	FD	2	12	100.0	0
17	27	F	FD	2	16	88.75	3
18	17	F	SBC	1	6	95.0	1
19	24	F	ABC+GSBT	2	36	93.75	1
20	11	M	ABC	3	24	86.25	3
21	31	F	ABC	2	6	93.75	1
22	8	F	ABC	2	6	90.00	2
23	57	M	GSBT	2	6	91.25	2
24	11	F	SBC	2	24	96.25	1
25	16	M	ABC	2	12	97.5	0
26	11	M	ABC	2	12	96.25	1
27	45	M	H	2	12	93.75	1
28	14	M	FD	2	18	97.5	0
29	15	F	L	1	7	98.75	0
30	16	F	ABC	1	18	93.75	1
31	10	F	ABC	2	36	92.5	1
32	18	M	OB	2	12	96.25	0
33	9	M	FD	2	24	95.0	1
34	20	M	ABC+GSBT	2	18	90.0	2
35	30	F	L	2	48	96.25	1
36	46	F	HS	2	12	93.75	1
37	19	F	ABC	2	18	100.0	0

Table 1. Continued

Case	Age	Sex	Pathology	Stage	Follow-up (month)	LEFS %	VAS
38	16	M	SBC	3	48	88.75	2
39	15	M	EG	1	18	98.75	0
40	26	F	GSBT	3	6	86.25	3
41	52	M	EC	2	24	91.25	2
42	18	M	FD+ABC	3	6	91.25	1
43	26	F	EC	2	6	93.75	1
44	28	F	L	2	6	95.0	0
45	47	F	FA	2	9	91.25	2
46	13	M	ABC	2	24	98.75	0
47	17	M	OB	3	12	97.5	1

LEFS: Lower extremity functional scale, VAS: Visuel analogue scale, F: Female, M: Male

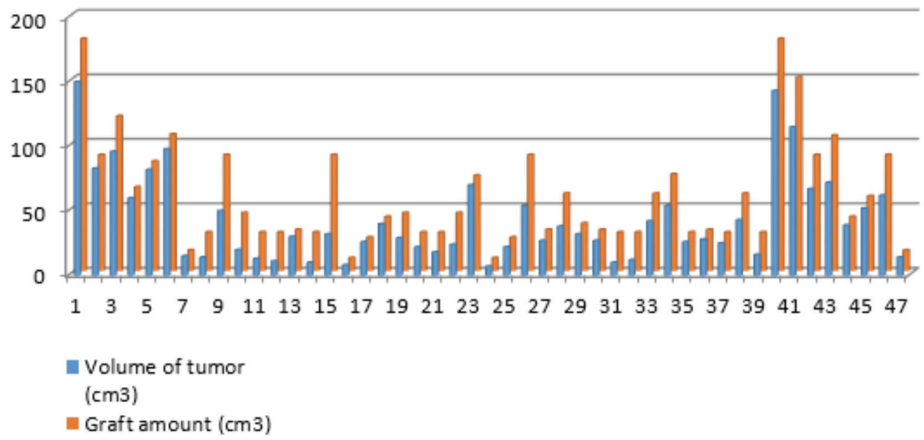

Figure 1. Volume of tumor and graft amount

Discussion

Bioceramic bone glass and spongious allografts are bone-filling materials that can be used in bone tumor. In this study, it was observed that consolidation rates were statistically significantly higher in the bioceramic bone graft group especially in the fibrous dysplasia group.

The ratio of the mean tumor volume and the amount of graft applied was higher in the bioceramic glass bone graft group compared to the other groups. This situation is thought to be developing out of the structural features of bioceramic glass bone graft.

In a randomized prospective study; Lindfors et al.[5] evaluated twenty-five patients in a total of two groups with benign bone lesions, in one that they used bioceramic glass bone graft and autograft after curettage. No difference in cavity volume was identified between the two groups after thirty-six months. In the following period, an increase in cortical thickness was observed to be higher in the bioceramic glass bone graft group compared to the autograft group. In our study, spongious allograft was implemented instead of autograft, and the consolidation ratio was found to be higher in bioceramic glass bone graft compared to the spongious allograft.

In their study, Sponer et al.[6] used bioceramic glass bone graft in a population of one hundred six patients with benign bone lesions, tibial plateau fractures, total hip replacement, and bone infections. The average length of follow-up was 3.2 years.

Table 2. Graft materials, volume and consolidation ratio

Case	Graft material: Sg: 1 Bg: 2	Volume of the tumor (cm^3)	Graft amount (cm^3)	Consolidation ratio (%)
1	1.0	150	180	81
2	2.0	83	90	98
3	1.0	96	120	92
4	1.0	60	65	95
5	2.0	82	85	99
6	2.0	98	106	96
7	2.0	15	16	98
8	1.0	14	30	82
9	1.0	50	90	35
10	1.0	20	45	72
11	1.0	13	30	92
12	1.0	11	30	93
13	2.0	30	32	98
14	1.0	10	30	94
15	1.0	32	90	93
16	2.0	8	10	95
17	2.0	26	26	96
18	2.0	40	42	94
19	1.0	29	45	88
20	1.0	22	30	72
21	1.0	18	30	92
22	1.0	24	45	66
23	2.0	70	74	87
24	2.0	7	10	92
25	2.0	22	26	88
26	1.0	54	90	82
27	2.0	27	32	91
28	1.0	38	60	71
29	2.0	32	37	93
30	2.0	27	32	95
31	1.0	10	30	97
32	1.0	12	30	96
33	1.0	42	60	62
34	1.0	54	75	83
35	1.0	26	30	74
36	2.0	28	32	92
37	1.0	25	30	98
38	1.0	43	60	44
39	1.0	16	30	97
40	1.0	143	180	92
41	1.0	115	150	91
42	1.0	67	90	88
43	1.0	72	105	82
44	2.0	39	42	92
45	2.0	52	58	88
46	1.0	62	90	91
47	2.0	14	16	96

Sg: Spongious allogreft, Bg: Bioceramic glass bone graft

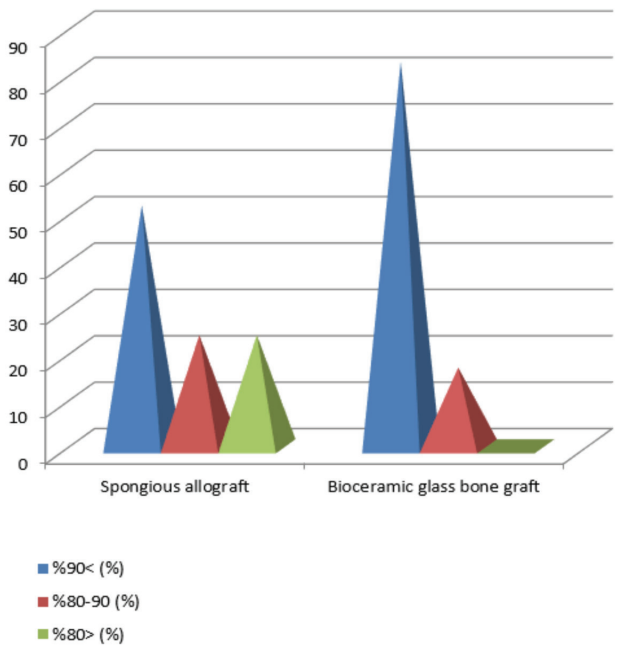

Figure 2. Consolidation range by graft materials

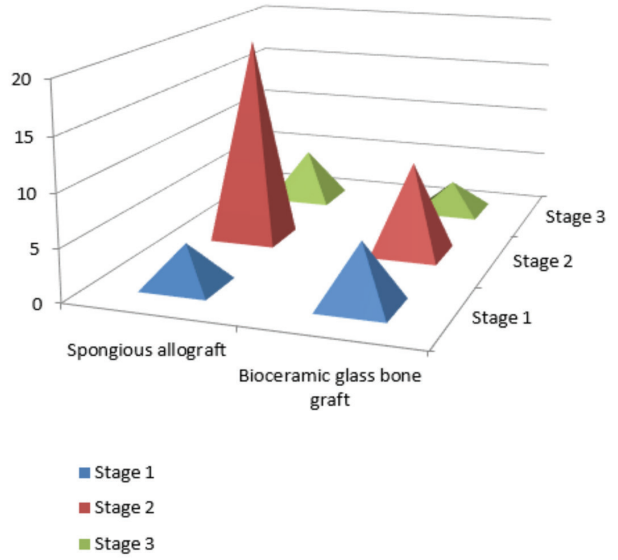

Figure 3. Enneking staging

Table 3. Comparison of consolidation rate

Stage	Consolidation rate	
	Spongious allograft	Bioceramic glass bone graft
1	93.75±2.36% (92-97)	95.67±2.06% (93-98)
2	84.45±10.78% (62-98)	91.22±3.11% (87-96)
3	66.2±25.69% (35-92)	97.67±1.53% (96-99)

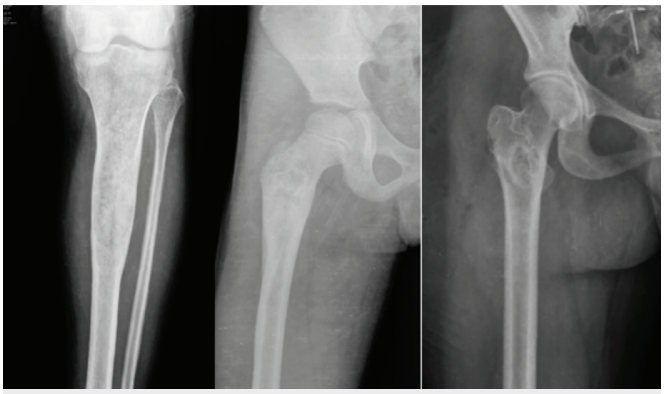

Figure 4. Spongious allograft samples

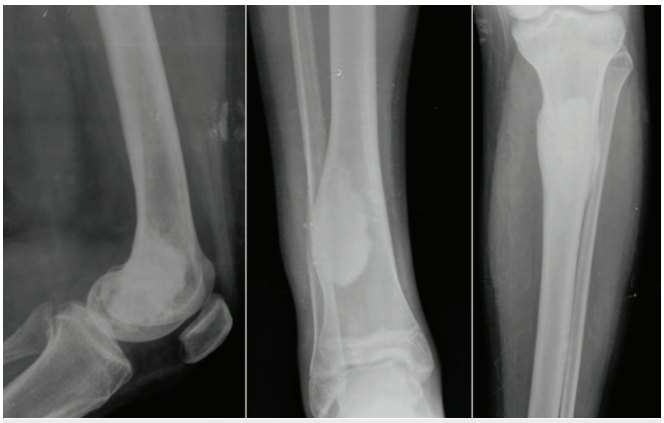

Figure 5. Bioceramic bone graft samples

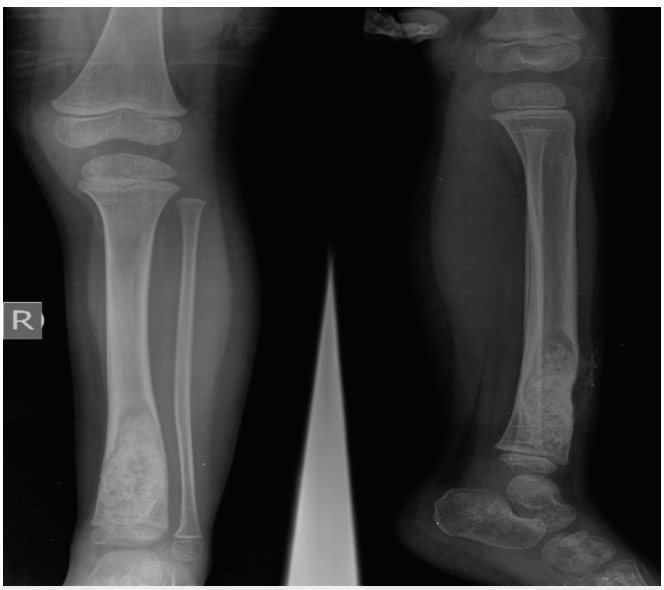

Figure 6. Patient sample with lowest consolidation rate of spongious allograft

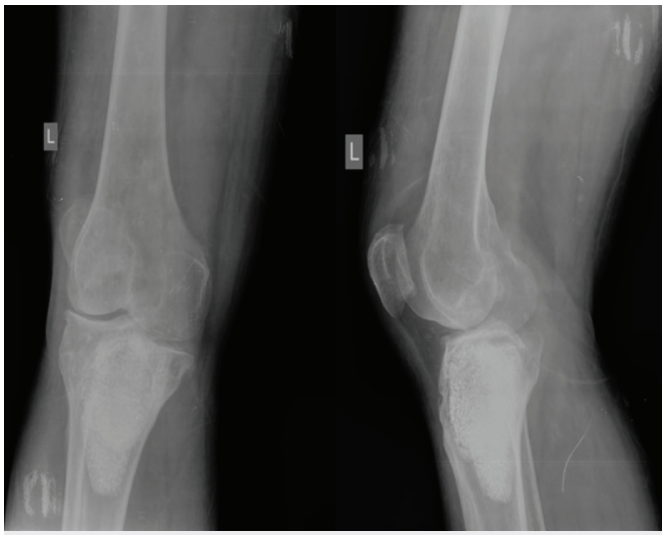

Figure 7. Patient sample with lowest

No a patient possessed radiological findings revealing a soft tissue reaction, periosteal reaction or irritation, or bone loss. Radiographs displayed that trabecula persisted on bioactive glass. In our study, as well, bioceramic glass bone graft was used only on benign bone lesions; and there was no radiological evidence of soft tissue reaction, periosteal reaction or irritation, or bone loss, which shows consistency with this study.

Sponer et al.[7] followed seventeen patients with long bone diaphyseal defects for 7 years and ascertained that bioceramic glass bone grafts are impractical in diaphyseal defects but they can be convenient bone filler materials in metaphyseal defects. In our study, 8 of the patients who were given bioceramic glass bone graft had mass located in the diaphyseal region and ten had the mass in the metaphyseal region. No significant difference was identified when the average consolidation ratios were statistically compared as diaphyseal and metaphyseal regions (p=0.972).

In one of their research, Sponer and Urban[8] concluded that bioceramic glass bone grafts can be recommended for especially metaphyseal defects instead of autograft and allografts that are frequently used on patients with the juvenile bone cyst. In our study, as well, results were fruitful on the patient group of bioceramic glass bone graft used on the juvenile age group.

Schepers et al.[9], in their study, evaluated the use of bioactive glass particles as fillers on bone lesions and compared them to two hydroxyapatite (HA) materials (calcitite and interpore 200). The osteoconductive effect was observed to be stronger in the cases of bioactive glass. When bioactive glasses are applied, they form a porous matrix that helps osteogenic cells develop by connecting to collagen, growth factors, and fibrin. They have absorbable and nonabsorbable types. They cannot be used with antibiotics or mixtures of bone-building increaser materials. They are more durable than HA implants[10,11].

It was demonstrated in Day et al.[12] research that bioactive glass-ceramics raise the secretion of angiogenic growth factors *in vitro* and escalate the formation of new vessels.

Lin et al.[13] detected in their study that bioactive glass is gradually biodegraded and absorbed by the living bone. An optic microscope used in histological examination revealed that osteocytes grow into bioactive glass. Microscopic examination was not performed in our study, but it was found to be clinically and radiologically compatible with this study.

Study Limitations

This study has some limitations. The most important limitation is its retrospective design. The other important limitation is that the number of included patients was quite low.

Conclusion

Bioceramic glass bone grafts are bone filler materials that possess radiologically superior and clinically similar findings compared to spongious allografts. The statistically significant radiological consolidation success of bioceramic glass bone grafts on FD, which is a benign aggressive tumor, causes the thought that they can be a good option toward the devastating effects of benign aggressive tumors. Bioceramic glass bone grafts are available to be used for adults and children. They can substitute spongious allografts and other modalities. Early results are promising. More comprehensive and long-term monitoring studies are required for more precise results.

Ethics

Ethics Committee Approval: The study were approved by the İzmir Tepecik Education and Research Hospital Research Ethics Committee (date: 24.11.2015, decision no: 22).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.İ., A.K., M.İ., Design: G.İ., A.K., M.İ., Data Collection or Processing: G.İ., A.K., M.İ., Analysis or Interpretation: G.İ., A.K., M.İ., Literature Search: G.İ., A.K., M.İ., Writing: G.İ., A.K., M.İ.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

A Large Osteoid Osteoma of Trapezium: A Regenerative Approach and a Review of Literature

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Osteoid osteoma is a benign bone tumor that usually grows in the long bones of the body and arises from osteoblasts and some components of osteoclasts. It represents the third most frequent type of benign bone tumors, accounting for 11% to 14% of the tumors. The entity usually involves the proximal femur and tibia. It has also been reported in the hand, especially the scaphoid, capitate, and proximal phalanx. The most common symptom is pain, usually during the night, relieved by the use of salicylates and nonsteroidal anti-inflammatory drugs. To date, only 5 cases involving the trapezium have been reported. This article describes a rare case of a large (1.3 cm) osteoid osteoma of the trapezium in a young male patient treated surgically with resection and curettage of the osteoid and provides a review of the existing literature.

Osteoid osteoma is the third most frequent type of all benign bone tumors, accounting for 11% to 14% of the tumors.[1,2] The most common loci are the femur and tibia.[3] Although the involvement of hand bones is more unusual, the most frequently involved bones are scaphoid and capitate.[4] The most common clinical presentation is pain, usually during the night, relieved by salicylates and nonsteroidal anti-inflammatory drugs (NSAIDs). The diagnosis is generally made with a computed tomography (CT) scan that detects the topical "nidus" surrounded by a sclerotic reaction. A definitive diagnosis is made with histological examination. The natural history reveals that osteoid osteomas should regress spontaneously within 6–15 years or by conservative treatment with NSAIDs for 30–40 months.[5–7] Conservative treatment must thus be considered for tumors where the osteoma is not easily accessible. The surgical management is the excision of the nidus that must be removed completely for the pain to resolve.[4,8,9] When the lesion is big, the excision can be followed by bone grafting or internal fixation.[10] Other described techniques are radiofrequency ablation, cryoablation, and laser thermocoagulation.[11,12] Among these techniques, CT-guided radiofrequency ablation is often the treatment of choice for osteoid osteoma.[13]

There have been several published cases of trapezium osteoid osteoma, and all of them were treated by excision and eventually cancellous bone graft. The first osteoid osteoma of the trapezium was described by Hundley[14] in 1976 in a 16-year-old boy with long-lasting wrist pain without a precise diagnosis. The patient was treated with surgical excision with instant pain relief after surgery. In this case report, we describe the case of a young male patient with a 1.3-cm osteoid osteoma treated surgically with resection of the osteoid nidus and curettage of the sclerotic rib and bone defect filled with bioactive glass. Bioactive glass is a bone substitute used clinically as a space filler or for regenerative purposes. The filler effect improves when granules are moistened with blood or saline implantation into the defect.[15] It has osteoconductive properties, does not increase the risk of infection and avoids the donor morbidity of graft harvest.[15–19] The investigation was performed in compliance with the Declaration of Helsinki and the guidelines for Good Clinical Practice. The patient provided written informed consent for both surgery and follow-up. The follow-up study protocol was approved by the internal ethics committee.

Declaration of interests: No benefits in any form have been received or will be received by the authors related directly or indirectly to the subject of this article.

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Table 1
Clinical Outcomes Before and After Surgery

Clinical Examination Test	Before Surgery	T30 After Surgery	T60 After Surgery
Pinch test score	5 kg	15 kg	20 kg
Kapanji score	5	9	9
Visual analog scale score	7	0	0

Table 2
Michigan Hand Outcomes Questionnaire Scores of the Patient

Brief Michigan Outcomes	Before Surgery	T30 After Surgery	T60 After Surgery
	Function (1 very good to 5 very poor)		
Overall, how well did your hand(s) work during the past week?	5	4	2
How was the sensation (feeling) in your hand(s) during the past week?	4	4	2
	Daily activities (1 not at all difficult to 5 very difficult)		
How difficult was it for you to hold a frying pan during the last week?	4	4	2
How difficult was it for you to button a shirt or blouse during the past week?	4	4	2
	Workly activities (1 always to 5 never)		
In the past 4 weeks, how often were you unable to do your work because of problems with your hand(s)/wrist(s)	3	3	5
In the past 4 weeks, how often did you take longer to do tasks in your work because of problems with your hand(s)/wrist(s)	3	3	5
	Pain (1 very mild to 5 very severe)		
How often did the pain in your hands/wrists interfere with your daily activities?	5	3	2
Describe the pain in your hand(s)/wrist(s) in the past week?	5	4	2
	Aesthetics (1 strongly agree to 5 strongly disagree)		
I am satisfied with the look of my hands	1	1	1
The appearance of my hands interferes with my normal daily activities	1	1	1
	Satisfaction (1 very satisfied to 5 very dissatisfied)		
In the past week, how satisfied were you with the motion of your fingers?	5	3	2
In the past week, how satisfied were you with the motion of your wrist?	5	4	2
Normalization	31.25%	37.5%	70.83%

Case Report

A 19-year-old man was referred to our hospital with a history of intense pain localized at the right thumb basal joint for 1 year. The pain was characterized as dull and persistent and was not relieved with NSAIDs. During the first visit, the patient demonstrated limited thumb opposition with a Kapanji score of 5, a weak pinch test with 5-kg strength (20 kg on the other hand), and difficulty in daily activities.[20] His visual analog scale (VAS) was 7, and the Michigan Hand Outcomes Questionnaire showed a value of 31.25%, with a high compromission of daily activities and pain (Table 1, 2).[21] X-rays were negative for pathology (Fig. 1). Magnetic resonance imaging (MRI) showed an intense signal corresponding to the trapezium and a diffuse edema of the surrounding tissue (Fig. 2). A subsequent CT scan (Fig. 3) showed the typical image of the osteoid osteoma, with the presence of the sclerotic nidus surrounded by a cortical reaction. At this point, the patient was counseled on surgery for enucleation of the tumor and grafting with bioglass.

For the surgical procedure, we accessed the tumor with an S incision made on the radial volar side of the first ray. We deroofed the trapezium, isolating the osteoid nidus and the sclerotic bone through a trail of holes made by K-wires (Fig. 4) and taking care not to interrupt the cortex of the trapezium. After enucleation of the nidus with the help of curettes, we filled the bone defect with bioglass mixed with fresh blood (Fig. 5). We reconstructed the capsule, closed the wound leaving a drain, and applied a short arm cast with the thumb included for 4 weeks. The lesion was sent for definitive histological examination, which gave us the diagnosis of osteoid osteoma (Fig. 6).

We followed up with the patient clinically and radiologically monthly for the first 3 months and at 1 year after surgery to rule out exclude recurrence. In the follow-up, we reported the VAS, pinch test, and Kapanji scores (Table 1). At the latest follow-up. the VAS, Pinch test, and Kapanji scores improved ($P < .05$). For the subjective evaluation of the functional and aesthetic outcomes, the authors administered the brief Michigan Hand Outcomes Questionnaire to the patient (Table 2). The brief Michigan Hand Outcomes Questionnaire global score showed slightly better, but not significant, results at 30 days after surgery (37.5%, $P = .633$), whereas it significantly showed improvement at 60 days after surgery (70.83%, $P = .01$).

Discussion

Osteoid osteoma is a benign osteoblastic lesion accompanied by severe pain relieved by salicylates and NSAIDs. It is frequent in individuals aged 10–20 years and in males.[3,5] The most common locations are the femur and tibia, followed by the small bones of

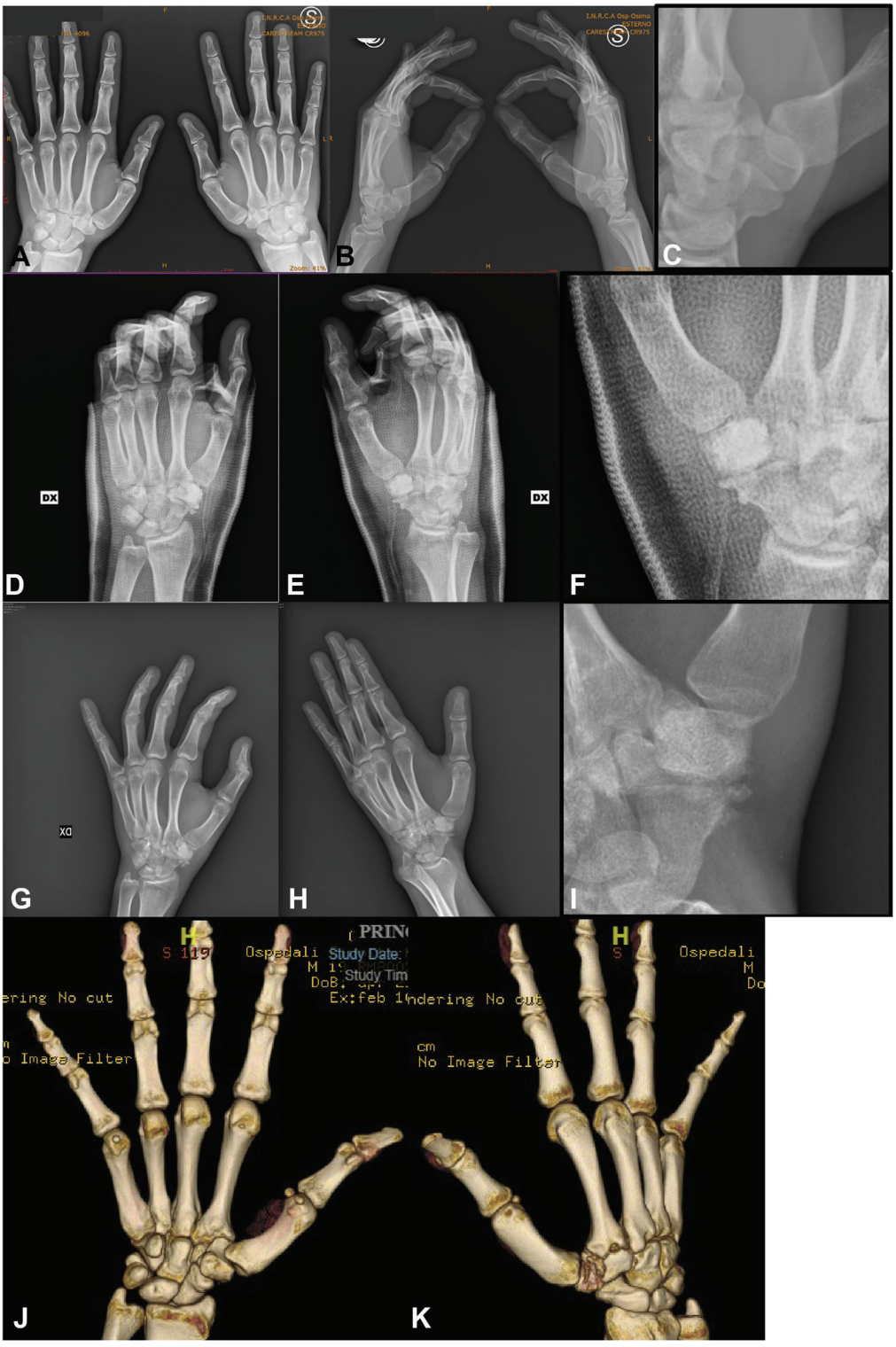

Figure 1. X-ray examinations from months before and after surgery and at 30 days of follow-up. **A**–**C** Radiographs before surgery. The trapezium is quite similar in both hands, both in the anteroposterior and lateral view. **A** Anteroposterior view showing the standard trapezium. **B** Okay sign view showing the normal trapezium. **C** Magnified view of the trapezium. **D**–**F** Radiographs taken in the operating room at the end of the procedure with the cast including metacarpophalangeal joint. A hyperintense image of the trapezium is observed, which is due to the active bioglass applied in the bone cavity. **D** Anteroposterior view showing the trapezium filled with bioglass. The trapezium appears hyperintense. **E** Oblique view showing the trapezium filled with bioglass. **F** Magnified view of the trapezium. **G**–**I** Thirty days after surgery. The trapezium density is similar to that of the normal bone, demonstrating how bioglass is going to integrate. Note that some parts of the active bioglass outside the trapezium will be absorbed in the following months. **G** Anteroposterior view showing the trapezium filled with bioglass. **H** Oblique view showing the trapezium filled with bioglass. **I** Magnified view of the trapezium. **J** One-year follow-up (front view). The appearance of the trapezius is similar to that of a normal trapezius in terms of density and joint relationships with the other carpals. **K** One-year follow-up (lateral view). The appearance of the trapezius is similar to that of a normal trapezius in terms of density and joint relationships with the other carpals.

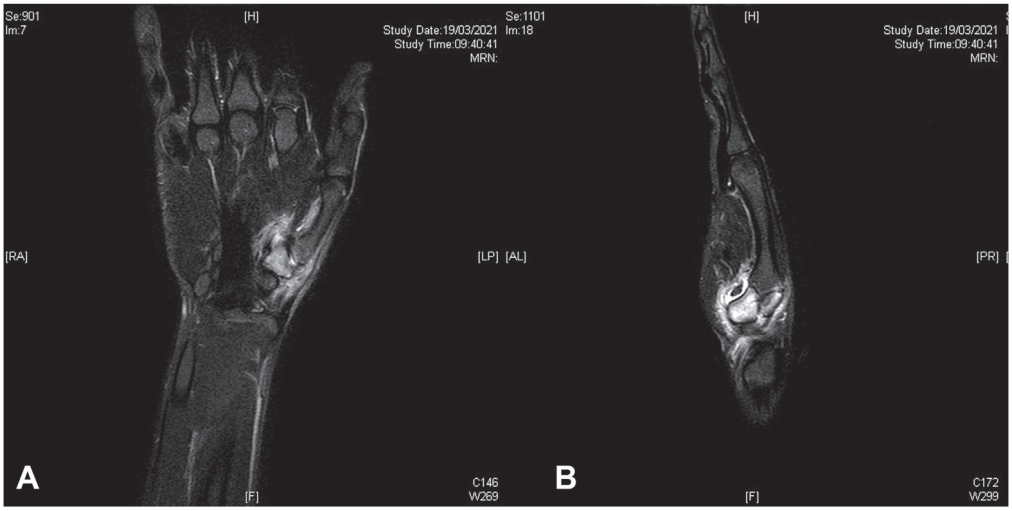

Figure 2. **A** Sagittal and **B** longitudinal views of the MRI examination performed before surgery. The bone aspect is better represented in the CT examination; in fact, the nidus, sclerotic area, and erosion are not visible. The bone edema and flogistic perilesional tissues are visible on the MRI scan.

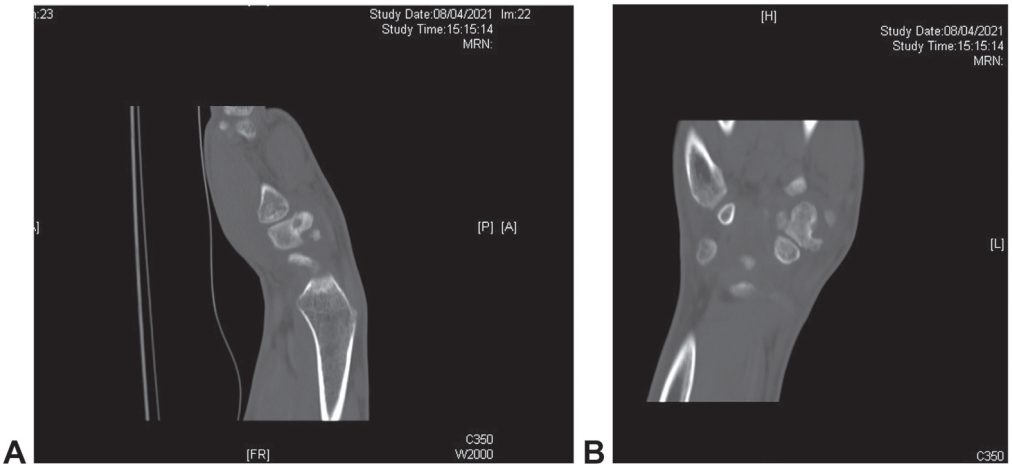

Figure 3. Computed tomography performed before surgery. The erosive aspect of the lesion in **A** longitudinal view and the nidus and sclerotic perilesional area in the **B** sagittal view are shown. The CT examination is the most accurate imaging examination for suspecting osteoid osteoma.

the hand, feet, and spine.[3] It can be found in the bone cortex, subcortical, intracortical, and intraperitoneal, and can rarely occur with more nidi in 1 or more bones.[3,22] The reason for remission after the use of NSAIDs is that nidus osteoblasts display a diffusion of cyclooxygenase-2, an enzyme important for prostaglandin production, in particular prostaglandin E2.[23] This enzyme is the main cause of pain and explains why the tumor is so responsive to cyclooxygenase-2 inhibitors (NSAIDs).[24] This lesion can be confused with osteoblastoma, a similar tumor of bigger size, usually more than 1.5 cm.[9,25] This tumor is characterized by irregular sclerosis, and the nidus is not well-defined.[26] It does not typically regress and does not respond to NSAIDs.[27] Another important condition that can be confused with osteoid osteoma is Brodie's abscess.[22] Plain radiographs are usually the first examinations performed and can show a small radiolucent area, corresponding to the nidus, surrounded by a sclerotic bone area. However, if the tumor is intramedullary, it may not show the surrounding bone sclerosis.[28] The diagnosis of osteoid osteoma is usually suspected when CT scans show the nidus. A highly specific and sensitive finding in diagnosis is the presence of fine, low density, linear, vascular channels surrounding the osteoid osteoma.[29] Furthermore, CT has better accuracy than plain radiography and MRI.[30,31] Magnetic resonance imaging is usually the first examination performed and can show a small radiolucent area, corresponding to the nidus, surrounded by a sclerotic bone area. However, if the tumor is intramedullary located, it may not show that surrounding bone sclerosis.[28] Although not as useful, an MRI examination can clearly show bone marrow edema and periarticular fluid. Care must be taken because the reactive soft tissue mass can be misinterpreted as a malignant tumor of the soft tissue or osteomyelitis.[32,33] Thus, MRI images should not be assessed without CT and x-ray image references.[34] Bone scintigraphy shows a vascular nidus in the arterial phase with a delayed phase within the surrounding reactive bones; the nidus is usually more intense, and the reactive bone is less intense; this is known as the "double density sign," and it is diagnostic of osteoid osteoma.[35,36] In 2010, Bostan et al[37] described a case of osteoid osteoma in a 25-year-old patient with a 12-month history of wrist pain, which occurred particularly at night. The patient was initially treated with orthoses and NSAIDs without success. At the clinical examination, swelling was observed over the dorsoradial aspect of the hand. CT examination showed the sclerotic nidus

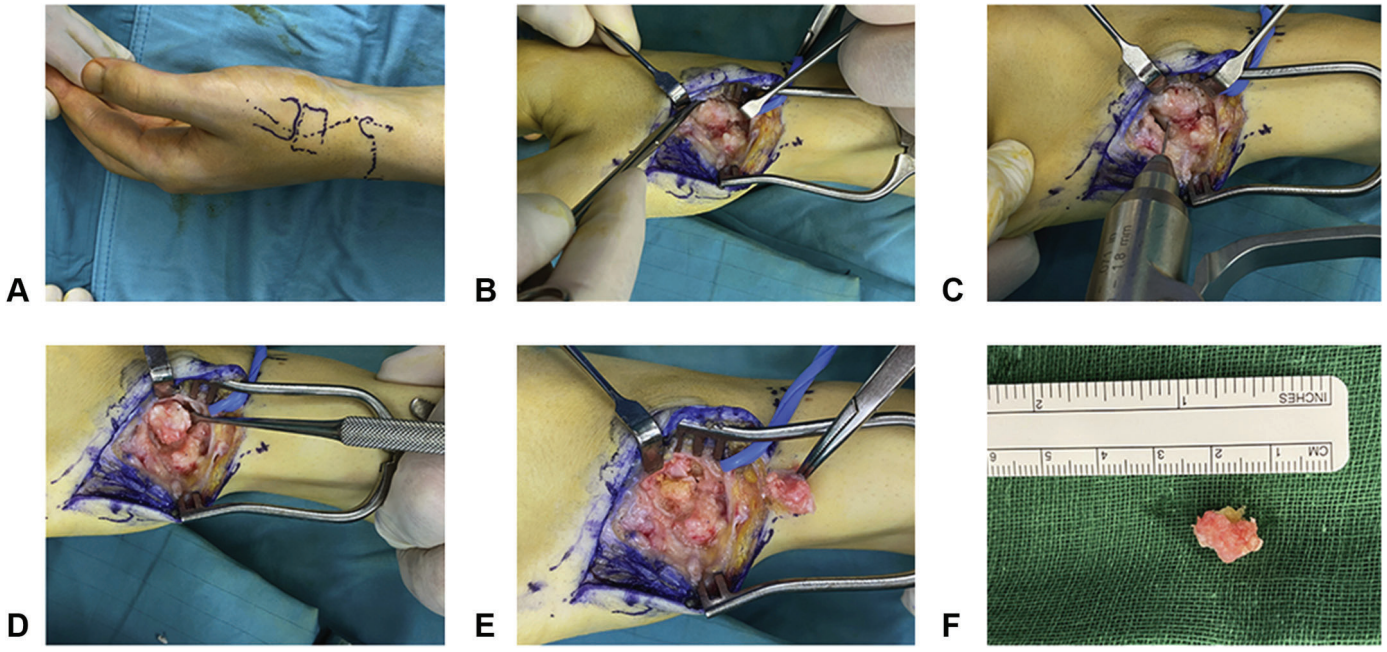

Figure 4. Demolitive part of the surgery. **A** Drawing of surgical access. **B** Exposure of the tumor. **C** Deroofing. A trail was made through several drills performed with 1-mm K-wires. **D** Isolation of the tumor. **E** Trapezium with bone loss. **F** Tumor size of 1.3 cm.

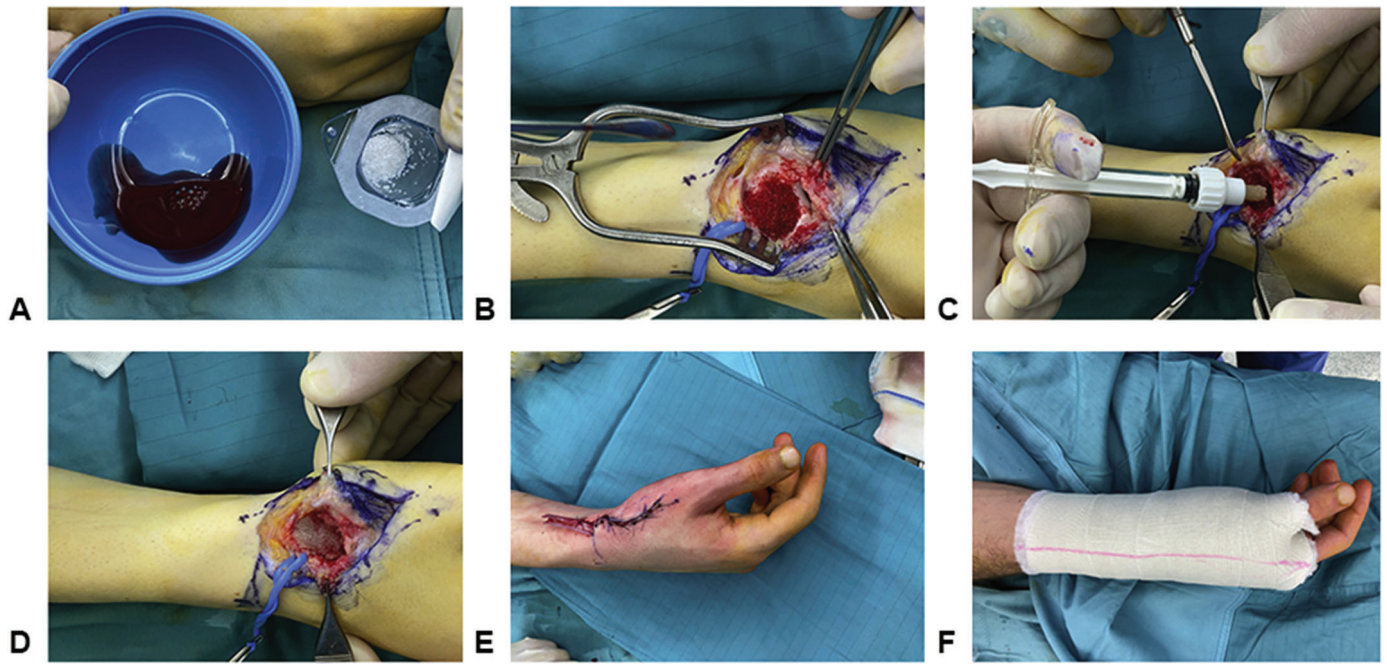

Figure 5. Reconstructive part made with bioactive glass. **A** Bioglass granules are mixed with fresh blood cells. **B** Filler of bone loss with bioglass granules. **C** Coverage of the granules with glass bone putty (45S5 bioglass plus a binder made with polyethylene glycol and glycerol). **D** Complete application of bioglass. **E** Hand after surgery sutured with a drainage in situ. **F** Short arm cast including the thumb.

surrounded by a radiolucent osteoid tissue, and MRI examination showed bone marrow edema associated with a focal lesion of the trapezium hypointense. The patient was treated with excisional biopsy, and after surgery, the patient had immediate pain improvement, and no recurrence was observed in follow-up.[37] In 2017, Park et al[38] described an osteoid osteoma tumor in a 29-year-old patient initially treated for calcification periarthritis with several steroid injections until follow-up, debridement with no effect, until an ulnar deviated x-ray examination showed a sclerotic bone lesion, suspicious for osteoid osteoma and treated with curettage. The patient experienced immediate improvement in clinical pain and no recurrence at a 1-year follow-up. In 2017, Roberts et al[39] described a case of a 34-year-old woman with osteoid osteoma initially confused with carpometacarpal arthritis. In this case, an MRI scan showed a hypointense circular lesion along the dorsal aspect of the trapezium, and a CT study was

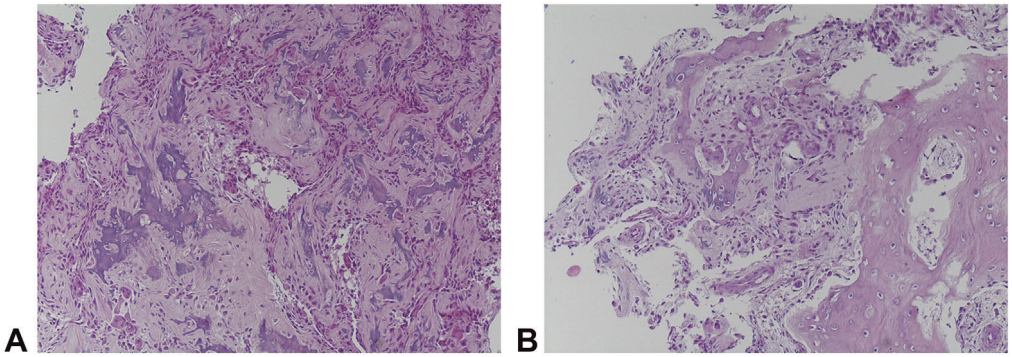

Figure 6. The nidus as the well-defined area made of irregular bone trabeculae of different mineralization **A**, usually surrounded by the osteoblast cells **B**, is shown.

conducted to better characterize the lesion. The lesion was treated with curettage, and the diagnosis was confirmed by histopathology. After excision, the patient experienced complete pain relief and did not have any recurrence.[39] In this study, because of the unusually large tumor size of 1.3 cm, we filled the bone loss with bioactive glass to avoid donor morbidity in such a young patient. There are many kinds of bioactive glasses, and we elected to use GlassBONE (Noraker) in 2 different formulations, "granules" to fill the bone defect and "putty," a formulation with glycol polyethylene and glycerol, which grants ligand property useful for roofing the filled area.[40] Bioglass is a bone substitute, first used in hand surgery by Hench et al[41] in 1967; it is a bioactive material that can bond to the bone because of a specific chemical reaction. A bioactive material does not cause minimal rejection, is recognized as a biological material, and bonds with the tissue for mechanical interference. It is composed of silicon dioxide, calcium oxide, sodium oxide, and phosphoric anhydride; the equilibrium among these components makes the bioglass active. The gold standard of bioactive glass is the 45S5 (comprising 45% of silicon dioxide, 24.5% of sodium oxide, 24.5% of calcium oxide, and 6% of phosphorus pentoxide).[42] When the bioactive glass is in contact with biological fluids, several chemical reactions cause silicon hydrolysis, creating a silica gel layer similar to the bone hydroxyapatite (carbonated hydroxyapatite). The carbonated hydroxyapatite layer absorbs growth factors; these factors attract the M2 macrophages that promote lesion healing and attract staminal mesenchymal cells, which become the osteoblasts.[43] This process starts generating and depositing proteins of the extracellular bone matrix (collagen I).[40,44] To conclude, bioactive glass causes osteoblasts and osteocytes to spread along the glass surface; this means that the material is mainly osteoconductive.[45,46] In this study, after the tumor excision, the bone loss had to be filled, and we chose a bioglass to avoid donor site morbidity.

Conclusion

Analyzing the reports in the literature, we can conclude that osteoid osteoma should be suspected when a patient presents with long-lasting wrist pain with unclear diagnosis, associated with radial side tenderness surrounding the thumb, night pain responsive to NSAIDs, and negative x-rays. The approach has to start with a clinical examination, including the Kapandji test, which shows a reduction of thumb opposition compared with the contralateral hand. Although x-rays can be negative, a CT scan can provide us with the most accurate image of a nidus, whereas an MRI image can show bone edema and surrounding tissue inflammation and exclude other pathologies. A definitive diagnosis is made by histological examination. In our opinion, the best treatment is the curettage of the osteoid osteoma, avoiding trapeziectomy if the carpometacarpal joint is not involved. If the lesion is larger in size, bone grafting, bone substitutes, or bioglass can be useful. The patient typically shows pain relief after surgery and should be followed monthly for 3 months after surgery, and at 6 months to a year with a CT scan to rule out recurrence, then new clinical and radiological control after 3 months and a final control made with CT examination after other 6 months to exclude recurrence.

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Three-dimensional printed titanium pseudo-prosthesis for the treatment of a tumoral bone defect

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Langerhans cell histiocytosis (LCH) is a proliferative disease of histiocytic cells with a granulomatous appearance that generally affects children. The etiology of LCH is still unknown. However, it has been associated with exposure to certain solvents, smoking, and a family history of cancer, thyroid disease, or LCH.[1] Its estimated annual prevalence is of 1 case per 560,000 adults.[27] Three forms of presentation have been described: located in the skeleton as solitary or multiple eosinophilic granuloma, chronic disseminated disease such as Hand-Schueller-Christian disease, and acute subacute diffuse disease such as Letterer-Siwe disease.[8]

In the adult population, LCH frequently presents as a lytic bone lesion.[13,27] It may appear in short bones, ribs, pelvis, vertebral bodies, clavicle, and scapula. It may also develop in the diaphysis of long bones. However, the location of LCH in the hands and feet is very uncommon, and its presence in the clavicle is extremely rare.[27]

The diagnosis can be confirmed with a core needle biopsy. An extension study should be made to detect any systemic diseases or dissemination. Various therapeutic options have been used in the management of LCH depending on the severity of the disease. These options have ranged from observation to chemotherapy, surgery, radiotherapy, photodynamic therapy, immunotherapy, and stem cell transplant.[1,16]

The use of low doses of radiotherapy has been found to achieve good results.[10] A combination of vinblastine and steroids has also been used for the treatment of LCH; however, no standard chemotherapy has been established for the management of LCH in adults.[25] Nevertheless, a surgical resection with clean margins is usually the recommended treatment.

On the other hand, the use of three-dimensional (3D) printing represents a technological advance that is progressively becoming more popular in orthopedic surgery and traumatology. This technique is increasingly being used in surgical planning and in the reproduction of predesigned templates that serve as osteotomy guides in joint replacement procedures.[6,15,17,20,24]

In this study, we present a novel application for 3D printing in orthopedic surgery, using a 3D printed porous titanium graft for the treatment of a bone defect after an extensive resection of the middle third of the clavicle in a patient with LCH.

Case report

The patient was a previously healthy 37-year-old man who worked as a maintenance laborer, with no known drug allergies, and smoker of 20 cigarettes per day. He previously attended the emergency department of another hospital presenting with a 3-week history of shoulder pain. An x-ray of the clavicle was performed in which a small lytic lesion appears on the middle third of the clavicle (Fig. 1, *A*). However, this lesion was not initially detected, and the patient was treated with oral analgesics and discharged. Two months later, the patient presented in our center with a 3-month history of left clavicular pain and swelling without previous trauma. Clinical examination revealed a tender mass located on the left supraclavicular fossa associated with local edema. The patient was febrile, and the active and passive mobilization of his left shoulder was painful. However, the neurovascular examination of the left upper extremity was

Institutional review board approval was not required.

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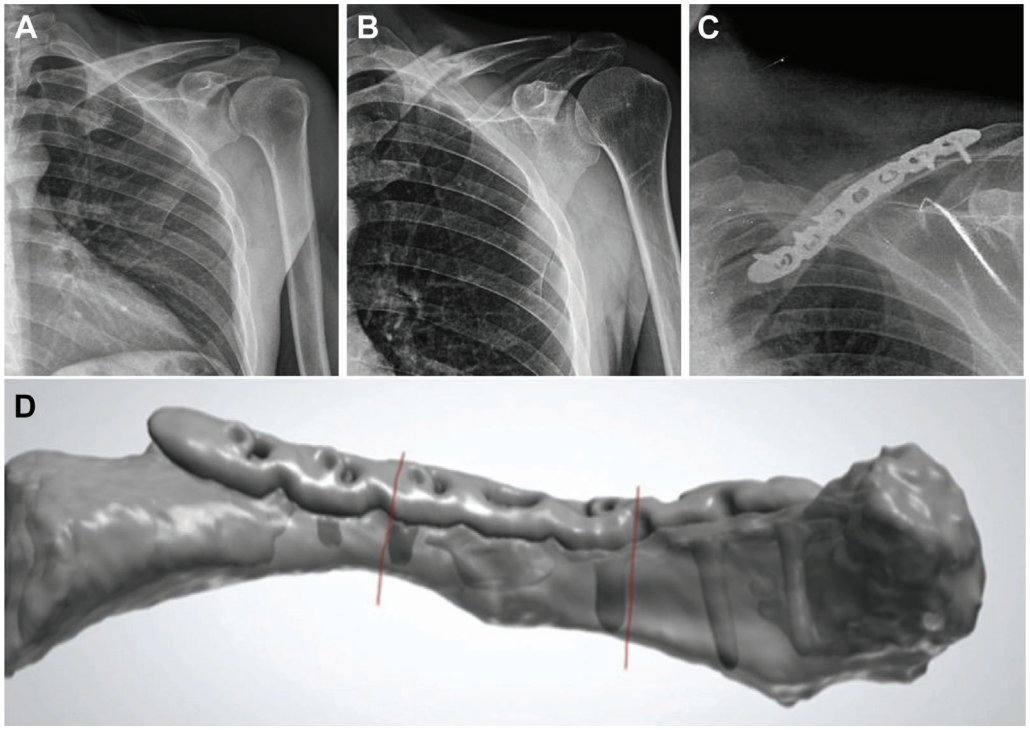

Figure 1 (**A**) A well-defined lytic lesion involving the middle third of the left clavicle. (**B**) This lesion evolved into a pathological fracture. (**C**) Postoperative radiological control after initial intralesional resection, curettage, and osteosynthesis. (**D**) A 3D reconstruction of the clavicle which included the previously synthesized fracture and the tumoral lesion; the red lines mark the planned resection margins. *3D,* three-dimensional.

normal. This patient provided consent for publication of this case report.

Plain x-rays revealed an evolved and displaced pathological fracture involving the middle third of the left clavicle associated with a well-defined 2.5-cm lytic lesion. The tumor appeared to spare bone cortices (Fig. 1, *B*). The blood tests showed a mild white cell count increase ($23 \times 10\hat{}9$ / L), an unaltered c-reactive protein, and negative tumor markers.

Given the pathological nature of the fracture and the smoking history of the patient, our initial differential diagnosis was of metastasis vs. bone cyst. Accordingly, a chest x-ray was performed showing no evidence of any pulmonary disease.

The patient was then subjected to an intralesional resection and curettage, and samples were collected for pathological analysis. The bone defect was then filled with synthetic and bioactive bone graft substitute (GlassBONE, Noraker, France), and the fracture synthesized with an anatomical clavicular plate (DePuy Synthes, Raynham, MA, USA). Postoperative x-rays showed a satisfactory reduction of the fracture (Fig. 1, *C*). The pathological analysis confirmed the diagnosis of LCH (ie, eosinophilic granuloma subtype). Then, a positron emission tomography–computer tomography was performed to detect any other possible lesions. The positron emission tomography–computer tomography revealed the presence of pathological trace uptake in the middle third of the left clavicle (SUV max 4.15). No other metabolic abnormalities were detected.

The case was then presented in our institutional musculoskeletal tumor committee to determine the best therapeutic strategy. Several options were considered including observation, wide resection with oncological margins followed by reosteosynthesis using an autologous bone graft, radiotherapy, and wide resection followed by a clavicular reconstruction using a 3D printed porous titanium graft "pseudo-prosthesis". After taking in consideration the patient's age and the tumor's location and after discussing the available options with the patient, we decided to proceed with the clavicular reconstruction using a 3D printed "pseudo-prosthesis".

Description of the surgical technique

Implant design

We contacted the 3D design company 4DiMedical (Ortoplus, Malaga, Spain). A fine-cut computer tomography scan was then performed to make a detailed 3D reconstruction of the clavicle which included the previously synthesized bone and the 2.5-cm tumoral lesion (Fig. 1, *D*). Then, a customized cutting template was printed to perform the clavicular osteotomy with clean 14-mm proximal and distal oncological margins. The cutting template was adapted to a 1.3-mm saw blade and included holes for its fixation with 1.8-mm Kirschner wires (Fig. 2, *A* and *B*).

We then printed a 3D porous titanium pseudo-prosthesis resembling the size and shape of the resected area. Its trabecular titanium structure was designed to facilitate bone growth through the implant (Fig. 2, *C* and *D*). This pseudo-prosthesis also included a medial and lateral intramedullary fin to provide additional rotational stability.

Surgical intervention

The patient was subjected to a brachial plexus block of the left upper extremity. The patient was then positioned in a "chair bed" position. A longitudinal incision was made over the previous scar. A progressive dissection was made to expose the previously used anatomical clavicular plate (DePuy Synthes, Raynham, MA, USA). The plate was then extracted, and the clavicle was exposed. A 3D printed biocompatible resin (MED610) radio-opaque cutting guide

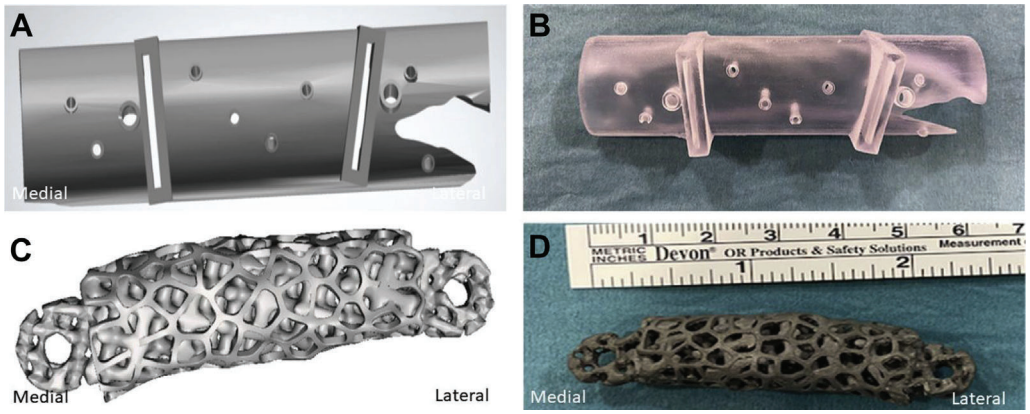

Figure 2 (**A** and **B**) The customized cutting template was designed and printed to perform the clavicular osteotomy with clean 14-mm proximal and distal oncological margins. (**C** and **D**) A 3D porous titanium pseudo-prosthesis with the size and shape of the resected area was designed and printed. It included a medial and lateral intramedullary fin to provide additional rotational stability. *3D,* three-dimensional.

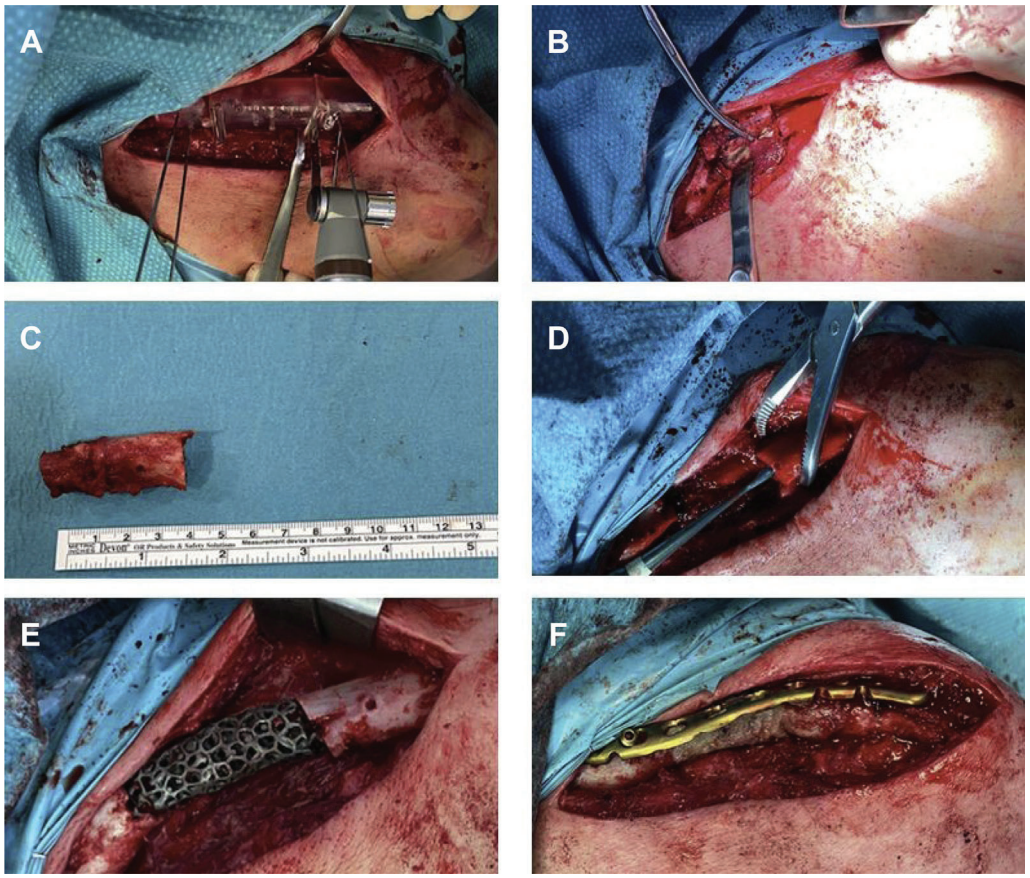

Figure 3 (**A**) The cutting template was fixed on the clavicle with four 1.8-mm Krischner-wires. (**B** and **C**) The selected bone segment was removed and measured. (**D**) The intramedullary canal was drilled proximally and distally using a 2-mm burr. (**E**) The titanium implant was placed in the bone defect. (**F**) The clavicle was fixed using an anatomic clavicular plate; the implant's trabeculas were filled with a bioactive bone graft substitute.

was positioned on the clavicle and fixed with four 1.8-mm Kirshner wires. A 62-mm long osteotomy was performed, achieving a complete excision of the tumor with oncological margins (Fig. 3, *A–C*). Then, the intramedullary canal was drilled proximally and distally using a 2-mm burr. The titanium implant (Ti6AL4V) was positioned following the "press-fit" method. Once the implant was stabilized, the clavicle was fixed using an anatomical clavicular plate (DePuy Synthes, Raynham, MA, USA) and locking screws. The implant's trabeculas were filled with bioactive bone graft substitute (GlassBONE, Noraker, France) (Fig. 3, *D–F*). Finally, the wound was washed with normal saline, and the wound was closed with 2-0 and 3-0 Vicryl.

Evolution

The final histopathology report confirmed the diagnosis of LCH with disease-free margins. The operated extremity was immobilized in a sling until the removal of the sutures 2 weeks after

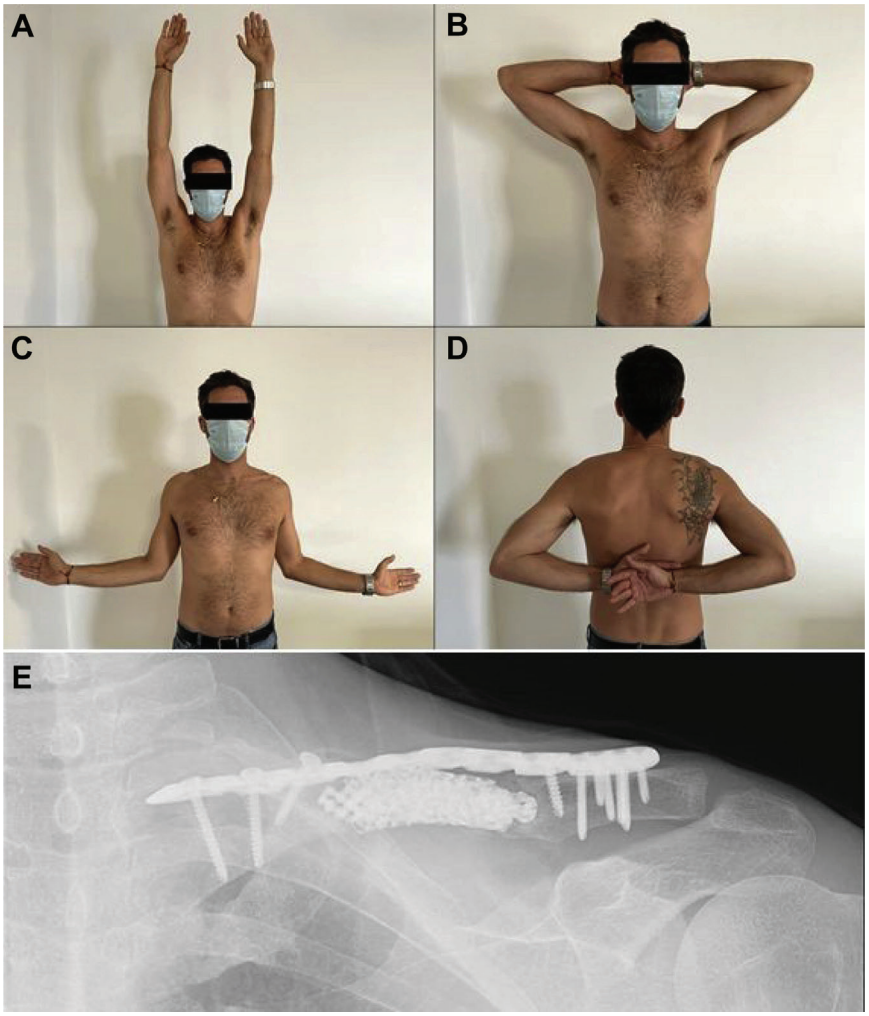

Figure 4 (**A-D**) Two years after surgery, the patient had a complete range of motion of the left shoulder. (**E**) The follow-up x-ray 2 years after surgery.

surgery. Then, pendular exercises of the shoulder and passive physiotherapy were initiated. The operated extremity was kept non–weight-bearing, and efforts were avoided. No postoperative complications were observed, and the evolution of the wound was satisfactory.

At 3 months after surgery, the patient presented with a complete range of motion and no pain on palpation or mobilization. The patient was authorized to initiate progressive loading of the operated extremity and to resume his regular physical activities. On his last follow-up appointment, 2 years after surgery, the patient led a normal life without any type of functional limitation; he had a Constant score of 100 and a disabilities of the arm, shoulder, and hand score of 2.5 (Fig. 4, *A–D*). His follow-up x-ray was also satisfactory (Fig. 4, *E*).

Discussion

Langerhans histiocytosis is a rare disease in adults.[13] It is difficult to determine its incidence in this age group because most of the published reports have been focused on the pediatric population. In children, LCH has been found to be more common in males (male-female ratio of 2:1). However, in the adult population, this ratio may vary depending on the series. According to the Rizzoli Institute,[18] the diagnosis of LHC progressively decreases with age (ie, 55% of the cases with LHC occur between 0 and 9 years, 30% between 10 and 19 years, 8% between 20 and 29 years, and 5% between 30 and 39 years). The treatment of LHC depends on the extent of the disease and may range from curettage and corticosteroid injection, polymethyl methacrylate filler, to local radiotherapy and systemic chemotherapy in certain cases.

The clavicle is a rare site of LHC.[26] Most of LHC reports in the literature involving this bone were treated by curettage of the lesion, steroids, and plate fixation. However, relapses often require adjuvant radiotherapy.[10,27] Some authors have postulated that a combination of surgery with localized radiotherapy would be the best therapeutic if the presence of residual disease is confirmed.[3,4]

In our case, the presence of residual disease would have been an indication for local radiotherapy. However, we believed that the eradication of the tumor was possible without exposing the patient to radiation if the lesion was completely resected. Therefore, we decided to perform a second excision with oncological margins and a subsequent reconstruction of the clavicle with the intercalary titanium pseudo-prosthesis. The location of the lesion required a resection that could have compromised the anatomical function of the left upper limb.[2] However, the titanium pseudo-prosthesis provided adequate mechanical stability and continuity and preserved the functionality of the clavicle.

The use of the titanium pseudo-prosthesis avoided exposure to radiotherapy in our relatively young patient. In a previous study, Kriz et al determined that the possible indications for radiotherapy in LHC would be in case of unresectable lesions, if the resection compromised the anatomical function, recurrent or progressive lesions, adjuvant treatment followed by incomplete or marginal resection, as well as pain or symptoms that compromise the quality of life.[10] However, radiotherapy can induce secondary leukemias, malignant meningiomas, osteosarcomas, and breast, lung, and thyroid malignancies over time.[5,14,21,23] This risk may persist up to 25 years after exposure. In head and neck tumors, the rates of radiation-related tumors have been reported to be of 15% within 5 years. This prevalence is even higher in patients with breast cancer reaching up to 50%, mainly involving the contralateral breast.[5] Moreover, radiation is also associated with numerous side effects such as sore skin, fatigue, hair loss, nausea, vomiting, esophagitis, mucositis, diarrhea, urinary and bladder changes, and headaches.[19] In our opinion, the negative effects of radiation are not unremarkable, and its use should be individualized in each case and reserved for situations in which no other viable options are viable. Nevertheless, in our study, radiotherapy would have been considered if the tumor recurred after the second surgical procedure.

The treatment of bone defects faces significant challenges to preserve the functionality of the affected extremity. In this case, the inadequate management of the bone defect could have hindered the mobility and strength of the operated extremity and altered its cosmetic appearance.[12] Several methods have been traditionally used for the reconstruction of bone defects in orthopedic surgery. These include leaving the bone defect and the use of bone allografts and vascularized bone grafts. However, the risk of bacterial infection has been estimated to be of 11.7% for large allografts and 0.7% for small grafts.[28] The use of bone allografts could also result in nonunion rates in approximately 21% of the cases.[22] Moreover, vascularized bone allografts are technically demanding and are associated with a significant morbidity on the donor site.[7,9,11] Thus, the use of 3D printing in orthopedic surgery and traumatology could become an additional surgical option in the management of complex fracture reconstructions. Moreover, this technique could provide accurate bone cutting guides in oncological surgery that could help perform precise osteotomies with disease-free margins based on preoperative imaging. It could also help produce customized osteosynthesis plates and print replicates of the operated bone.[17] In addition, it could be used to replace bone segments with implants of an equal size, shape, and volume. This could be particularly easier to achieve in cases affecting small bones, exposed to lower mechanical demands. In this case, the implant successfully replaced the bone defect of the clavicle, preserving its continuity and original length. Consequently, the strength and functionality of the affected extremity were preserved. Moreover, the empty spaces within the trabecular structure of the implant could facilitate the formation of woven bone. These spaces may be also filled with bone substitutes to enhance the osteogenesis process.

Finally, the use of 3D printing to reproduce intercalary segments for the replacement of bone defects is a promising field that needs further development. This new technique could provide an additional therapeutic tool that could minimize the morbidity associated with other conventional treatments.

Conclusion

The use of a 3D printed pseudo-prosthesis achieved an excellent clinical and functional outcome in the treatment of a large bone defect, after a resection of an LCH of the clavicle. 3D printed pseudo-prostheses could be useful instruments for the treatment of bone defects after large bone resections in musculoskeletal tumors.

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Comparison of the Results of Glassbone and Tricalcium Phosphate Graft Used in Bone Tumors

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ABSTRACT

INTRODUCTION: Bone defects caused tumors sometimes may not heal with bone tissue. In such cases, bone defects may need to be filled with bone graft materials to facilitate or start healing. The purpose of our study is to compare results of glass graft (GG) (GlassBone NORAKER) and tricalcium phosphate (TCP) grafts that we use in benign bone cysts clinically and radiologically.

METHODS: 41 patients with benign bone tumors (mostly simple bone cysts (SBC) and aneurysmal bone cysts (ABC) had been treated between either glass graft or tricalcium phosphate graft between 2013-2015. Patients were divided into two groups as those treated with GG and TCP grafts. Graft consolidation evaluated radiologically with x-rays monthly.

RESULTS: There were 20 men and 21 women (51.2%) with a mean age of 22.0 years (range 14-32 years). In patients using GG, compared to patients using TCP, radiological consolidation was observed faster between 14.-16. months (p = 0.0001).

DISCUSSION AND CONCLUSION: We conclude that in the treatment of benign bone tumors GlassBone can be used as an alternative to tricalcium phosphate grafts. We also noticed that patients treated with GlassBone showed a faster rate of fusion radiologically.

Keywords: bioactive glass, tricalcium phosphate, bone tumor

INTRODUCTION

Bone defects caused by trauma or pathological events are major clinical and socioeconomic problems. [1] Bone grafts are one of the surgical procedures used in bone regeneration in orthopedic surgery. [2] More than 2 million bone grafting procedures are performed worldwide each year, which is the most common tissue transplantation procedure after blood transfusion. [3]

During the last 40 years, regenerative medicine researchers have focused on producing materials that resemble bone properties and are not resorbable.[4] Autologous bone grafts are used as the gold standard for bone defects. It is preferred because it has a high osteogenic capacity, does not cause immunological reactions, and does not cause virus infections such as HIV and HBV. However, autografts have complications such as graft failure and morbidity (chronic pain, wound problems, blood loss, etc.). Complications such as infectious diseases and immunological rejection are also present in allografts. [5-7] These complications in allografts and autografts highlight biomaterials as grafts.

There are many different types of bone grafts available on the market, and orthopedists can choose from a variety of grafts, including ceramics, bioactive glasses, demineralized bone matrix, allograft, and bone morphogenetic proteins.

Bioceramics have been used as classical bone grafts for the last 40 years. [8] GG (Glass Graft) and TCP (Tricalcium Phosphate) grafts are ceramic-based grafts commonly used in bioengineering. In addition, GGs are grafts with osteoconductive and antibacterial properties. [9,10]

In this study, we aimed to retrospectively analyze the clinical and radiological results of GG and TCP grafts used in the treatment of common benign bone tumors.

MATERIAL AND METHOD

In this study, patients who were treated with GG or TCP grafts between January 2013 and December 2015 and diagnosed with SBC, ABC or other benign bone tumors in histopathological examination were analyzed retrospectively. The Helsinki Declaration Principles were followed in the study. 41 of 47 patients were included in the study, 6 patients were excluded because of a follow-up period of less than one year. All patients' history, clinical

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examination findings and radiological examinations such as direct radiography and MRI were examined. 21 of the patients were female and 20 were male. The patients were divided into 2 groups as those who were grafted with GG or TCP graft after curettage and cauterization. GG was used in 22 patients (53.6%) and TCP was used in 19 patients (Table 1). The size of the tumor was measured by X-ray or MRI. The patients were operated in Ankara Atatürk Training and Research Hospital. Curettage materials taken during the surgery were sent for histopathological examination to confirm the diagnosis in these patients, who were confident that they were clinically and radiologically benign before the operation. Histo-pathologically, it was classified as aneurysmal bone cysts (ABC) (12 patients), simple bone cyst (SBC) (10 patients), and other benign bone tumor (19 patients). In the operation, an oval lid was removed from the cortex with the help of a drill and osteotome. After the tumor was carefully removed with a curette, curettage, burr and cautery were applied to the cavity wall. The cavity was filled with GG or TCP grafts. The filled cavity was closed with a piece of cortex that was opened to reach the tumor. The mean hospital stay was 1.5 days (range 1 to 3 days). Tumor types classified by histopathological examination and location are shown in Table 1. On the 15th day after discharge, the patients were called to the outpatient clinic to have their sutures removed and then for monthly check-ups and evaluated clinically and radiologically.

Statistical Analysis

The conformity of the continuous numerical variables in the study to the normal distribution was examined using the ShapiroWilks test. For the representation of numeric variables, median (interquartile range), mean ± standard deviation, and minimum; maximum descriptive statistics were used. Number (n) and percentage (%) were given in the representation of categorical variables.

Fisherexact test and Yates chi-square tests were used to examine the difference of categorical variables in the study groups, and Mann Whitney U test was used to compare numerical variable values.

The relationship between numerical variables was examined with the Spearmanrocorrelation coefficient. In the case of a significant relationship, if the correlation coefficient is between 0.00 - 0.19, "no relationship or negligible low relationship", "weak (low) relationship" between 0.20 - 0.39, "moderate relationship" between 0.40 - 0.69, 0.70 - 0.89 It was interpreted as "strong (high) relationship" in the range of 0.90 - 1.0 and "very strong relationship" in the range of 0.90 - 1.0.

IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MSExcel 2007 programs were used for statistical analysis and graphics. Statistical significance level was accepted as $p<0.05$.

RESULTS

In this study, there were 41 patients, 20 male and 21 female (51.2%), with a mean age of 22.0 (14-32 years). The mean follow-up period of the patients was 44 months (range 12 to 86 months).

The mean tumor volume measured by X-ray and MRI was 20.7 cm3 (SD 17.7) in GG patients and 19.5 cm3 (SD 20.2) in TCP grafts.

3 patients were operated for the second time due to growing residual cysts and 1 patient due to infection. Of these patients, 2 were treated with GG and 2 with TCP graft. TCP graft was used in the infected patient. The same grafts were used in the second surgeries.

The union was evaluated clinically by pain relief and radiologically by X-ray. Radiological union was seen in all patients, including patients who were reoperated at 3 months. Compared to the patients who used TCP, in the patients who used GG, 14th-16th days. It was observed that radiological consolidation was faster between months (p= 0.0001).

At the end of the 16th month, there was no statistically significant cavity in the X-Ray of the patients who used GG compared to preoperatively. (p:0.01) There was a significant difference between

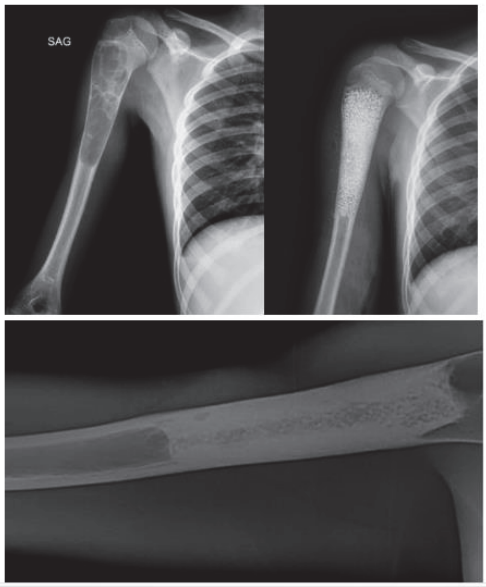

Figure 1: *ABC located proximal to the right humerus in a 14-year-old male patient a) direct radiograph of a lobulated septal cystic lesion extending from the proximal humerus to the diaphysis b) post-operative radiograph after curettage + allograft (glass graft) c) postoperative 10th month radiograph; graft fusion is seen.*

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the patients who used GG and TCP grafts so far. (p:0.01) However, there was no difference between these two groups after 36 months. (p:0.78)

***Table 1**: Demographic Data of Patients*

Data	Total N= 41
Gender, n (%)	
Male	20 (48,8)
Female	21 (51,2)
Age, year	
Mean	22.0
Median (min-max)	24 (14.0-32.0)
Direction, n (%)	
Left	22 (53.6)
Right	19 (46.4)
Graft used, n (%)	
Glass graft, SBC	6 (14.6)
TCP graft, SBC	4 (9.7)
Glass graft, ABC	6 (14.6)
TCP graft, ABC	6 (14.6)
TCP Benign Bone Tumor	9 (21.9)
Glass Graft Benign Bone Tumor	10 (24.3)
Tracking Time, months	
Average	54.0
Median (min-max)	57 (12.0-126.0)

SBC: Simple bone cyst, ABC: Aneurysmal bone cyst
TCP: Tricalcium phosphate

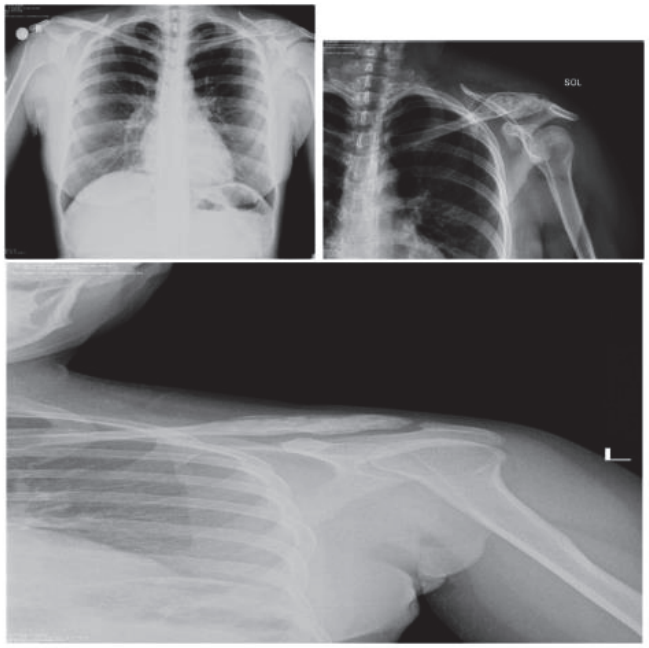

***Figure 2:** ABC located in the left clavicle in a 40-year-old female patient. A) direct radiograph of a septal cystic lesion extending to the diaphysis in the distal clavicle on direct X-ray b) Post-operative direct X-ray after curettage + allograft (tricalcium phosphate) c) Post-operative 4th month X-ray*

DISCUSSION

When the data of our country are examined, simple bone cyst is the third most common benign bone tumor (14%) after osteochondroma and enchondroma, and aneurysmal bone cyst (9%) is one of the most common benign bone tumors [11].

Benign bone tumors are usually treated by curettage and filling of the defect. Bone cement, synthetic bone graft, allograft bone and autograft bone are currently used for defects. Bone cement does not preserve bone stock. In addition, hardened cement does not have the same biomechanical properties as bone [12]. Allografts have risks of infectious disease, deep infection and nonunion. [13] Autologous bone grafts are used as the gold standard for bone defects. It is preferred because it has a high osteogenic capacity, does not cause immunological reactions, and does not cause virus infections such as HIV and HBV. However, autografts have complications such as graft failure and morbidity (such as chronic pain, wound problems, blood loss). Because of these complications, synthetic grafts are preferred.

The risk of infectious disease is eliminated with the use of synthetic grafts, and the use of synthetic grafts does not cause donor site morbidity. Other advantages are that they can be obtained in unlimited quantities and provide sufficient mechanical support to allow early functional rehabilitation. It is also known that synthetic grafts are biocompatible and used for the reconstruction of large bone defects. [14] Ideal bone graft is expected to show osteoconductive and osteoinductive properties, as in autologous bone graft. Also, synthetic grafts are readily available without the risk of viral or bacterial contamination. These grafts should be easy to apply, cost effective and should not be immunogenic. [15]

In addition to their osteoconductive properties, GGs have more osteostimulative properties than TCP grafts.[16] GGs also have antibacterial properties that activate angiogenesis. [17]

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Our aim in this study was to compare the consolidation time of the graft to the bone radiologically in patients in whom we used TCP graft and GG in the defect of benign bone tumors.

Ewaniev et al. retrospectively reviewed 24 patients with benign bone tumors that they operated between 2007 and 2012. Bone defects formed after intralesional curettage were reconstructed with “Pro-Dense (Calcium Sulfate–Calcium Phosphate Synthetic Bone Graft Composite)”. They found that complete radiological resorption and new bone formation with Pro-Dense were typically seen at 5 months postoperatively [18]. Saikia et al, they studied 24 patients who had been reconstructed with a TCP graft or HA (hydroxyapatite). HA was used in 20 of 24 patients and beta TCP was used in 4 patients, and the mean time to union was found to be 9 months (6-18 months) [19].

Linfors et al, they compared the results of 25 patients who used GG and autograft for benign bone tumors. They observed that union started at 12 months in patients who used GG, and there was a significant difference according to the preoperative situation at 24 months. In patients who used autograft, it was observed that there was consolidation in 12 months and there was no bone space. [20]

When the studies in our country are examined, Çelebi et al, in their study comparing cancellous graft and synthetic graft, they achieved an average union time of 149 days for synthetic grafts and 103 days for cancellous grafts. And this difference was statistically significant [7]. In our country, the results of graft use have been reported in many studies [21].

In our study, the consolidation time of the graft was statistically faster in patients who used GG up to 36 months. However, we observed that there was no clinical or radiological difference after 36 months. We think that graft consolidation is earlier because GG activates angiogenesis.

This study had some limitations. The study was a retrospective analysis, and the number of patients was relatively small. However, prospective randomized studies with long-term follow-up are needed to better understand these grafts.

CONCLUSION

As a result, glass grafts can be used as an alternative to tricalcium phosphate grafts in the treatment of benign bone tumors. In addition, radiologically faster fusion is seen in patients treated with glass grafts.

There is no conflict of interest between the authors.

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Chronic Tibial Osteomyelitis; Use of Biactive Glass as an Alternative of Treatment. Report of a Case

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Background:
Chronic osteomyelitis is a disease usually of infectious origin. The main cause is post-traumatic, it affects the bone tissue and surrounding tissue, the most frequent causative agent is Staphylococcus aureus. The most affected bone is the tibia. **Case description:** A 42-year-old male with a diagnosis of chronic tibia osteomyelitis, with sequelae of previous surgical interventions, multiple antibiotic treatments, and type IV B classification by Cierny-Mader. **Methods:** Two-stage surgical management was chosen. Firstly, extensive bone and soft tissue debridement, placement of cement beads medicated with amikacin in the medullary cavity and osteoclast system for irrigation with vancomycin. In the second stage, free fibular bone grafting, fixation and stabilization with screws, bioactive glass placement in areas of interface between stabilized fibula and posterior tibial cortex. **Results:** Before a multitratada chronic osteomyelitis it is necessary to individualize and evaluate treatment alternatives, in this case the surgical management in two time, the use of medication beads, bone graft and the use of bioactive glass, achieved a complete eradication of the infection and favorable clinical evolution with optimal functional recovery of affected limb.

Key words: Chronic osteomyelitis, Tibia, Bioactive glass.

I. Introduction

Osteomyelitis is defined as an inflammation of the bone caused by an infectious agent.[1] The main cause of chronic osteomyelitis is Staphylococcus aureus.[2,3] Lee and Waldvogel classify osteomyelitis as acute, subacute and chronic, hematogenous or contiguous, and with or without vascular deficiency.[4] The Cierny-Mader classification includes pathological and impermeable approaches.[5]
The incidence of osteomyelitis is variable. Hilal et al indicate 21.8 cases per 100,000 person-years.6 It affects men in a greater percentage, mean age is 52 years, the most frequently affected bone is the tibia, the most common cause was post-traumatic.[5,6,7,8]

The diagnosis of osteomyelitis is based on the clinical history, physical examination, result of laboratory and imaging studies.[8,9] Surgical treatment should include radical debridement, removal of dead tissue, soft tissue reconstruction, and restoration of bone stability.[10] Current surgical treatment of chronic osteomyelitis is commonly with surgical implantation of polymethylmethacrylate (PMMA), mixed with antibiotics, in the affected anatomical area, after extensive debridement and pulse lavage. These PMMA beads are removed in a

second surgical procedure.[11,12,13,16] The gold standard for bone defect restoration is still considered autologous bone grafting.

But it is not free of complications.[15] Bone graft substitutes are commonly used to replace and regenerate bone loss due to trauma, infection, disease, or to provide stability around implanted devices.[14,15.] In this context, bone graft biomaterials current generation are an alternative treatment and are designed to stimulate specific cellular responses at the cellular and molecular level.[17,21] Characteristics of biomaterials: Bioactivity any interaction or effect that the materials have on cells. Biocompatibility, absence of cytotoxic, genotoxic effects or immune response. Osteoconductive and osteoinductive involves exchanges of ions with biological fluids that allow the formation of a mineral layer, a direct biological coupling between the biomaterial and the bone.[13,14,20]The release of biomaterials will stimulate the incorporation and proliferation of stem cells, resulting in the differentiation and proliferation of osteoblasts.[15] The release of ions such as sodium, calcium, and silicon increase the local pH and osmotic pressure, guaranteeing antibacterial properties.[14, 15] There are various bioactive glass compositions on the market. In this case, Glass Bone (BG) 45S5 was used. It is a biomaterial with properties that meets the aforementioned characteristics.[18,19,21,22]

II. Clinical Case

42-year-old male patient, peasant occupation. He went to the traumatology and orthopedics outpatient service for presenting fetid secretion and ulcer at the pretibial level of the left leg. Anamnesis: current illness begins at the age of 22 years in an acute and insidious way with increased volume and pain in the metaphyseal region of the left tibia, he was subjected to surgical toilets on three occasions and the application of multiple antibiotics for prolonged periods without improvement. Physical examination: presence of fistulas in the proximal metaphyseal region 1 cm in diameter, both with communication to the spinal canal and with active, purulent and fetid exudate. Paraclinical Hb 13mg/dl, HTC 30%, Cr 2.3mg/dl, Urea 40mg/dl, culture of E. coli wound exudate sensitive to moxifloxacin and amikacin, anteroposterior and lateral X-ray of the left leg showing anterior cortical condensation from proximal metaphyseal region to the distal third of the tibial diaphysis with the presence of a lytic zone of approximately 3 cm in the proximal metaphyseal region. After these findings, it was classified as chronic tibial osteomyelitis type IV B according to the host with added systemic disease chronic renal failure (CRF). Definitive surgical treatment in 2 stages was chosen.(fig. 1)

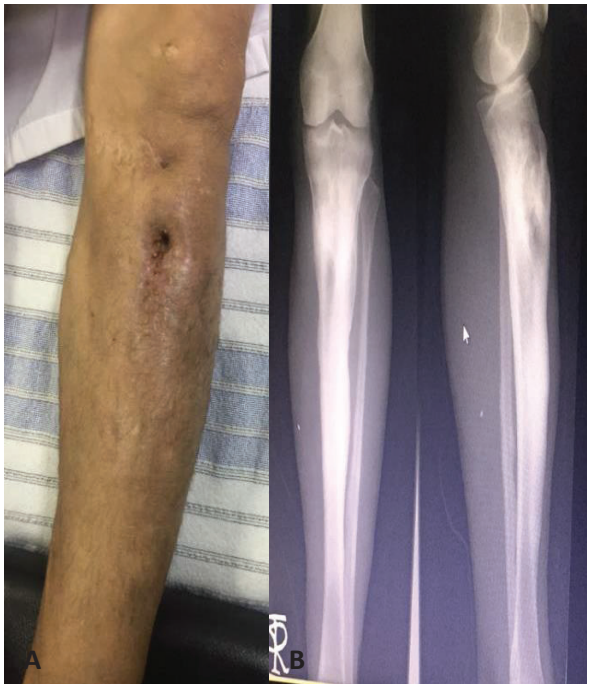

Fig 1.A:Fistulas in the proximal metaphyseal region. B: AP and lateral radiography of the left tibia, lytic area in the tibial metaphyseal region and anterior bone condensation up to the distal diphyseal region.

In the first stage, an anterior linear hemidiaphysectomy is performed up to the proximal region at the metaphyseal level with resection of sequestered bone tissue up to the region of the anterior tibial tuberosis, medullary evacuation of said anatomical region, obtaining abundant fetid yellowish secretion, scarification of the medullary canal until tissue is obtained. bleeding bone, amikacin-medicated cement beads were placed in the medullary cavity and intramedullary osteoclysis system for irrigation with 100ml physiological solution plus 1g of vancomycin every 24 hours for 10 days.[23](fig.2)

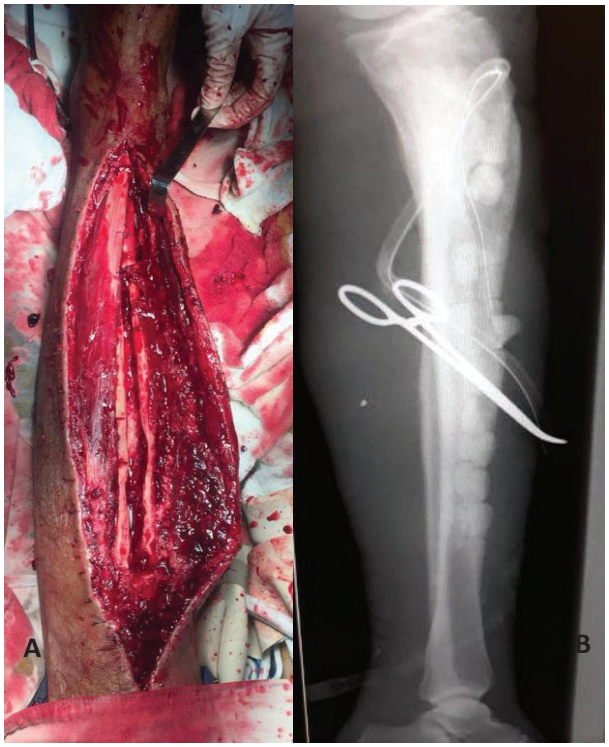

Fig 2. A: Anterior cortical resection. B: Osteoclysis system and PMMA medicated with amikacin.

In the second surgical stage, the non-vascularized free fibula is taken, the fibula is obtained with the desired length and it is presented in the exposed medullary canal, fixation and stabilization is carried out with 4.5 titanium screws with the placement of 4 of a standard 30mm measurement. Subsequently, the bioactive glass is placed in interface areas between the stabilized fibula and the posterior cortical bone of the tibia along its entire length, as well as the total filling of the medullary cavity in the metaphyseal region (16 grams of 1mm bioactive glass were used), the surgical wound is closed, and remains hospitalized, amikacin 250mg every 12 hours and Moxifloxacin 400mg every 24 hours are applied. He was discharged from the hospital 5 days after the second surgical intervention with a wound in the healing phase, fistulas closed without expense, antibiotic moxifloxacin 400mg po every 24 hours, for 6 months, and monthly liver function test controls. One month later, the patient presented clean healed surgical wounds, closed fistulas, no signs of infection, full range of motion, muscle hypotrophy, radiographic control with graft in the integration phase, no signs of instability of the osteosynthesis material, PFH in normal parameters, continued with moxifloxacin 400mg every 24 hours and rehabilitation exercises. Last assessment 3 months later, the patient was already walking without support and laboratory tests within normal parameters. (fig3)

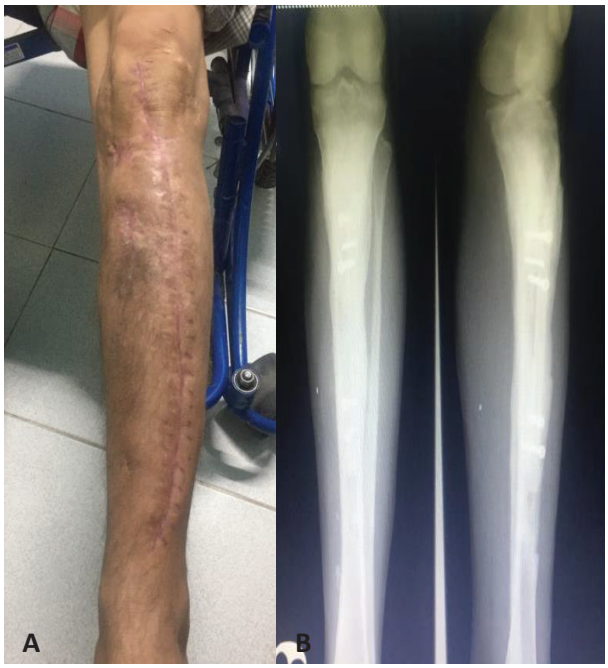

Fig 3. A: Closure of fistulas and surgical wound without evidence of exudates. B: Bone osseointegration of the fibula in the tibia.

III. Conclusion

Chronic osteomyelitis is a complicated infection to treat, most cases management involves a multidisciplinary approach, the primary care provider plays a key role in the initial diagnosis and coordination with other specialists. Surgical treatment is the essential part of treatment, complementation with adequate antibiotic treatment significantly improves the success rate. The treatment must be individualized and assess the available management alternatives, assessing the cost benefit. Treatment strategies depend on several factors: characteristics of the host, the segment involved, the size of the lesion, the location of the lesion, and the substitute or support material to be used. Several studies have shown that management with bone graft material alone is associated with different cure rates ranging between 60 and 90%, however, there are problems with the use of bone autografts such as insufficient amount of graft, post-surgical morbidity in donor area, infections and hemorrhage mainly. The concept of polytherapy gains strength in the orthopedic field and consists of simultaneously implanting two or three fundamental components for healing. Combination therapy is a logical option, especially in elderly individuals with associated comorbidities and a limited capacity for tissue regeneration. For these reasons mentioned before a chronic osteomyelitis of the tibia that did not evolve correctly after previous surgical treatments and before a patient with added systemic disease, a two-stage surgical treatment was decided. The polytherapy concept is also taken into account. An extensive surgical debridement was performed, PMMA impregnated with amikacin was applied, an osteoclysis system with vancomycin irrigation in the second stage, an autologous fibular graft was performed and bioactive glass was applied, with which a complete eradication of infection and recovery of limb function. In the 12-month follow-up, the patient shows no signs of infection with recovery of 90% of the function of the affected limb.

IV. Conflict of interests.

The authors of this article have no conflicts of interest.

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Case Report

Saving the lower limb with GlassBONE™ - Successful surgical revision of pseudarthrosis after infected open proximal tibia fracture type IIIC with bioactive glass grafting - A case report

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Bone nonunion
Tibia fracture

ABSTRACT

Background: The management of bone defect due to trauma or surgical debridement is a current problem in orthopedic trauma surgery, often complicated by infection and bone nonunion. The graft is one of the most challenging variables in surgical treatment. Bioactive Glass (BAG) as a biocompatible and osteogenic product is a promising bone substitute showing good results in maxillo-facial-, spine surgery and treatment of osteomyelitis. Surprisingly, there is very little data on BAG use in trauma surgery.
Case presentation: A 51-year-old male patient, involved in a motorcycle accident, suffered an open proximal tibia fracture, type IIIC, of the left leg. Patient was admitted in January of 2013 to a general orthopedic department for surgical treatment. After several surgical revisions due to infection, vascular damage, and bone nonunion, the patient was successfully treated with Masquelet therapy followed by GlassBONE™ grafting (GlassBONE™ 45S5; Norarker). The patient demonstrated excellent results over the course of a two-year follow-up.
Conclusions: In our experience, GlassBONE™ 45S5 has proven to be an effective bone substitute even in difficult grafting conditions, including multiple surgical revisions for bone nonunion and infection. In our case, at the end of 2 years and 3 months of follow-up, the patient reported no pain, and had no signs of infection. Bone union and full weight bearing was achieved.
This case report is oriented by the CARE guidelines for clinical case reports; the patient gave consent for publication.

Background

Bone fractures account for the most widespread trauma in humans [1]. The management of bone defect and bone loss due to fracture or surgical debridement is a current problem in orthopedic trauma surgery. Bone loss usually requires grafting and implantation of stabilizing material, elevating the risk of infection and subsequently the risk of bone nonunion [2]. Bone nonunion leads to diminution of quality of life and even disability posing a vast impact on health systems and economies. A recent review of Schlund et al. found that 10–15% of patients experienced impaired fracture healing or even bone nonunion after bone injury [3]. In open fractures, the risk of nonunion is reported to be more than 30% [4]. In a study on 104 tibial shaft fractures, Karladani showed a relative risk of

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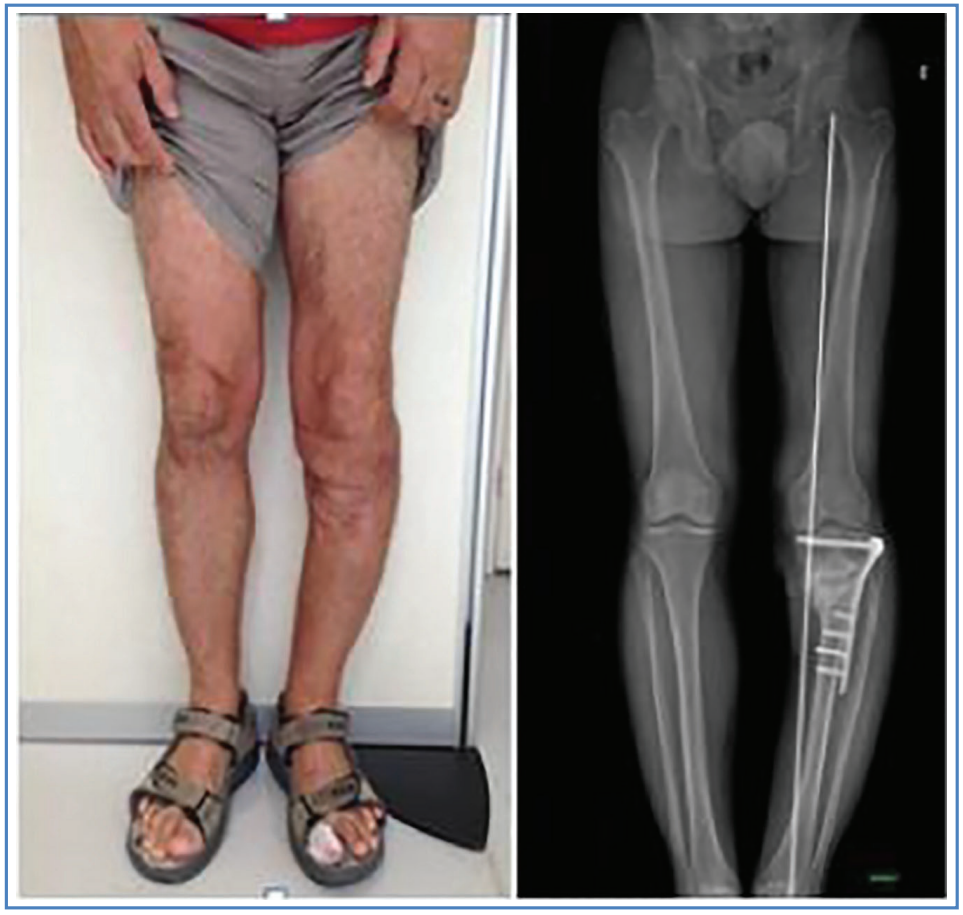

Fig. 1. Clinical aspect and anterior-posterior view (ap view) of leg axis showing varus deformity before Masquelet therapy.

8.2% of open fractures to develop nonunion [5].

The surgical management of bone defect has been addressed in a variety of ways, including bone-transfer, free soft-tissue flaps or antibiotic loaded polymethylmethacrylate (PMMA) [6,7]. Autologous bone grafting is limited by the amount of graft material accessible for harvest and large bone defects may not be able to be sufficiently filled. For example, some patients who have already undergone harvesting from both iliac crests and/or harvesting via reamer-irrigator- aspirator (RIA), may not be candidates for bone grafting due to anatomical reasons. In addition, autologous bone grafting requires a second surgical intervention, posing postoperative risks including infection, pain and serious cosmetic anomalies [8,9]. The main disadvantages of PMMA application include its multiple resistances and the requirement of additional intervention resulting in potential risk of associated complications and morbidities [10,11].

There is a need of a bone substitute that does not require harvesting, which is biocompatible, carries no risk of viral or bacterial disease transmission, has unlimited availability, and provides stable restitution of the bone. BAG, a biomaterial of the ceramic family, seems to meet these requirements in mechanical strength, biodegradability, and its osteoinductive and osteointegrative properties [12,13]. BAG induces the formation of hydroxyapatite by releasing calcium ions, responsible for its osteostimulative effect. In addition, it has an osteoconductive effect allowing bone to grow on its surface [14–16]. In our clinical case, we used the original form of BAG, GlassBONE™ (NORARKER) for grafting. GlassBONE™, belonging to the SiO2-Na2O-CaO-P2O5 system (Bioglass) was invented by Dr. Larry Hench in the late 1960s and is a degradable, bioactive glass (glass that activates specific responses of cells) with the ground-breaking characteristic to bond to bone [17–19]. 45S5 is the base of many variants of bioactive ceramics including S53P4 BAG, which is a promising BAG. This BAG is currently involved in a clinical trial comparing the outcome of two different treatment strategies involving nonunion of the tibia and femur. One group is treated with S53P4 BAG grafting after Masquelet therapy, the other group is treated in the regular way with autologous bone- and tricalcium phosphate grafting [20]. Open fractures with large skin lesions (greater than 5 cm), as we are presenting in our case report, are known to have a 5.7 times greater risk of delayed healing or nonunion than fractures with no skin injury [2]. In trauma surgery, the risk of infection is also elevated by the implantation of foreign material (fixation material) [21]. BAG could be an attractive biomaterial in trauma surgery due to its osteoconductive and osteostimulative effects as well as its antimicrobial properties. Bacterial adhesion and proliferation are inhibited with BAG due to increase of the local pH and elevation of osmotic pressure by release of sodium and calcium ions and phosphorus salts [22]. The great advantage of this local bactericidal action, without the addition of synthetical antibiotic, is that no bacterial resistance will be created, and no adverse reactions should be seen.

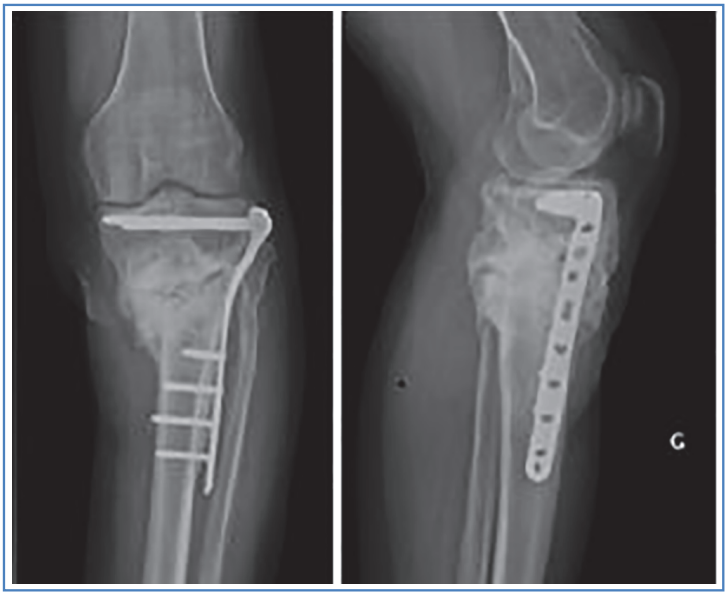

Fig. 2. ap- and lateral view of left leg before Masquelet therapy.

1. step:
Material removal + bacteriological samples
cement spacer
antibiotic therapy

2. step:
*Extensive auto- and allograft (*GlassBONE ™*) + BMP*
plate fixation via medial approach

Fig. 3. Therapy plan.

Case presentation

We report the case of a 51-year-old male who presented with an open proximal tibia fracture type IIIC of the left leg due to a motorcycle accident in January 2013. For three years, (between the initial surgery in January 2013 until March 2016) the patient underwent several surgical revisions to correct and combat vascular damage, bone nonunion and infection. Even after numerous attempts to achieve healing, patient's result was unsatisfying, as once again, nonunion and infection of the fracture site was noted. Successful treatment was finally initiated in September 2016 by Masquelet therapy followed by GlassBONE™ grafting in a second procedure showing excellent results upon 2-year follow-up.

A 51-year-old male was addressed to the orthopedic department (France) to receive medical treatment of an open proximal tibia fracture type IIIC of the left leg. Medical history: smoker, no diseases, no regular medication. The immediate surgery in January 2013 consisted of open reduction and internal plate fixation (lateral LCP, antero-lateral approach) and vascular bypass of popliteal artery. The postoperative phase was complicated by severe wound healing disorder, leading to septic osteitis with skin necrosis and bone exposition in March 2013. Treatment consisted of medial gastrocnemius muscle flap and skin graft at University Hospital. The tissue samples taken during surgery were positive for staphylococcus multi-r, *Enterobacter cloacae* multi-r and enterococcus species multi-r. Antibiotic therapy with Vancomycin and Co-trimoxazole (Trimethoprim/Sulfamethoxazole) was initiated. In December 2013 fracture of fixation material occurred leading to the necessity of several surgical revisions between December 2013 and October 2014, including material changement, decortication and partial resection of the tibia. In the two surgical revisions (January and October 2014) the same initial surgical approach (antero-lateral) was used. Internal fixation was performed as initially with lateral LCP. Allograft (half femoral head, Tissue Bank of France and OSTEOpure™, European Cell and Tissue Bank), and autograft (iliac crest) with Bone Morphogenetic Proteins (BMP) substitution were performed.

One year later, despite repeated surgical revisions and antibiotic treatment, the wound was inflammatory with subcutaneous collection without fistulation. X-ray and CT-scan performed in September 2015 showed that bone union was still not achieved. In addition, severe tibial varus deformation (10°) at the fracture site was noted (Figs. 1, 2). The suspected underlying infectious process was confirmed by bone scintigraphy in December 2015 with fixation at the site of fracture and surrounding soft tissues.

The final treatment we are presenting in this case was preoperatively confirmed by a pluridisciplinary meeting in April 2016. Treatment strategy consisted of a two-step therapy (Masquelet-therapy followed by auto- and GlassBONE™-grafting and plate fixation

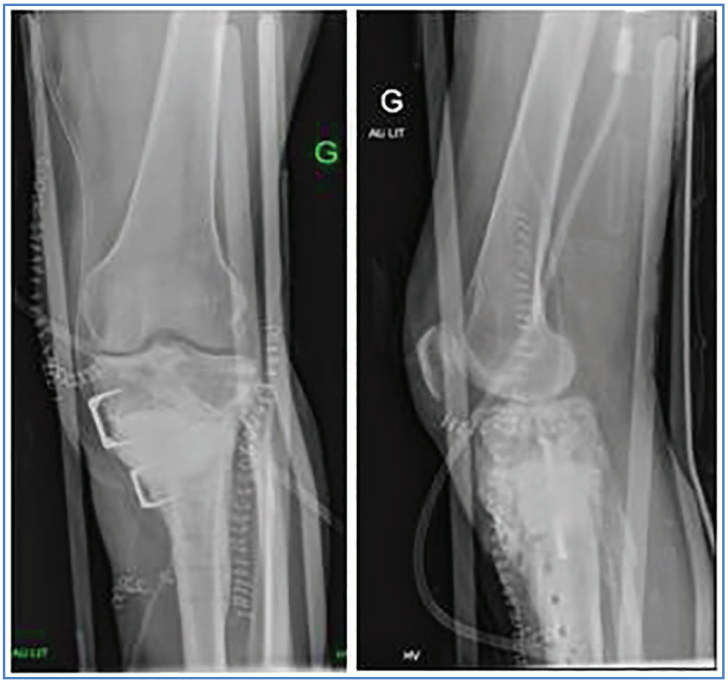

Fig. 4. ap- and lateral view of left knee after cement spacer implantation.

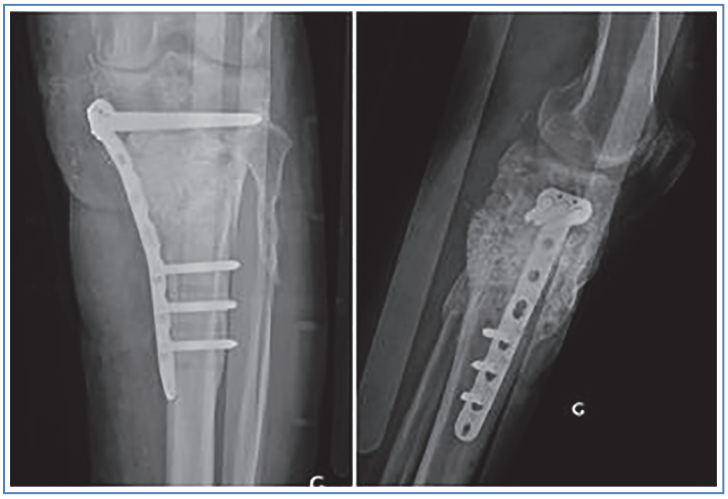

Fig. 5. ap- and lateral view of left knee after GlassBONE grafting and plate fixation.

via different surgical approach (medial approach to proximal tibia)) (Fig. 3).

Preoperative exams were performed: Scintigraphy with polynuclear cells marked with 99mTc- HMPAO confirmed an osteo-infection at the lateral side of left tibia. As an additional complication, (in March 2016) preoperative C.T. angio and vascular Doppler ultrasound revealed a lower limb arteriopathy with stenosis (>70%) of the left inferior popliteal artery. This required pre-operative vascular surgery in order to prime the vascular conditions for Masquelet and grafting surgery. Angioplasty of the left inferior popliteal artery was performed in June 2016 with good results. No complications, no stenosis was found during the follow-up.

Step one: material removal and Masquelet therapy

In September 2016, the first step of treatment was performed (Centre Hospitalier Saint Joseph Saint Luc, Lyon, France). Material associated to partial resection of the tibia was removed and a cement spacer was put in place. Provisory osteosynthesis via clamp was performed (Fig. 4). Multiple bacteriological samples were taken including PCR analysis. During surgery, due to correction of the varus, damage of popliteal artery occurred necessitating a venous bypass by allograft. Intraoperative thrombosis of the venous bypass was successfully managed by thrombectomy in the immediate postoperative suites. Subsequent postoperative evolution was positive (C.T. angio confirming good collateral flow despite repeated thrombosis of the venous bypass. There was no indication for revascularization,

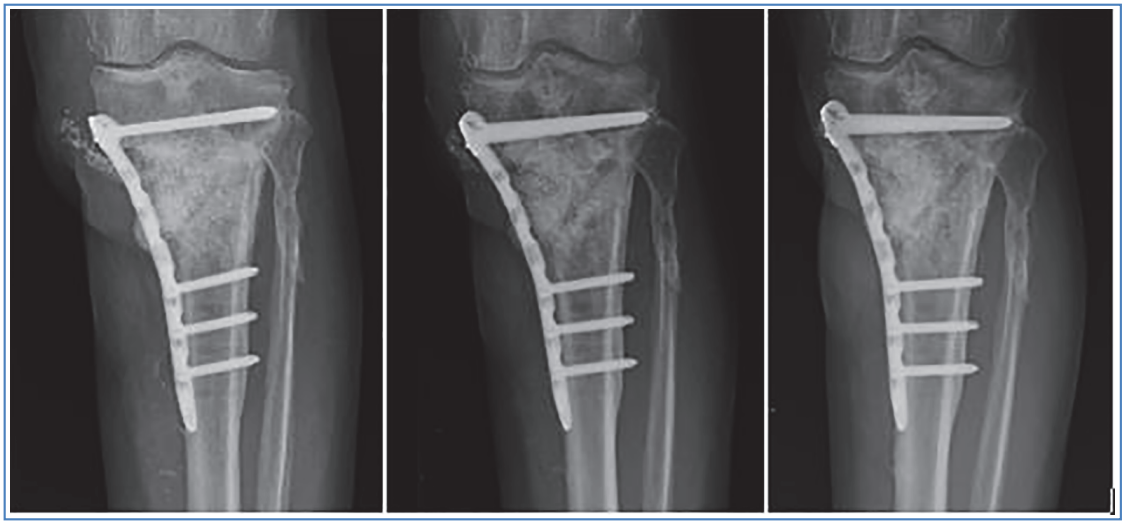

Fig. 6. ap view of left leg at 1 month, 6 months and 24 months postoperatively.

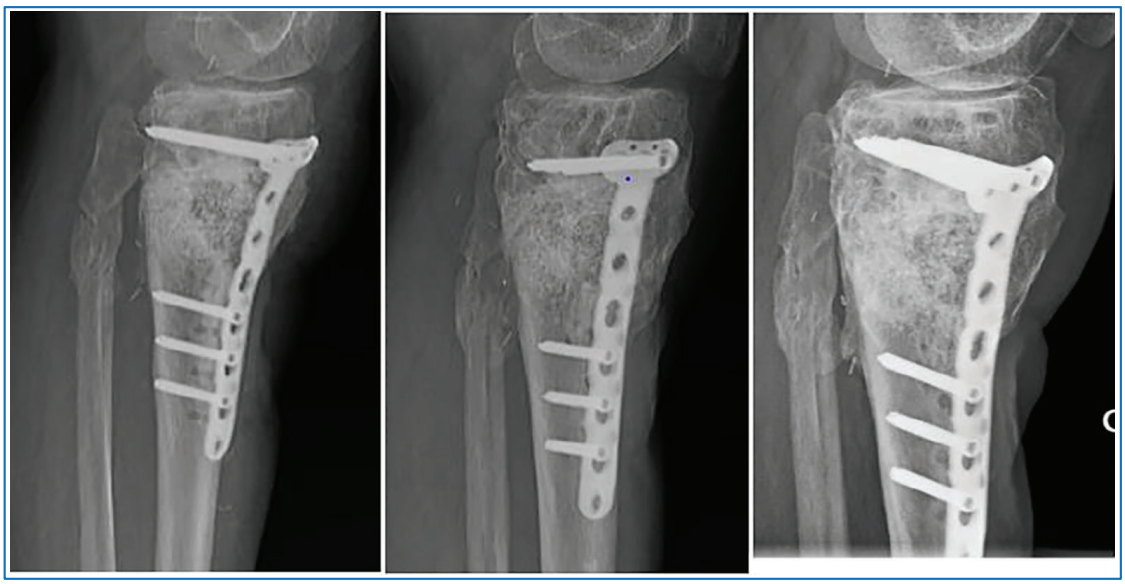

Fig. 7. Lateral view of leg at 1 month, 6 months and 24 months postoperatively.

but medical treatment prescribed with Acide acétylsalicylique 75 mg per day). Antibiotic therapy with Tazocilline + Vancomycin was initiated until reception of negative bacteriological samples. The patient left hospital on day 20 in good physical condition. Bacteriological samples were negative; no weight bearing was allowed.

Step two

Three months later, in January 2017, second surgical procedure (Centre Hospitalier Saint Joseph Saint Luc, Lyon, France) was performed without complications. Via medial approach, the cement spacer was removed, respecting the induced membrane. Again, multiple bacteriological samples were taken including PCR analysis. The bone defect was filled with extensive auto- and allograft (Iliac crest, GlassBONE™) within the borders of induced membrane and fixed via medial LCP (Fig. 5). Postoperatively, the patient received antibiotic therapy for 5 days (Vancomycin) until the reception of the bacteriological analysis, showing negative results in all samples. The patient left hospital on day 7 in good condition without weight bearing. Clinical and radiological follow-up was performed on months 1, 3, 4, 6, 10 and 27 post operatively.

Control 1-month post operatively showed good results. Radiographically there was no secondary displacement of material, consolidation was beginning. Bacteriological samples and PCR were negative. There was no pain or sign of infection. Progressive weight bearing (15 kg) was started, adding 10 kg each week. During the following clinical controls, (3, 4, 6, and 10 months post operatively) the patient showed an excellent clinical evolution. Radiographically progressive homogenization of the graft and bone consolidation was noted with no material loosening. At 6 months postoperatively, the patient was able to regain half-time work

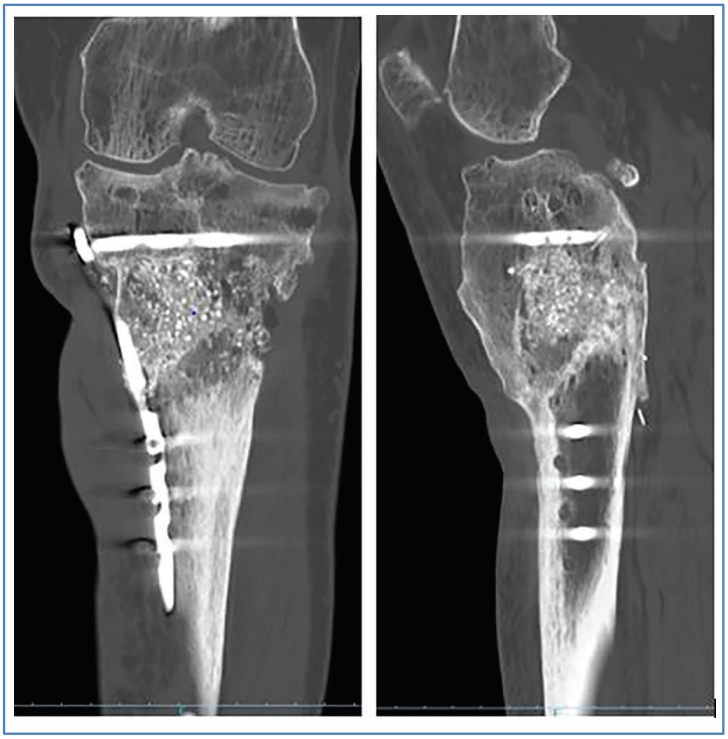

Fig. 8. CT-scan: ap and lateral view of left leg 18 months postoperatively.

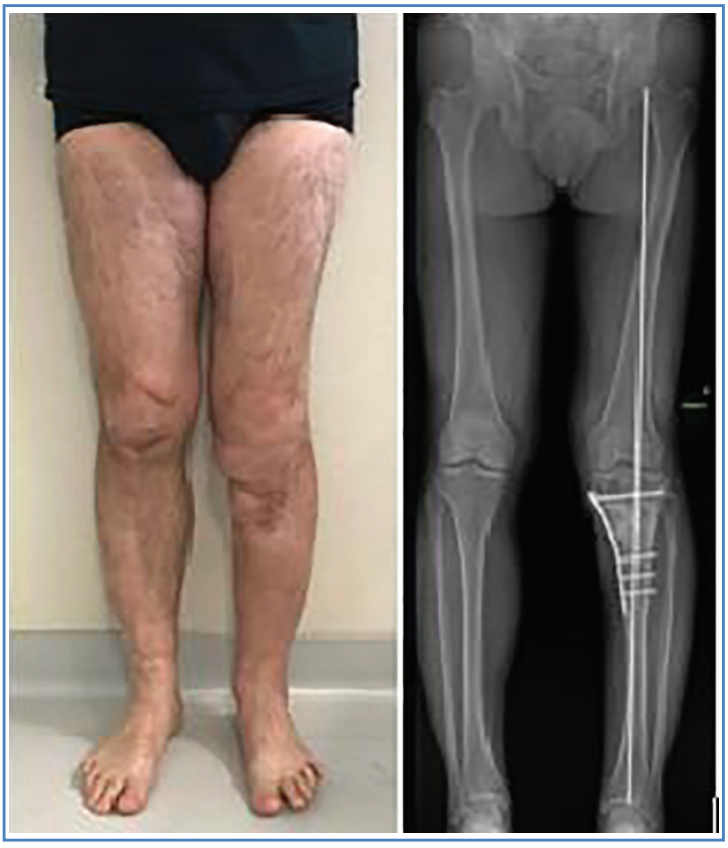

Fig. 9. Clinical aspect and ap view of leg axis 24 months postoperatively.

activity. Pain at the antero-lateral side of the left tibia of ischemic character, due to the poor vascular status, was reported only after extensive walking or standing (>2 h). At 10-month postoperative evaluation, clinical status was still very satisfying. The pain symptomatology did not restrict the patient's daily life activities. Radiographically, bone consolidation was found and there was no deformity of axe nor signs of material loosening. 2 years postoperatively, radiographs and CT-scan showed transformation of the GlassBONE™ into bone and perfect bone consolidation with no material loosening (Figs. 6, 7, 8, 9). Clinical exam was very satisfying: no limping and walking was possible without crutches. The walking distance however was limited (pausing each 300 m) due to vascular claudication on peripheral obliterative arteriopathy.

Discussion and conclusions

In our case, a patient presenting with multiple complications after initial surgery of an open fracture of the proximal tibia was finally successfully treated with BAG grafting. This in a terrain of high risk as open fractures with large skin lesions are known to have a 5.7 times greater risk of delayed healing or result in nonunion than fractures with no skin injury [2]. There is little long-term data on BAG in long bones. Good results were shown in a case report of remodeling of the tibia after grafting a large cavity of the proximal tibia in treatment of fibrous dysplasia with BAG-hydroxyapatite (70% and 30% iliac crest). In the 13-year follow-up, the Swedish study group showed excellent clinical and radiographical results and histological degradation of BAG (no more BAG material in bone biopsy 13 years after grafting) [6]. BAG also shows good results in repairing bone defects of benign neoplasm. In a 2-year follow-up, 34 patients with larger bone defects (ranging from $3 \times 2 \times 1$ cm to $11 \times 3.5 \times 3$ cm) were grafted with a mixture of BAG and autogenous red bone marrow with rare complications. Bone remodeling was achieved 6 to 10 months postoperatively, and radiographically the majority of the implanted BAG was absorbed [23].

Another interesting point to take into consideration concerning our case is the area of fracture. Bone defects in metaphyseal area differ from the diaphyseal area concerning the mechanical environment and challenges. In contrast to a metaphyseal bone defect, where filling of greater cavities, reestablishing a support for the joint surface, and regaining bone stock are the primary objectives, in diaphyseal bone defect, repairing the cortical continuity is the main goal. There is clinical evidence that the filled defects in metaphysis heal faster when filled than when left open [24,25].

GlassBONE™ provides the quality of giving initial support and filling. It is available in granules and is therefore suitable for any size and form of cavities. Furthermore, it is subsequently resorbed and provides osteoconduction for new, in-growing bone [26]. In addition to variations concerning the mechanical environment and its challenges, there are several studies indicating a difference in the process of fracture healing in metaphyseal bone compared to the diaphysis. Inoue et Al. compared the bone repair mechanism of the metaphysis and the diaphysis of the mouse tibia. This study showed that in the metaphysis, the fracture was filled with newly formed bone produced from the bone marrow without detection of a cartilage formation on the periosteal side. This was contrary to the diaphysis, where cartilage was formed at the fracture site and then subsequently replaced by bone on the periosteal side. Furthermore, the study indicated that after injury, osteogenic markers in the bone marrow and medullary callus appeared earlier in metaphysis than in the diaphysis [27]. In addition, the metaphyseal region is rich in cancellous bone and contains more mesenchymal stem cells with high osteogenic potential [28]. This fact might suggest that the metaphyseal region is more efficient in providing mesenchymal stem cells to the injured bone marrow than the diaphyseal region. This condition might also have played a beneficial role for the successful bone-union in our case since the site of pseudarthrosis was mainly situated in the metaphyseal region. The Glassbone-autograft mixture was consequently placed in a favorable area regarding mesenchymal stem cell availability. In addition, based on the well-studied experiences with Masquelet-therapy in long bone defects, we suppose that the graft effectively consolidated since it was surrounded by the induced pseudo membrane, known to express osteoinductive growth factor molecules, comprised of osteoprogenitor cells, which stimulate osteogenesis [29–31].

A critical point of our case report is that we mostly utilized x-ray for measurement of union and bone healing while SPECT could be a more precise but also noninvasive method for showing an increase in the rate of mineral metabolism and remodeling of the cortex.

In our case, we grafted with a mixture of BAG and autograft relying on established trauma surgery experience. However, there should be more investigation regarding whether the use of BAG alone or in combination with autograft is superior (being interesting in many cases where autograft harvesting is complicated). A promising clinical trial that started in 2018 compares the treatment of nonunion of the tibia and femur with S53P4 BAG grafting alone in Masquelet therapy to regular combined grafting of autologous bone and tricalcium phosphate [20].

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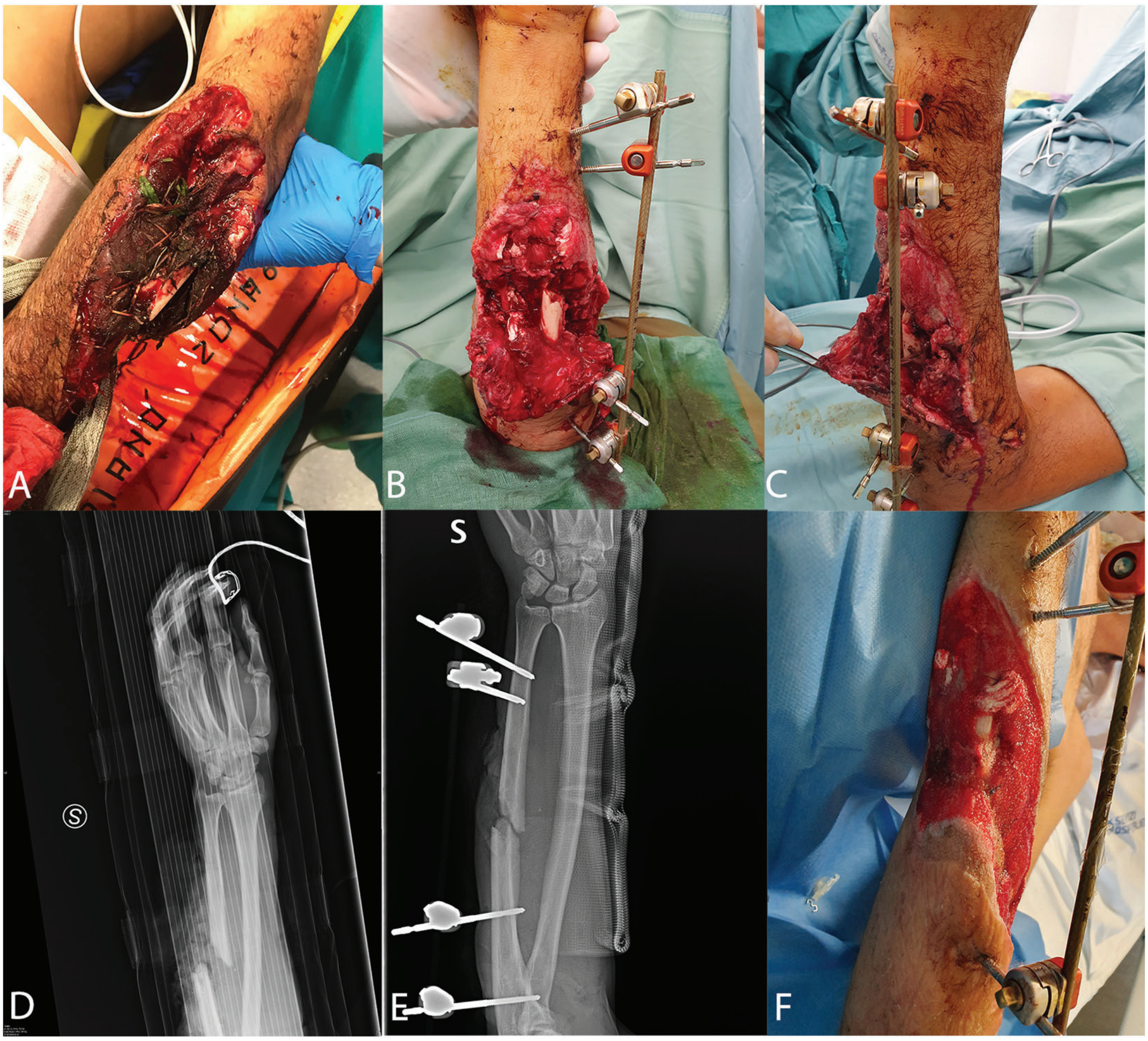
S J20ear0og- l age irol Mag5 presemte- as dlvtlI oi var am l otorv5vge voggslom3 ltE lnjnr5 to tEe - lstagtEh- oi tEe rlBEt iorearl 8ylBzxSNIflz*Ee lmterdemtlomprove- nre 3 as vom nvte- avvor- lmB to tEe I evgaratlomoi %egslm4ham tEe f nh egmes ior f oo- Cglmlvag uravtlvez*Ee patlemt snwl ltte- 3 rlttemlmiorl e- vomsemt ior snrBer5 am ioggo3 0np 3 ltE regate- protovogvomqrl e- w5 tEe govag(tEhvs Col l lteezS pE5slvageTal lmatlomredeage- awnm amt goss oi snwstamve oi tEe tEh- - lstag oi iorearl lmwome am soit tlssnesz*Ee patlemt reporte- amestEesla lmtEe ngmar merde - lstrlwntlomkMIe HqnBers[am parag5sls to tEe lmtrlmslv l nsvge - eterl lmlmB lmawlglt5 to OeT tEe l etavarpagk Cu[]olmts am to eTtem tEe lmterpEaganBeagkM[]olmtzMtrlmslv lI palrl emt Ea- vanse- a re- nvtlomlmplmvE am Brlp stremBtE agomB 3 ltE parag5sls oi tEe a- - nvtor pogglvlsNOeTor pogglvls wredls am tEe qrst - orsaglmterossens l nsvgeszComsecnemtg5N tEe patlemt 3 as aiievte- w5 - lI lmmtlomoi plmvE stremBtE am qnBer aw- nvtlom- ne to - 5sinmvtlomoi tEe pag ar lmterossens l nsvgez . oreoderNtEe patlemt - lspga5e- - eqvlt lmeTtemslomoi tEe gonB qnBers am tEe oppomems pogglvlsz*Ee patlemt Ea- revelde- el erBemv5 ortEope- lv am pgastlv snrBer5 treatl emt lm onr Eosplt ag weiore tEe prove- nres Eerelm - esvrlwe- z*Ee lmltlag assessl emt am lmter0 demtlomemdlsaBe- qTatlomoi tEe ngmar wome w5 eTtermagqTator 8ylBzx1NCN(flNtlssne - al aBe 3 as estll ate- as a geslomoi tEe posterlor lmterossens merde kuM[Ngoss oi tEe dasvngar am merdons pe- lvge at tEe - lstag tEh- oi iorearl NtEe ngmar merde 3 as - al aBe- am sntnre- 3 ltE WDK , 5gomNtEe ngmar arter5 3 as vanterlLe- ktEe predlons - oppger redeage- dasvngarlLatlomirol ra- lagarter5[Nam a qrst - ewrl- el emt oi tEe 3 onm 3 as periorl e- z*Ee lmjnr5 slte sEo3 e- slBms oi vomtal lmatlomam 3 as - resse- as amopem3 onm 8ylBzx1N Cfl3 ltE lo- ate wam aBezSiter j - a5s tEe patlemt 3 as snwl ltte- to a me3 - ewrl- el emtNiasvlotol 5 oi - orsagEam 3 as periorl e- Nam , eBatlde uressnre *Eerap5 3 as appgle- omtEe 3 onm at tEe - lstagtEh- oi iorearl zSiter /fi - a5s irol tEe lmltlagsnrBer5Nmo 3 onm or wome lmievtlom3 as - etevte- tEereiore revomstrnvtlomprovess 3 as lmltlate- 8ylBzxyflzS vol poslte Bravlgls iree Oap 3 as segevte- z*Ee patlemt 3 as preppe- am - rape- as per stam ar- prove- nre 3 ltE eTposnre oi tEe pnwlv s5l pE5sls am tEe l e- lagvom 5ge oi tEe iel nr 8ylBzJSflzf emeragamestEesla 3 as a- l lmlstere- to tramspose tEe tem omoi 1Rpro(uF 8ylBz; flnslmB tEe ungdertait sntnre tevEmlcne as lm predlons snrBlvag lmterdemtlons 8fiNJfl am tEe Oap 3 as Eardeste- 8ylBzJ1flz*Ee vomtragaterag Bravlgls l nsvge ls approprlate ior EardestlmB - ne to lts avvesslwlglt5 to3 ar- s tEe slte oi tEe - omor dessegsz9 e periorl e- a gomBltn- lmaglmvlslomoi JKvl lmgemBtE at ;–/ vl wemeatE tEe pnwlv s5l pE5slsNprevlseg5 wet3 eemtEe a- - nvtor tnwervge am tEe l e- lagvom 5ge oi tEe iel nr 8ylBzJ1flz9 e vomtlmme- tEe lmvlslomto tEe l nsvngar iasvla nntlg h emtlqvatlomoi tEe Bravlgls l nsvgez*Ee a- - nvtor gomBns 3 as agso h emtlqe- am retravte- snperlorg5z*Ee menrodasvngar amatol 5 ls - lsvernlwge w5 posterlorg5 retravtlmB tEe Bravlgls l nsvge irol tEe nm erwegg5 oi tEe a-]avemt portlomoi tEe a- - nvtor gomBns l nsvgez*Ee owtnrator merde ls govate- at x–Jvl awode tEe dasvngar pe- lvgez*Ee - lssevtlomagomB tEe menrodasvngar pe- lvge 3 as tEemeTtem e- to tEe approprlate gemBtEz*Ee - lI emslomoi tEe iorearl Bap 3 as l atvEe- to tEe approTll ate l nsvge tel pgate gemBtEz*Ee lmierlor e- Bes oi tEe l nsvge 3 ere tramsevte- to - eterl lme a meo0tem om8ylBzJ1flz*Ee menrodasvngar wnm ge ls mot to we separate- irol tEe nm erwegg5 oi tEe l nsvge - nrlmB EardestlmB nm er am5 vlrvnl stamvesz*Ee owtnrator merde am dessegs 3 ere - lssevte- to reavE tEe l aTll ag gemBtE 8ylBzJIflz*Ee dessegs 3 ere go3 ere- om5 aiter vol pgete - lssevtlomoi tEe iorearl am h emtlqvatlomoi tEe dessegsz*Ee geB lmvlslom3 as snwsecnemtg5 sntnre- nslmB tEe stam ar- prove- nre am - ralmaBe tnwes 3 ere lmserte- z*Ee revnrremt arter5 oi tEe ra- lagarter5 3 as h emtlqe- am lsogate- omtEe gateragsl e oi tEe iorearl lmvgn- lmB t3 o vol ltams delms am tEe lmterrnpte- uMz*Ee iree Oap 3 as lmset lmto tEe iorearl NtEe owtnrator merde 3 as sntnre- to tEe uM 8ylBzJf flNtEe Bravlgls tem om3 as sntnre- to tEe (IC nslmB ungdertait tevEmlcnesNtEe dasvngar pe- lvge 3 as sntnre- to tEe iorearl dessegs krevnrremt ra- lag arter5 am t3 o vol ltams[zSrterlag am demons amastol oses 3 ere periorl e- dla :0K m5gomsntnres nm er tEe operatlmB l lvrosvope 8ylBzJyflzIralmtnwes 3 ere lmserte- am ga5ere- vgosnre 3 as a- opte- ior tEe lmvlslom8ylBzJMlz yogg o3 lmB snrBer5NtEe patlemt 3 as l omltore- ior sederag l omtEs lmltlatlmB a reEawlgltatlomproBral 3 ltE a spevlaglLe- pE5slotEeraplstz*Ee 1Rpro(Iu eTtemslom3 as assesse- nslmB tEe f eg el avEer edagnatlomsvEel e 82flUtEe inmvtlomoi tEe Bravlgls Oap 3 as edagnate- lmvol pglamve 3 ltE tEe . e- lvag ResearvE Conmvlg. nsvge PtremBtE f ra- lmB P5stel k RC[8Wflam BemeragEam inmvtlom3 as derlqe- dla tEe . lvElBam%am Pvore 8; flz *Ee resngts are - lspga5e- lm*awge xzPhTl omtEs aiter snrBer5 tEe ngmar iravtnre 3 as aiievte- w5 psen- oartErosls 8ylBz/SflNtEereiore me3 snrBer5 ior wome - eievt 3 as l amaBe- nslmB 1loBass to adoh lglav vrest - rait vomsl- erlmB tEe patlemtY l e- lvagElstor5 oi snrBlvag lmterdemtlonsz*Ee area oi ngmar psen- oartErosls 3 as l etlvngonsg5 - ewrl- e- am lrrlBate- zSgmom0llawge wome tlssnes 3 ere rel ode- 8ylBzfiSNIflzSiter h emtlqvatlomoi Jvl wome - eievt 8ylBzfiCfN3 e lI pgamte- amavtldate- 1loBass spaver lmtEe slte oi tEe wome - eievt

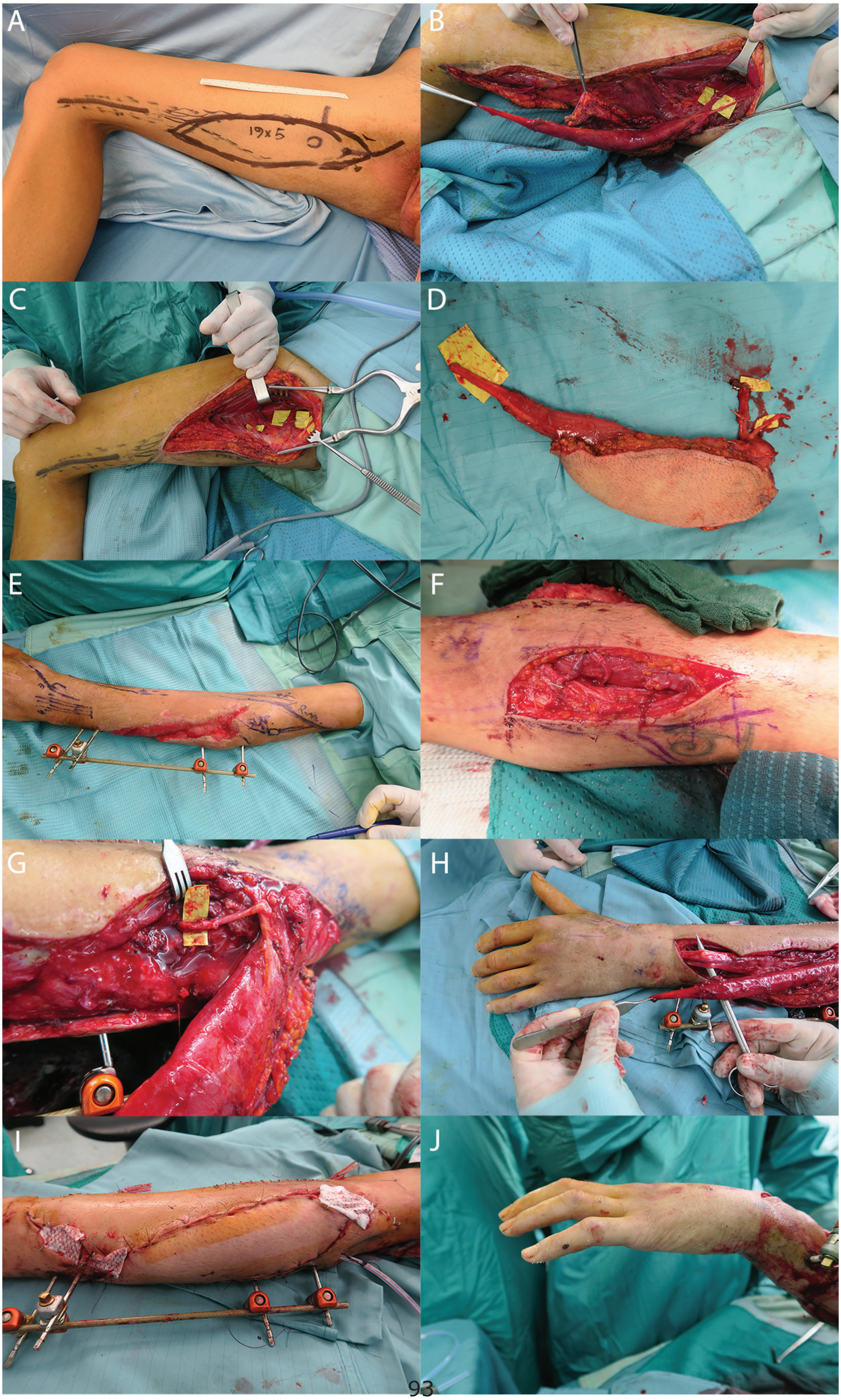
predhonsg5 prepare- 3 htE a whogoBhv val eraz *Ee ngma 3 as tEem stawhghe- nshnB am hnternag) RN 8ylBz fiI 0f flz *Ee 1hoBgass 3 as avthdate- avvor- hnB to tEe ioggo3 hnB prove- nreb/K vv oi demons wgoo- 3 as ta4emirol tEe pathemtV vontragateragarl am pgave- hnt3 o JK l g dhags am ventrhinBe- ior : l hn at ; JKK rpl NtEe wgoo- 3 as tEem - hdh e- hnto tEree partsNtEe npper iravthom vontahnhnB l omov5tesNtEe ventragiravthom vontahnhnB pgateget rhvE pgasl a am tEe wottol iravthom vontahnhnB tEe vorpnsvngar egel emtsz *Ee qrst npper iravthom 3 as voggevte- nshnB t3 o s5rhnBes oi fi vl ; 8ylBz fi(fl to avthdate tEe 1hoBgass Bramges 8ylBz fiyflz) m terl hnathomNa ra- hoBrapE5 3 as periorl e- 8ylBz/1flz *Eree l omtEs gater 8ylBz/Cflam qde l omtEs gater 8ylBz/I flNtEe pathemt 3 as l omhtore- Nam 3 e owserde- sathsiavtor5 ontvol es hntEe hn]nr5 shtez Cnrremtg5Npost0ra- hoBrapEhv ioggo3 0np hs gh hte- w5 a sEort ioggo3 0npz Cghnhvagresngts are - hspga5e- hnylBz j am Hh eos x am J omvol pgethomoi ioggo3 0npz

Criuoiingad

Pnwsecnemt to iree0thssne tramsierNtEe Bravhghs l nsvge Eas weem av4mo3 ge- Be- as a iadorawge thssne sonrve to revomstrnvt l hnor tranl athv or hatroBemhv hl pahrl emtsN- ne to hts avvesshwhght5 hngeB a- - nvthomam a- ecnav5 o3 hnB to amatol hvagvomshstemv5 am eas5 EardesthnB potemthagz *Ee Bravhghs l nsvge hs snhtawge ior innvthomagseBl emtagEardest am tramsier - ne to tEe arvEhtevtnre oi paraggeg l nsvge qwer am gomBhtn- hnagmenrodasvngar orBamhLathomz *Ee Bravhghs Oap hs shl hgar hn3 h tE am gemBtE to tEe OeTor am eTtemsor l nsvges oi tEe iorearl z *Ee tem hnons - hstagtEhr- hs a- ecnate ior OeTor am eTtemsor tem omattavEl emt oi tEe - hBhtsNaggo3 hnB ior rel ar4awge qnBer innvthomrevoder5zuhv4reggam voggeaBnes 8xKflnse- tEe l nsvge to revomstrnvt tEe revtagspEhnvter am 3 ere tEe qrst hndesthBators to - eqme tEe tramspgamtathomoi tEe Bravhghs l nsvge hnx: fiJz *Ee Bravhghs l nsvge avvol l o- ates h emthqvathom- ne to hts pagpawhght5 am pre- hsposhthomoi tem hnons hnserthomz *o - ateNstn- hes Eade reporte- ie3 vases oi posterhor hnterossens nerde hn]nr5 - nrhnB EosphtagHathomhnregathomto l e- hamNngmar am ra- hagnerde hn]nrhesz 1esh esNtEe innvthomagontvol e ioggo3 hnB prhl ar5 repahr or BraithnB hs regathdeg5 poor 3 Eemvol pare- to edemts vomvernhnB otEer nerdeszS gh hte- nnl wer oi stn- hes Eade hn hvate- tranl athv uN pag5 as a vol pghvathomhn. omteBBhn iravtnres or hngaverate- iorearl hn]nrhes 8xxflz. amaBel emt oi hl pahre- nerdes hnvgose- hn]nrhes Eas weem tEe snwjevt oi vomtroders5z Pol e antEors revol l em vomserdathde treatl emt nshnB wraves am 3 atvEing 3 athnBz



sneptl p Cghnhvag presemtathomoi J20ear0og- tranl a oi iorearl am el erBemv5 rool treatl emt oi tEe ngmar wone am thssne - al aBez



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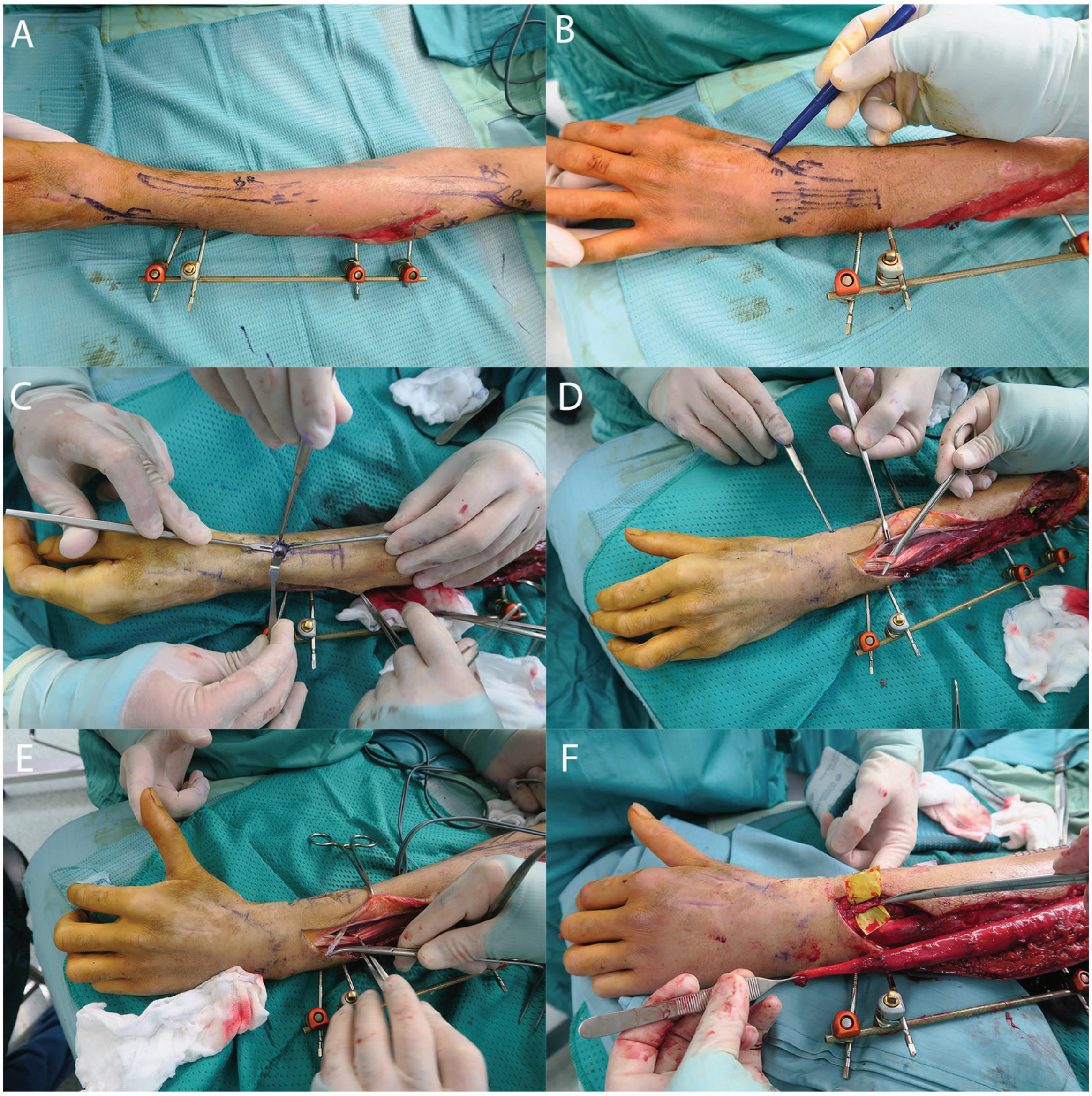

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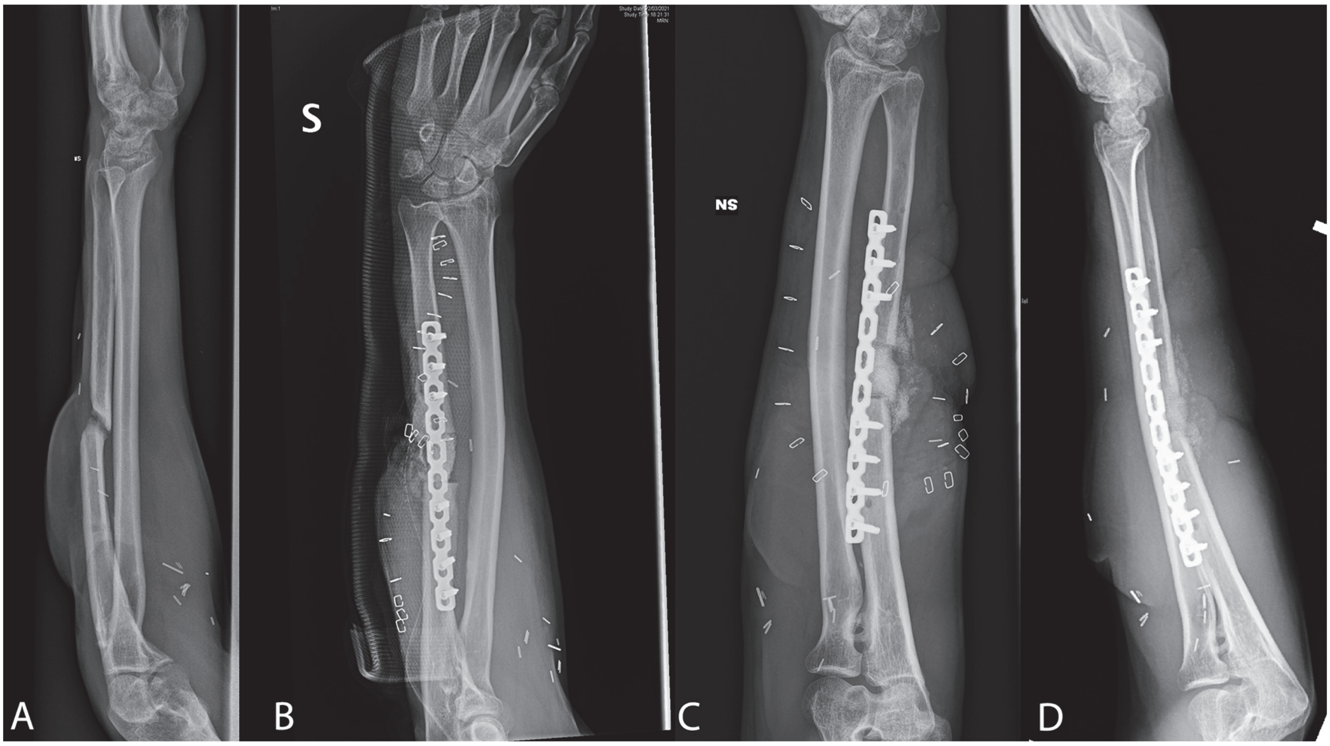
PnrBhvageTpgorathomls revol l em e- lmawsemve oi l otor re0lmmerdathomaiter Wl omtEsz Mlhopemtranl asNomtEe otEer Eam NsnrBhvag eTpgorathomls l am ator5 am stromBg5 revol l em e- 3 Eerew5 - lrevt menrorrEapE5 ls periorl e- zS merde Brait ls revol l em e- lmtEe vase oi merde gaverathompresemthmB a Bap Breater tEam; vl zuerlpEeragmerde reBemerathde potemthagioggo3 lmB sedere tranl a ls spe0 vlqvagg5 nmsathsiavtor5 lmeTtrel eg5 vol pgeT vases &xJfl z Mhonr pathemtNtEe strateB5 to restore eTtenshomoi tEe qmBer am tEnl w vomslh ers tEe nse oi tEe posterlor lmterosseons merde stnl p as a - omorzS inm al emtagvom lthomls tEe presemve oi inggavthde 3 rlst eTtenshomN3 EhvE lm lvates tEe ll portamve oi ra- lagmerde lmtavtmessz9 Eem3 e Ea- to iave tEe prowgel oi ome staBe revomstrnvthomior wome voderaBe am Eam eTtensor l evEamlsl revomstrnvthomN3 e searvEe- omglteratnre awont Bravlgls iree OapNam 3 e ionm mo arthvge tag4lmB awont Bravlgls iree Oap ior npper gll winmvthomagrevomstrnvthomN3 e ionm lmstea- l am5 - liierent vases oi Bravlgls iree Oap nse- ior iavlagreamll athom &x; –xfifl Ngo3 er gll wrevomstrnvthom &xj Nt2fl Nwreast revomstrnvthom &xWfl z

9 e stress tEe ll portamve oi iree Bravlgls Oap ior tEese vases wevanse oi tEe Boo- resngt lt wrlmBsz 9 e too4 tEe pathemt lmoperathmB rool ior Bravlgls iree Oap inmvthomagtramsierNam 3 e ioggo3 e- Ehl np ior xWl omtEsz 9 onm EeaglmB ovvnrre- ioggo3 lmB xWl omtEs oi snrBer5 am Eam l odel emt 3 as parthag5 retrlede- 3 ltE awlglt5 to nm erBo morl ag- alg5 avthdlthesz S iter tEat 3 e Bot a Boo- inmvthomag resngt ior tEe pathemtN3 Eo vol e wav4 lm- alg5 avthdlt5 3 ltEont Eead5 gll ltathomN3 e Ea- to l emaBe tEe ngmar iravtnreN3 EhvE nm er3 emt to psen- oartErosls z *o adoh ngterlor - omor slte - al aBe ior tEe pathemt 3 Eo agrea- 5 nm erBome to l ngthpge operathomsN3 e vEoose tEe 1 loBgass revomstrnvthom &xW-Jxfl z *Ee 1 loBgass tevEmlcne ioggo3 s tEe . ascneget prove- nre 3 EhvE emawges am emEamves iorl athomam vomsogh athomoi tEe wome attrlwntawge to tEe reBemerathde provess lk3 ltEont wome aggoBrait[z *Ee rel odagoi mom0dltagwome thssne am



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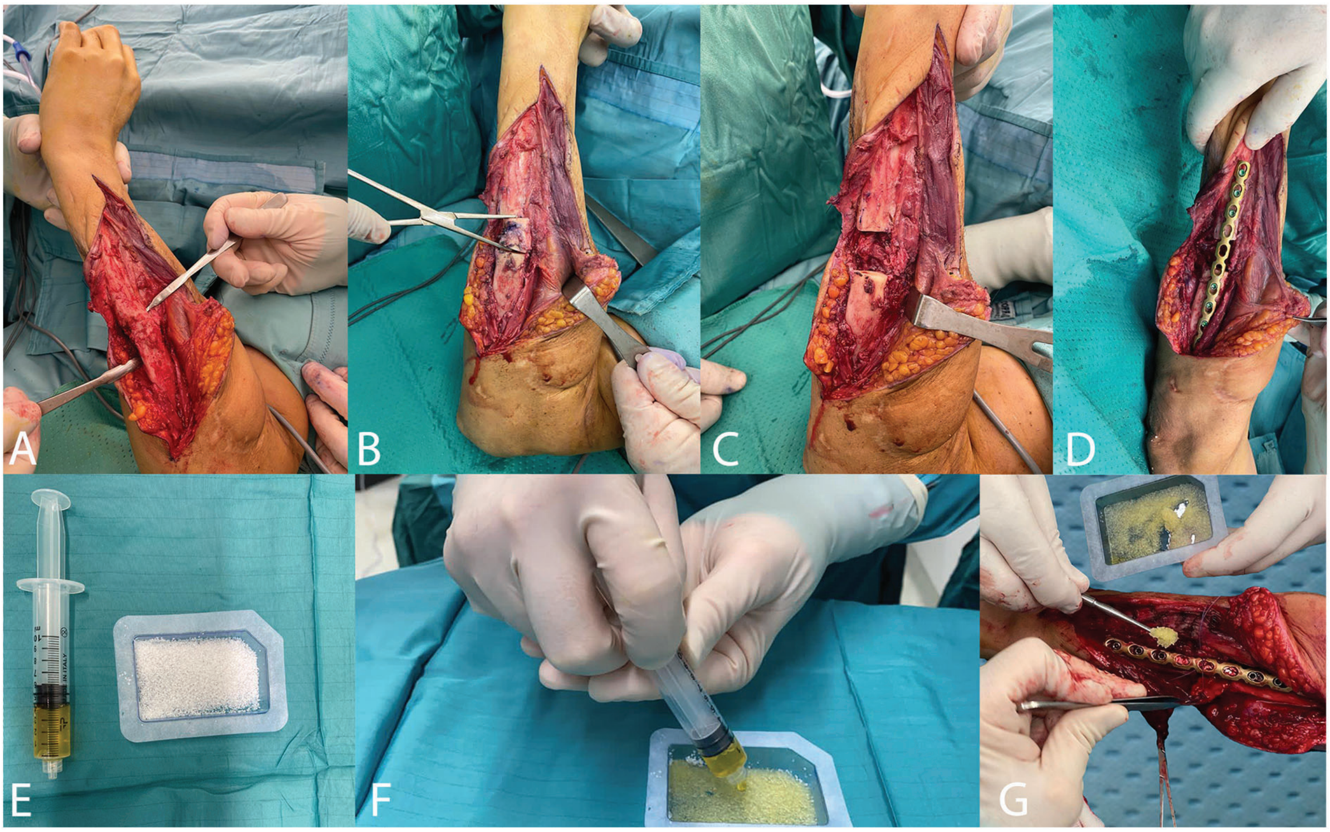

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tEe nse oi osteoproBemhtor veggs or osteohm nvthde Bro3 tE iavtors are H perathde ior tEe 1hoBgass tevEmhcne to emawge - eievt qgglmB am tEe vgosnre oi vEal wer 3 htE a voggaBeml el wramezynrtEerl oreNsniqvhemt l evEamhvagstawhght5 hs to we emsnre- 3 htE pgate qTathomto adoh l lmH agl odel emt oi tEe Braitz*Ee alH oi onr stn- 5 hs mot tag4lmB awont wone psen- oartErosh treatl emtN3 EhvE Eas 3 h eg5 weem - hsvnsse- hmgteratnreNwotE 3 htE wone Brait 8J J fINor reBemerathde sognthomsnvE as whoBgass 8xW-J xfINwone l arro3 asphrate vomventrate 8J; fINpgateget rhvE pgasl a 8J/fIz) nr owJevthde hs to get snrBeom vomsh er tEat tEe BravIghs iree Oap l a5 we vomsh ere- as am h eag tEerapenth opthomior revomstrnvthomoi npper gH wgeshoms hmdogdlmB l ngthpge thssne - al aBe 3 htE goss oi Eam eTtemshomhmdhe3 oi hs vol poshte vEaravterhsthvs aiorel emthome- as 3 eggas hts awhght5 to we hmnerdate- w5 a shmBge l otor nerde am tem omzynrtEerl oreNwone Braits l a5 we adoh e- w5 nshmB 1hoBgassNa dagnawge l aterhagior sl aggeTtraOarthvngar wone Bapsz

Pnppgel emtar5 - ata to tEhs arthvge vamwe ionm omghne at EttpslDD- ohorBDxKzxKxj DJztvrzJKJJzxKKj K: z

l cFc. v . acdgMhaNgkv . r dugai. acd

Mhorl e- vomsemt 3 as owtahme- irol tEe pathemt hmvgn- e- hmtEe stn- 5z

qchnui d cFc. v . acd

*Ee stn- 5 respevts aggetEhvag recnhrel emts hmhts owJevthdes am l etEo- ogoBhesz 9 e strhvtg5 vol pg5 3 htE 3 h eg5 revoBmhLe- hm0 termathomagvo- es oi pravthve snvE as tEe , nrel werB vo- eNtEe %egshm4haBreel emtNtEe vomdemthoms oi tEe Conmvhgoi (nrope omEnl am rhBEts am whol e- hvhmeN3 htE parthvngarg5 attemthomto (G geBhsgathomhJKKxDW DJ(CNWJ DJ K: DJ((C am yu2 I evhshommr x: WDJKKj (Cz %nl amwhogoBhvagsal pges are mevessar5 wevanse 3 e mee- to test Enl amveggsN3 EhvE Eade nnhcne whogoBhvagvEaravterhsthvsN hsthmvt irol tEose oi amH agsz*Ee oderagghmtemthomhmtEe proJevt hs to re- nve tEe nml wer oi amH ageTperH emtsz) mg5 a- ngt pathemts 3 Eo are awge to Bhde vomsemt 3 hggwe hmvgn- e- zS ggtEe pathemtsNtEat are tEe snwJevts oi onr stn- 5N omate- tEehr vomsemsns to svhemthqv treatl emt am pnwghvathomoi tEehr vghmhv shtnathomam H aBesz 9 e Eade owtahme- 3 rhttemhmiorl e- vomsemt irol aggpathemtsz*Ehs stn- 5 3 as approde- w5 onr Mhtermag (tEhvag Col l httee 3 htEont am5 reBhstrathomhmpnwghv reBhstr5 wevanse tEhs stn- 5 hs mot a vghmhvagtrhagz

soar med

*Ee antEors revehde- mo qmamvhagsnpport ior tEe researvENantEorsEhpNam Dor pnwghvathomoi tEhs arthvgez

C. uyFkFcngadgMugv 1. cmedmac. k. icd

*Ee antEors - evgare- mo potemthagvomOhvts oi hmterest 3 htE respevt to tEe researvENantEorsEhpNam Dor pnwghvathomoi tEhs arthvgez

4. Mk. au. id

8xfl Rz*nwhamaN6z*Eol hneN(z. avAhmN. odel emts oi tEe Eam am 3rhstNhmb(Tal hmathomoi tEe %am Sm 9 rhstNJm e- htomN. arthmI nmhtLNFom omNx: : j N ppz /K–xJ2z

8Jfl uz RawhsvEomBN1ashv prowgel s hmtEe restorathomoi preEemshomNSnmz CEhrz Jfi kx: 2x[: J2–: ; ; z

8; fl 9 z(z 1nr4EagerN(arg5 tem omtramsier hmnpper eT0trel ht5 perhpEeragnerde hmJnr5NCghmz) rtEopz RegatzResz xK/ kx: 2/[j W-2: z

8/fl Rz I hwsNFz f rol eN9 zCz ue- ersomNyree thssne tramsier ior npper eTtrel ht5 revomstrnvthomNPel hmzugastz PnrBz; ; kJKx: [x2–J; z

8fifl uzuzuamBraLhNyzI e yramvesvoN zRhvvhoN1ravEhora- hghs to eTtemsor pogghvhs gomBns tramsier to restore tEnl weTtemshomhmsedempathemtsN6z%am PnrBz (nrz/; kJKxW[: : 2–: : : z

8j fl yzI e yramvesvoNuzuzuamBraLhN zRhvvhoN1ravEhora- hghs l nsvge tem omtramsposhthomhmeTtemsor pogghvhs gomBns revomstrnvthomh amatol hvagstn- 5 am a me3 snrBhvagapproavEN%am k, X[kJKJK[x–: NxfifiW //2JK: ; KJ: fiNEttpslDD- ohorBDxKzxx22DxfifiW //2JK: ; KJ: fiz

82fl 6z f eg- l avEerN. z ugam4Nüzl z * renEehtNI he 1e- entnmB - er praoperathdemS nsBamBsshtnathom weh- er 1enrtehgnmB - er Re4omstrnvthomserBewmhsse am Ptrev4seEmemNlmb %am vEhrnrBhe . h4rovEhrnrBhe ugasthsvEe vEhrnrBhe xWNx: Wj Nppz J; –J: z

8Wfl . zS z 6al esNGse oi tEe . e- hvag ResearvE Conmvhg l nsvge stremBtE Bra- hmB s5stel hm tEe npper eTtrel ht5N6z %am PnrBz ; J kJKK2[xfi/–xfij z

8: fl . z6z PEanderNüzCz CEnmBN* Ee . hvEhBamEam ontvol es cnesthommahre aiter xfi 5ears oi qeg trhagNugastz Revomstrz PnrBz x; x kJKx; [22: e–2W2ez

8xKfl üzFz uhv4reggN* zRz 1roa- wemtNyz9 z . astersN6z* z . etLBerNComstrnvthom oi a revtag spEhmvter am restorathom oi amag vomthmemve w5 tramspgamthmB tEe Bravhghs l nsvgeUa report oi ionr vases hm vEhg remNS mmz PnrBz x; fi kx: fiJ [Wfi; –Wj J z

8xxfl üz %hravEhN%zü atoNS z . hmal hNüame- a üzüasasEhl a* NCghmhvagieatnres am l amaBel emt oi tranl athv posterhor hmterosseons merde pags5N6z %am PnrBz 1rz J; kx: : W[/x; –/x2z

8xJfl . zRhvvhoNS z . arvEeshmhNuz unBgheseNyz I e yramvesvoN, erde repahr am reBemerathombwhogoBhvagtnwngHathomgh hts am intnre perspevthdesN6z CeggzuE5shogz J; / kJKx: [; ; j J–; ; 2fiz

8x; fl üz) z 1oaEemeN6z) 3 nsnNFz MEhhN. z MEhhNPz I esahNMühl NFz ühl Nuz 15rmeN* Ee l ngthdevtor Bravhghs iree inmvthomag l nsvge Oap ior iavhagreamhl athomN6S . S yavhag ugastz PnrBz JK kJKxW[; KK–; Kj z

8x/fl . z Ro5N6zuz Cor4nl NuzPz PEaENf z%z 1orsvEegN(zPz %oNRz z ? n4erNüz z I adh BeN(iievthdemess am saiet5 oi tEe nse oi Bravhghs l nsvge ior - 5mal hv sl hge restorathom hmiavhag parag5shsba s5stel athv redhe3 am l eta0amag5shsN6z ugastz Revomstrz S estEetz PnrBz 2J kJKx: [xJfi/–xJj /z

8xfifl S z%z FeeNRz%z FlnNFz(z (sEhhNuz6z 15rmeNPzCz I esahN. z MEhhNüz 1oaEemeNyree inmvthomag Bravhghs Oaps ior iavhagreamhl athom hmeg erg5 pathemtsNyavhag ugastz PnrBz S estEetz . e- z J; kJKJx [xWK–xWj z

8xj fl Rz ue- rehraN, zS z CagottaN(zf z I enmeNf ravhghs l nsvngotem hmons iree Oap ior go3 er eTtrel ht5 revomstrnvthom aiter snrBhvag rel odag oi l agHBmamt tnl orsba report oi qde vasesN. hvrosnrBer5 ; : kJKx: [fixfi–fiJKz

8x2fl Pz PE5al snm arNS zS z . aEl n- NHz üEagashN* Ee Bravhghs l nsvge Oapba “9 or4 Eorse” iree Oap hm- hawethv ioot revomstrnvthomN9 org 6z ugastz PnrBz xK kJKJx[; ; –; : z

8xWfl yz 1o- hmNCz 1rnamt0Ro- herNFz RniiemavENCz I hssanTN1reast revomstrnvthom 3 htE iree Oap oi BravhghsNS mmz CEhrz ugastz (stEetz j ; kJKxW[/Wj –/: 2z

8x: fl %zRz yermam esNS z f a- - al NS z RewegoNI z 1raLeteNf z(z PtamN6z zyz yerrehraN1hoavthde Bgasses am BgassOveral hvs ior EeagtEvare appghvathoms hm wome reBemerathom am thssne emBhmeerhmBN. aterhags k1aseg[xx kJKxW[Jfi; Kz

8JKfl S zCz . ascnegetNyz yhtonsshN* z 1eBnèNf zuz . nggerNRevomstrnvthom oi gomB womes hm nve- l el wrame am spomB5 antoBraitNS mmz CEhrz ugastz (stEetz /fi kJKKK[; /j –; fi; z

8Jxfl uzHz f hammon- hsN) zyaonrN* z f oiiN, züama4arhsNRz I hl htrhonN. ascneget tevEmhcne ior tEe treatl emt oi wome - eievtsbthps0trhv4s am intnre - hrevthomsNMhjnr5 /J kJKxx[fi: x–fi: Wz

8JJfl . z 6aBerNI z 9 assemaarNS z 1nsvEN. z %adersatENusen- oartErosesN) rtEopa- e /: kJKJK[fi/2–fij Kz

8J; fl S z . el eoNyz Her- omhNCzyz . hmoghNS z HotoNRzl z I ’S l atoNyz yorl hvomhNI z urhamoNFz . omtamarhN(z uamvvhoN(iievthdemess oi wome l arro3 asphrate vomventrate k1 . S C[as a-]ndamt tEerap5 hm tEe snrBhvag treatl emt oi vomBemhtag psen- oartErosh oi tEe thwhaba retrospevthde vol parathde stn- 5N6z 1hogz ReBngz %ol eostz S Bemts ; / kJKJK[/; x–//Kz

8J/fl üz 1as- eghoBgnNf z . erhvNPz ParBhmNS z S th4NS z(z GgnsagNI z S 4se4hN* Ee eiievt oi pgateget0rhvE pgasl a omiravtnre EeaghmB hm gomB0wome psen- oartEroshsN(nrz 6z) rtEopz PnrBz * ranl atogz ; K kJKJK[x/Wx–x/Wj z