The Journal of Foot & Ankle Surgery 000 (2021) 1–6

Contents lists available at ScienceDirect

The Journal of Foot & Ankle Surgery

journal homepage: www.jfas.org

Original Research

Open Curettage With Bone Augmentation for Symptomatic Tumors and Tumor-like Lesions of Calcaneus: A Comparison of Bioactive Glass Versus Allogeneic Bone

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ARTICLE INFO

Level of Clinical Evidence: 3

Keywords:
allograft
Bioglass® 45S5
bone graft
bone ingrowth
bone repair
lesion

ABSTRACT

Few studies have characterized the clinical outcomes of 45S5 Bioglass® applied as a bone graft to that of allogeneic bone applied in calcaneal open curettage. Therefore, the purpose of the present investigation was to compare the outcomes of patients with calcaneal tumors and tumor-like lesions treated by open curettage with 45S5 Bioglass® or allogeneic bone. Of the 31 patients who underwent open curettage (18 cases of unicameral bone cysts, 7 cases of aneurysmal bone cysts, and 6 cases of intraosseous lipoma), 16 (52%) received grafts with 45S5 Bioglass® and 15 (48%) with allogeneic bone. All the feet achieved bone fusion according to the modified Neer radiographic classification system at the last follow-up examination. The mean bone ingrowth time for the grafts with 45S5 Bioglass® versus allogeneic bone was 3.71 ± 0.86 versus 4.46 ± 1.04 months (p = .038), the mean bone healing time was 4.86 ± 0.93 versus 5.73 ± 1.07 months (p = .021), and the mean incision drying time was 7.2 ± 1.8 versus 8.2 ± 1.5 days (p = .047), respectively. No differences were found in the postoperative American Orthopaedic Foot and Ankle Society ankle-hindfoot scale scores between the 2 groups (p = .213). These results show that 45S5 Bioglass® can better facilitate the formation of new bone with a faster drying time of the incision than allogeneic bone. Although both materials can benefit the clinical outcomes of calcaneal tumors and tumor-like lesions, further studies are needed to observe the long-term complications and lesion recurrence rates.

Calcaneal tumors and tumor-like lesions refer to an expansive, vascular, and locally destructive calcaneal condition, characterized by unicameral bone cysts (UBCs), aneurysmal bone cysts (ABCs), and intraosseous lipoma (IOL). Levy et al (1) reported that UBCs affect males more often than females at a 2.5:1 ratio and that calcaneal UBCs occur more frequently in middle-age populations. Most ABCs occur in the second decade of life, with a slight female predominance (2). Toepfer et al (3) reported that an IOL is diagnosed at a mean age of 38 years. However, IOLs can affect a wide age range, from the second to eighth decade of life, with a predominance of males to females at a ratio of 4:3, in accordance with a report by Muramatsu et al (4). Generally, most of these lesions are asymptomatic, especially UBCs and IOLs (2,5). Thus, the true number of patients might be greater than reported (4,6,7). With disease progression, especially for lesions occurring in weight-bearing bones, symptoms can occur, including heel pain, gait difficulties, and even pathologic fracture, and can indicate the need for intervention.

However, because of the complexity and diversity of these lesions, the type of intervention remains controversial. The most common interventions have been footwear modifications combined with the use of nonsteroidal antiinflammatory drugs (8), injection of methylprednisolone or bone marrow (9), and decompression with demineralized bone matrix (10). Although open curettage with bone augmentation seems to achieve the most significant clinical outcomes (1), autologous bone grafting remains the reference standard to promote healing (11,12). However, the limitations of autologous bone grafting and donor site morbidity have prompted the application of bone graft substitutes.

Previous studies have reported the biocompatibility of 45S5 Bioglass® (NovaBone, Alachua, FL) (13,14), which exhibits both

Financial Disclosure: None reported.
Conflict of Interest: None reported.
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https://doi.org/10.1053/j.jfas.2021.02.010

osteoconductive and osteoinductive properties (15-18). However, few clinical studies of 45S5 Bioglass® have been reported; thus, the effectiveness and safety of this material for reconstruction of bone defects caused by resection of calcaneal tumors and tumor-like lesions remain unclear. Furthermore, no comparisons of 45S5 Bioglass® with allogeneic bone for grafting of calcaneal defects have been performed.

The aims of the present study were to compare the outcomes between open curettage with 45S5 Bioglass® (NovaBone) versus allogeneic bone for the treatment of defects caused by calcaneal tumors and tumor-like lesions and to assess the safety, complications, and recurrence of lesions associated with the use of 45S5 Bioglass® in bone reconstruction after curettage of calcaneal tumors and tumor-like lesions.

Patients and Methods

From July 2012 to April 2017, patients with a diagnosis of UBC, ABC, or IOL using imaging studies and pathologic biopsy examination, who had calcaneal pain, for which conservative therapy had failed, were selected for inclusion in the present study. The following criteria were used for exclusion: current calcaneal pathologic fracture, previous calcaneal curettage with bone graft, and follow-up period of <12 months. The ethics committee of the First Hospital of China Medical University (Shenyang, China) approved the present study, which was conducted in accordance with the tenets of the Declaration of Helsinki. All participants provided written informed consent before participation.

A total of 36 patients (15 females and 21 males) underwent reconstruction of calcaneal defects after curettage of calcaneal tumors and tumor-like lesions with 45S5 material or autologous bone. Two patients were lost to follow-up and three lived far away and declined to participate in the study. Therefore, the study cohort included 18 (58%) patients with UBCs, 7 (23%) with ABCs, and 6 (19%) with IOLs. The median patient age was 26.0 (range 17-52) years, and the duration between symptom onset and surgery ranged from 2 to 13 months. The patients were randomly assigned to the 45S5 Bioglass® (NovaBone) group (45S5 group) or the allogeneic bone group (allograft group) according to random number method.

The 45S5 group included 16 (52%) patients (6 females and 10 males) with a median age of 25.5 (range 17-52) years. In the 45S5 group, 9 (56%) patients had UBCs, 4 (25%) had ABCs, and 3 (19%) had IOL. The allograft group included 15 (48%) patients (6 females and 9 males) with a median age of 26.0 (range 17-51) years. In the allograft group, 9 (60%) patients had UBCs, 3 (20%) had ABCs, and 3 (20%) had IOLs.

No significant differences were found in patient characteristics (i.e., sex, age, type of calcaneal tumor or tumor-like lesion, duration, body mass index, and implant volume) between the 45S5 and allograft groups (Table 1). The location and shape of the lesions were determined using radiographs. All lesions were approximately located in the central calcaneal body. In the 45S5 group, 10 (62%) lesions were linear or elongated and 6 (38%) were ovoid or round. In the allograft group, 8 (53%) lesions were linear or elongated and 7 (47%) were ovoid or round. No statistically significant differences were found in the lesion characteristics between 2 groups (p= .722).

Intervention

All surgical procedures were performed by the senior author (M.W. Y.) with ~20 years of surgical experience. After general or regional anesthesia, a thigh tourniquet was applied with the patient in the supine position. The lesion location and volume were estimated based on the imaging studies, especially computed tomography. Through a lateral curvilinear incision, curettage of the lesion was performed until the appearance of normal bone. The resected specimens were sent for histologic examination. Sterile saline was injected into the defect to determine the appropriate volume of bone filling material needed. The defect was rinsed and filled with bioactive glass (45S5 Bioglass®; NovaBone) or freeze-dried allogeneic bone (OsteoRad; Shanxi OsteoRad Biomaterial Co., Ltd., Shanxi, China) that had been soaked in saline for ~10 minutes. After drainage, prolonged and unnecessary exposure of the material was avoided. Once the wound was closed, the foot was bandaged with elastic bandages and immobilized with a short cast. The plaster cast and sutures were removed after 2 weeks, and ankle range of motion exercises and toe-touch weightbearing were initiated. Partial weightbearing with a cane was started at 4 weeks after surgery. Patients implanted with allogeneic bone resumed full weightbearing at 6 weeks, and the patients who had received implants with 45S5 Bioglass® (NovaBone) started to ambulate with full weightbearing at 8 weeks. Each patient was advised to avoid activities involving direct force over the calcaneus for the first 3 months after surgery. The patients returned to the clinic every month for clinical and radiographic evaluation for the first 6 months after surgery, every 3 months thereafter for 1 year, and, finally every 6 months or 1 year afterward.

Table 1
Demographic data of the study population (n = 31 feet of 31 patients)

Variable	45S5 Group	Allograft Group	Statistics	p Value
Sex			NA	1.000
Male	10	9		
Female	6	6		
Age (y)	25.5 (13.8)	26.0 (10.0)	$Z = -0.337$	.740
Lesion type			$\chi 2 \approx 0.111$	1.000
UBC	9	9		
ABC	4	3		
IOL	3	3		
Symptom duration (mo)	6.00 (9.75)	8.00 (11)	$Z \approx -0.653$	.545
BMI (kg/m^2)	22.98 ± 1.94	22.45 ± 1.85	$t \approx 0.786$	.439
Implanting volume (cm^3)	8.00 ± 1.20	7.87 ± 1.26	$t \approx 0.287$	.776

Data presented as n (%) or mean ± standard deviation.
Abbreviations: ABC, aneurysmal bone cyst; BMI, body mass index; IOL, intraosseous lipoma; NA, not applicable; UBC, unicameral bone cyst.

Clinical Evaluation

Bone fusion was assessed according to the modified Neer radiographic classification system. The bone ingrowth time of the 2 materials was compared. The American Orthopaedic Foot and Ankle Society (AOFAS) ankle-hindfoot scale was used to assess the functional outcome. The drying time of the incision was recorded to evaluate incision recovery.

Bone ingrowth was defined as obvious formation of fresh trabecular bone and fusion of graft bone particles with the host bone (19). The modified Neer radiographic classification system was used to classify bone fusion into 1 of 4 categories (20-22): healed, healed with a defect, persistent cyst, and recurrent cyst. Healed was defined as a cyst filled with new bone, with or without a small radiolucent area <1 cm in size. Healed with a defect was defined as static, radiolucent areas <50% of the diameter of the bone with adequate cortical thickness to prevent fracture. A persistent cyst was defined as a radiolucent area >50% of the diameter of the bone, with a thin cortical rim and no increase in the cyst size, with continued restriction of activity recommended or repeat treatment required. A recurrent cyst was defined as cyst reappearance in a previously obliterated area or a residual radiolucent area that had increased in size. The time of bone ingrowth or bone fusion in months was defined as the total number of days after surgery divided by 30.

The primary goals of open curettage with bone augmentation were recovery of foot function and improvement in quality of daily life. The AOFAS ankle-hindfoot scale is the conventional method to evaluate foot function, which was assessed using a questionnaire survey distributed on postoperative months 3, 6, and 12.

Although several calcaneal incision procedures and complications have been reported (23,24), the exudation and drying time of calcaneal curvilinear incisions after curettage with bone graft of the calcaneus remain unclear. Also, the incidence of exudation-related infection, necrosis of the incision, and progression to osteomyelitis are unknown. In the present study, the drying time was defined as the number of days from the first day after surgery to the day that no exudation occurred and the bandaging materials were dry.

Statistical Analysis

All statistical analyses were performed with SPSS, version 19.0, software for Windows (IBM Corp., Armonk, New York). A probability (p) value of .05 was considered statistically significant. Quantitative

variables with normal distribution and homogeneity of variance are expressed as the mean ± standard deviation, otherwise as the median ± quartile range. Qualitative variables are expressed as frequencies. The body mass index, quantity of bone graft, bone ingrowth time, and bone fusion time were assessed using the paired Student *t* test. Differences between sexes and the shape of calcaneal lesions were assessed using the Fisher exact test. Age and duration of recovery were assessed using the Mann-Whitney *U* test. Comparisons of the type of calcaneal tumor and tumor-like lesion were performed using the $\chi 2$ test. Analysis of variance with repeated measures was used to compare the AOFAS ankle-hindfoot scale scores between the 2 groups.

Results

The bone ingrowth time was significantly shorter in the 45S5 group than in the allograft group (3.71 ± 0.86 vs 4.46 ± 1.04 months, respectively; t = −2.172; *p*= .038; Table 2; Fig. 1). The bone fusion time was significantly shorter in the 45S5 group than in the allograft group (4.86 ± 0.93 vs 5.73 ± 1.07 months, respectively; t = −2.437; *p*= .021; Table 2; Fig. 1). At the last follow-up visit, all calcaneal lesions in both groups were classified as "healed" (Figs. 2 and 3), because the radiographs showed bone replacement of the calcaneal lesion with or without small static radiolucent areas <1 cm in size.

Table 2
Comparison of bone ingrowth time and bone healing time between groups (months) (n = 31 feet of 31 patients)

	45S5 Group	Allograft Group	*p* Value
Bone ingrowth time	3.71 ± 0.86	4.46 ± 1.04	.038*
Bone healing time	4.86 ± 0.93	5.73 ± 1.07	.021*

Data presented as mean ± standard deviation.
Abbreviations: 45S5, 45S5 Bioglass® (NovaBone); Allograft, allogeneic bone.
* The bone ingrowth time and bone healing time was significantly shorter in the 45S5 group than in the allograft group ($p < .05$).

No significant differences were found in AOFAS ankle-hindfoot scores between the 2 bone graft materials (F = 1.624; *p*= .213). The scores at postoperative month 12 in the 45S5 and allograft groups were 94.19 ± 2.79 and 93.27 ± 2.60, respectively, and were greater than the preoperative scores. The scores at postoperative month 3 were lower than the preoperative scores in both groups (Table 3). Using analysis of variance, the p value of the spherical degree test was 0.511, which obeys the variance matrix spherical test without calibration results.

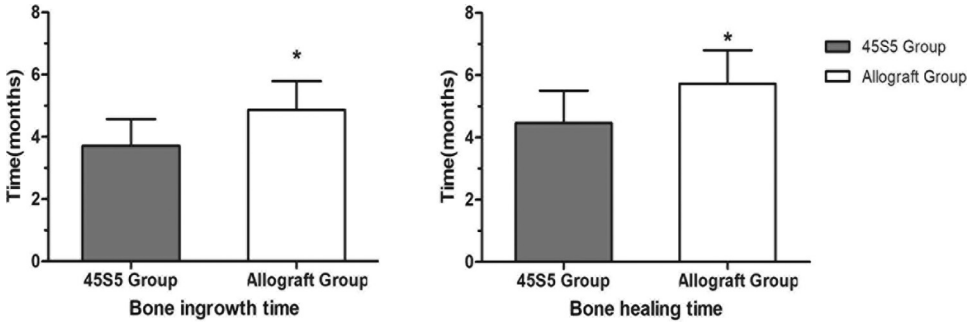

Fig. 1. Bone ingrowth and healing time between groups (n = 31 feet of 31 patients). * Bone ingrowth and healing time was significantly shorter in the 45S5 group than in the allograft group($p < .05$)

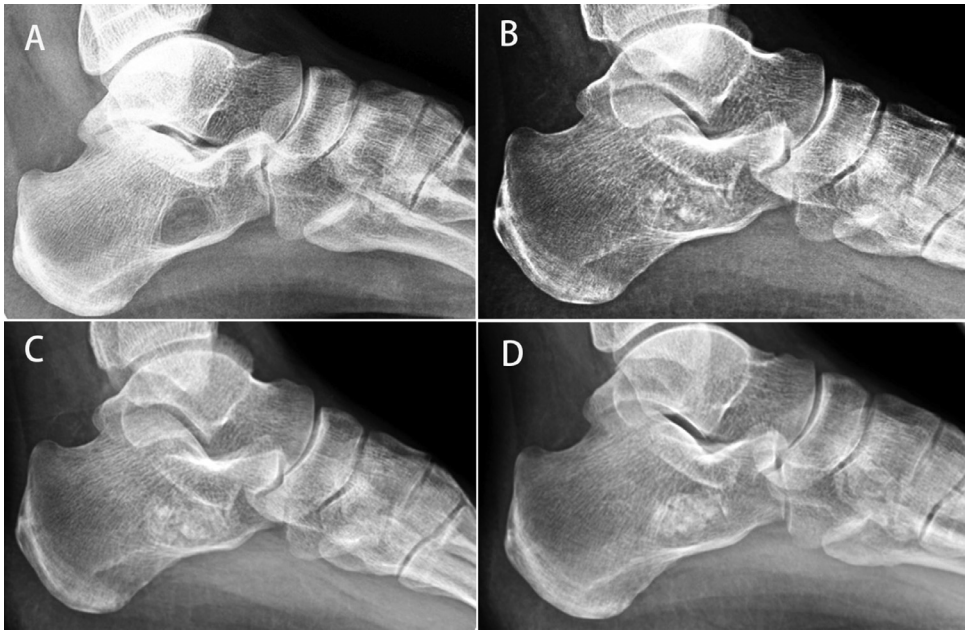

Fig. 2. Lateral radiographs of the left calcaneus of a 42-year-old male with histologically confirmed intraosseous lipoma. Allogeneic bone was used to reconstruct the central calcaneal defects after curettage of the lesion. Radiographic images *(A)* before surgery and *(B)* 2 days after surgery. *(C)* Bone ingrowth at 16 weeks postoperatively. *(D)* Bone healing at 21 weeks postoperatively.

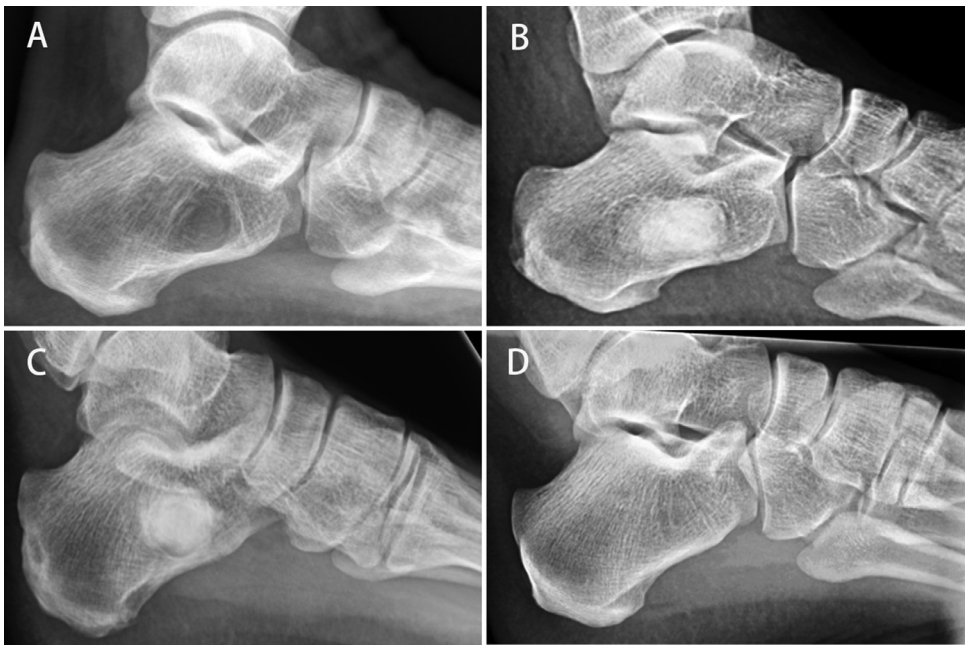

Fig. 3. Lateral or oblique radiographs of the left calcaneus of a 36-year-old male with histologically confirmed intraosseous lipoma. Bioglass® 45S5 was used to reconstruct central calcaneal defects after curettage of the lesion. Radiographs *(A)* before surgery and *(B)* 5 days postoperatively. *(C)* Bone ingrowth at 12 weeks postoperatively. *(D)* Bone fusion at 17 weeks postoperatively.

Table 3
Comparison of American Orthopaedic Foot and Ankle Society ankle-hindfoot scale scores between groups (n = 31 feet of 31 patients)

Questionnaire Timing	45S5 Group	Allograft Group	*p* Value
Preoperatively	69.81 ± 4.86	70.33 ± 6.24	.312
Postoperatively			
3 mo	60.93 ± 6.09	59.93 ± 7.07	.511
6 mo	87.94 ± 4.63	81.60 ± 5.64	.153
12 mo	94.19 ± 2.79	93.27 ± 2.60	.213

Data presented as mean ± standard deviation.
Abbreviations: 45S5, 45S5 Bioglass® (NovaBone); Allograft, allogeneic bone.

Dressing changes, raising the affected limb high, and limited activity after surgery was performed to facilitate drying of the incision. The drying time was significantly shorter in the 45S5 group than in the allograft group (7.2 ± 1.8 vs 8.2 ± 1.5 days, respectively; $p = .047$).

No pathologic fracture, graft rejection, or lesion recurrence was detected during the follow-up period in either group. Although fever occurred in 6 patients (3 in the 45S5 group and 3 in the allograft group), the body temperature of each returned to normal with physical cooling. A few patients complained about swelling around the incision after engaging in physical activity.

Discussion

45S5 Bioglass® (NovaBone) has been widely used in cell research and animal studies (18,25,26). This material, in our experience, has also been applied clinically in the United States and China for many years, although caution is needed when it is used in weightbearing applications because of the lack satisfactory strength, which can result in collapse of the bone or pathologic fracture. However, few studies have addressed the clinical application of 45S5 Bioglass®(27), and few have reported on its use as a bone filling material after resection of calcaneal tumors and tumor-like lesions. Thus, the radiographic outcomes and incidence of postoperative complications, including lesion recurrence, remain unclear. In addition, no comparisons have been performed between 45S5 Bioglass® (NovaBone) and allogeneic bone for calcaneal reconstruction, although no significant difference exists in the costs of the 2 materials. The results of the present study showed that the time required for bone ingrowth, bone healing, and drying of the incision was reduced with the use of 45S5 Bioglass® compared with allogeneic bone.

The modified Neer radiographic classification system (3,20-22) is widely used to evaluate the results of curettage of bone tumors and tumor-like lesions repaired with bone filling material. In the present study, the bone healing time was shorter in the 45S5 group than in the allograft group, suggesting that the use of 45S5 Bioglass® (NovaBone) can facilitate faster bone fusion than with an allograft, although bone healing was eventually achieved in all patients. Similar to the present study, Toepfer et al (3) treated 10 cases of calcaneal tumors and tumor-like lesions by endoscopic resection with an allograft, and all 10 patients were eventually classified as “healed.” Takada et al (20) also reported complete healing in 16 cases of calcaneal UBCs after open curettage with tricalcium phosphate grafts. However, Hou et al (21) reported that a few patients with UBCs in the long bones failed to heal after open curettage and grafting with a calcium sulfate bone substitute, suggesting that this bone material substitute is insufficient to achieve healing. Nonetheless, the characteristics of the implant, viability of the host bone, surgical technique, rehabilitation exercise program, and bone tumor volume can all affect the surgical outcome.

The modified Neer radiographic classification system emphasizes the results of bone grafting but does not include bone ingrowth as a criterion. Therefore, we focused on the bone ingrowth time using radiographs, rather than histomorphometry (17,18,28), which is more informative but requires more time and is comparatively inconvenient for the patients because they must undergo clinical and follow-up radiographic evaluations in busy outpatient departments. Bone ingrowth determined from radiographs is not as precise as using histomorphometry but is more convenient for the surgeon to evaluate the postoperative outcome and is of great importance for evaluating the outcome of implantation. Once bone ingrowth has occurred, further activity of the foot is allowed and needed. This clinical significance is

the reason we added the bone ingrowth time assessed using radiographs. Thus, we recommend this method for postoperative estimation for small clinics and hospitals that are unable to apply histomorphometry. In the present study, the bone ingrowth time in the 45S5 and allograft groups was ~3.7 and ~4.5 months, respectively. This difference can be attributed to the distinct mechanisms of the 2 materials. The 45S5 Bioglass® (NovaBone) and freeze-dried bone are both polyporous materials with osteoconductive properties. However, the remaining factors in freeze-dried allogeneic bone benefit new bone formation by creeping substitution (29). Use of 45S5 Bioglass® can induce the proliferation of osteoblastic cells and mesenchymal stem cells by ion exchange and signal transduction (30,31) and also promoting angiogenesis (32,33). Cortez et al (18) and Wheeler et al (28) detected bone ingrowth at ~4 weeks after surgery, which was far earlier than in that the present study for various reasons, including the sensitivity of histomorphometry and the different criteria used for bone ingrowth.

Because the tolerance of 45S5 Bioglass® (NovaBone) to force was not determined at beginning of the study, the patients in the 45S5 group were advised to not resume full weightbearing until 8 weeks after surgery to prevent possible calcaneal fracture. This time to heal was longer than that for the allograft group, which might be the reason the AOFAS score for the 45S5 group was lower than that for the allograft group at postoperative month 3. However, 4 patients resumed full weightbearing prior to 8 weeks after surgery, none of the patients in the 45S5 group developed a calcaneal fracture, illustrating the tolerance of 45S5 Bioglass® to force. Moreover, the calcaneal lesions of patients in this study were located in central calcaneal body, where part of the calcaneus is not exposed to a load, which might be the reason patients in 45S5 group avoid calcaneal fractures with early load-bearing.

The average score of the 45S5 group at postoperative month 6 was greater than that of the allograft group, possibly because of the force distribution between the hard outer surface of the allograft and the donor bone, which can produce pain, possibly explaining why the scores of the allograft group were lower. As indicated by the scores at postoperative month 12, the activities and formation of new bone were similar between groups. Toepfer et al (3) reported a postoperative AOFAS score of 94.4 ± 9.3 after endoscopic resection and allografting, and Innami et al (34) reported similar functional results with an overall AOFAS of 98.0 ± 4.2 after endoscopic resection of lesions with grafting performed with an injectable bone substitute. These 2 scores were both higher than our score of 94; thus, endoscopic resection might be more beneficial to the postoperative score than open curettage, although the timing of the AOFAS score evaluation is also important.

The calcaneus is mostly composed of cancellous bone that easily bleeds after surgery. Because the soft tissue of the lateral calcaneus is thin, greater exudation from the calcaneal lateral incision can be expected. This unique characteristic can cause infection, disunion, and even necrosis of the incision; thus, a shorter drying time of the incision is of great significance. The drying time was significantly shorter in the 45S5 group than in the allograft group ($p = .047$). We ascribed this phenomenon to the decrease in inflammation (14) and the better biocompatibility of 45S5 Bioglass® (NovaBone), which resulted in less rejection. However, because of the critical p value and the small number of patients, the possibility that actually no significant difference was present between the 2 groups could not be excluded. Thus, further research is needed to evaluate the differences in the drying times of the 2 materials.

Immunologic rejection, infection, bone nonunion, postoperative fractures, and lesion recurrence are relatively common complications. Immunologic rejection can be negatively correlated with biocompatibility and osteoinductivity of the bone filling material. Although 6 patients in the present series developed a fever after surgery, physical cooling was sufficient to eliminate the symptoms; thus, the fever could be ascribed to a slight infection or postoperative heat absorption. To prevent postoperative fracture, the patients were advised to avoid premature and excessive activities. Although the use of crutches and casts was also needed, these measures sacrificed the early postoperative activity of patients. In our experience, the type and site of the lesion, bone graft material, and surgical technique can influence the incidence of recurrence. No recurrence was noted in our patients during the follow-up period, which ranged from 1 to 3 years, similar to that in a previous report (3).

The limitations of the present study included the small number of patients and a relatively short follow-up period; thus, the incidence of long-term complications, including lesion recurrence, remains unclear and warrant further research.

In conclusion, 45S5 Bioglass® (NovaBone) and allogeneic bone can both be used as viable alternatives to autologous bone for calcaneal reconstruction after curettage of calcaneal tumors and tumor-like lesions. However, 45S5 Bioglass® can shorten the bone ingrowth time, bone healing time, and incision drying time compared with allogeneic bone, and 45S5 Bioglass® showed good tolerance to early weightbearing, although it might be inferior to allogeneic bone. Compared with allogeneic bone, we recommend 45S5 Bioglass® as a bone filling material for reconstruction of central calcaneal defects after resection of tumors and tumor-like lesions.

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