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Preservation Surgery of Septic Osteoarthritis and Osteomyelitis in the Diabetic Foot Using S53P4 Bioactive Glass—A Case Series

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Abstract: (1) Background: Preservation surgery of the diabetic foot aims at tissue sparing to avoid further pathological changes from developing, while ultimately preserving the limb. For this purpose, osteoregenerative, antimicrobial, and osteostimulative materials are now available. The aim of this case series is to demonstrate several clinical situations in which the use of bioactive glass, a third-generation biomaterial, can potentially be of benefit. (2) Methods: In this retrospective case series, we present patients with a diabetic foot complication with septic osteoarthritis, treated at the University Medical Centre Ljubljana, in the years 2020–2022. Patients received surgical care with resection of the affected joint and bone and placement of bioactive glass material. We observed patient characteristics, recurrence of septic osteoarthritis or osteomyelitis, and the need for amputation in the follow-up period. (3) Results: Of the 16 included patients, 8 received treatment of the metatarsophalangeal joints, 4 of the midfoot joints, and 4 of the ankle joints. Ten suffered from Charcot neuroarthropathy. None required readmission within 30 days or suffered early complications. One complication with recidivant septic osteoarthritis and osteomyelitis was observed. (4) Conclusions: Our case series presents possible applications for treatment with bioactive glass in various joints and bones affected by septic osteoarthritis of the diabetic foot.

Keywords: diabetic foot; osteomyelitis; bioglass; Charcot arthropathy

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1. Introduction

Lower extremity changes present some of the most frequent pathologies present in patients with diabetes mellitus, including ulcers, which present a frequent and significant complication. Data from the U.K. show that at any given moment, 2.5% of the diabetes patient population has an active lower limb ulceration, while data from the U.S. estimate a lifetime prevalence of 25% [1,2]. Lower limb ulcerations can present an entry point for pathogens to develop into infections involving the bone and joints, which are significant due to the advanced risk of amputation that they present—this risk is estimated to be up to four times larger than in the absence of bone involvement [3]. Such an infection presents the first step on the road to amputation. The treatment goal for a patient presenting with a diabetic foot pathology should be limb integrity and function preservation, as this is important for their functional status, self-image, and social actualization [4]. However, advanced pathologies and infections of the diabetic foot result in loss of quality of life as well as function and, eventually, loss of limb [5].

The complex pathogenetic processes that occur in patients with diabetes mellitus include numerous changes in the vasculature and innervation of the foot, leading to a combination of enduring changes, such as the atrophy of foot musculature, fibrous changes, and repositioning of fat tissue pads. All these changes affect the biomechanics of walking and lead to specific predilection sites for ulcer formation [6]. In the case of reduced sensitivity, as the patient does not feel the consequences of increased pressure, deformations of the tissue can occur relatively unnoticed, and any potential affection of macro- or microvasculature inhibits the healing capacity of tissue. The formation of ulcers above joints enables pathogens' direct entry into bone and joint tissue [1,6,7].

Due to the biomechanics of walking and the typical changes in the context of diabetic foot pathology, the first metatarsophalangeal joint presents a common predilection site [1,6–8]. Standard surgical therapy conventionally used in such cases is resection of the affected bone and joint, as well as extensive adjacent soft tissue necrectomy [9–11]. This approach presents risks of gait destabilization and shift of weight, which can lead to additional pathological changes and formation of ulcers at other sites. However, other sites of bone and joint infections can also arise, such as osteomyelitis as a complication of previous injury or other pathologies particular to the diabetic foot, such as Charcot neuroarthropathy.

Preservation surgery and salvage treatment of the diabetic foot follow the principle of tissue sparing, with the goal of avoiding further deformation, recurrence of similar pathological processes, and ultimately limb preservation and prevention or deferring amputation [4]. Materials ideal for the treatment of diabetic foot pathologies are required to have an antimicrobial effect, the ability to fill bone defect cavities, and to promote healing. To achieve the necessary effects, materials acting as bone substitutes are coming into use. An increasing number of reports are available in the literature concerning the use of third-generation biomaterials. Stratified in this category due to its properties enabling osteoregeneration and osteostimulation is S53P4 Bioactive Glass (BAG). Bioactive glass was originally invented at the University of Florida in 1969 and has since been approved for use in the treatment of osteomyelitis in specific regions around the world [12]. However, descriptions of its use in diabetic foot infections and specific pathologies etiologically related to diabetes mellitus are infrequent. The efficacy and safety of S53P4 BAG in treating diabetic foot pathologies have been the subject of a small number of retrospective observational studies focusing on specific predilection sites of septic osteoarthritis, a case report of its use in Charcot neuroarthropathy, and a prospective case series [8,13–16]. Studies focusing on the properties of BAG provide insight into the potential effects on target tissues, which could help explain why its use shows promising results in this population. Not only are there observed antimicrobial effects on a variety of bacteria, including anaerobes and potentially even multi-drug-resistant bacteria, the material has been hypothesized to have angiogenetic effects, promoting neovascularization [17,18].

Due also to the lack of clear consensus and evidence to support clinical decisions, treating diabetic foot osteomyelitis and osteoarthritis remains a great challenge. The aim of this retrospective case series was to highlight the possible use of BAG in pathologies of the diabetic foot through an overview of our relevant clinical experience with its use in preservation diabetic foot surgery.

2. Materials and Methods

2.1. Study Design

We present a retrospective case series including patients who presented with a diabetic foot complication requiring surgical treatment in the period between 1 January 2020 and 1 October 2022. The single-center study included consecutive cases.

2.2. Patient Population and Inclusion and Exclusion Criteria

We included patients treated at the University Medical Centre Ljubljana, Clinical Department for Surgical Infections, in the years 2020–2022. Basic demographics were collected (age, sex, and comorbidities). The inclusion criteria were defined as the presence of osteomyelitis/osteoarthritis in the diabetic foot where conservative management was not possible or was unsuccessful and surgical treatment was indicated, or Charcot neuroarthropathy where surgical treatment due to infection of the bone and/or joint was indicated. None of the patients included had advanced peripheral artery disease (critical ischemia) that would preclude the postoperative wound from entirely healing.

For the purpose of this report, cases were stratified into three groups according to the affected site of where BAG was applied: Group A, with metatarsophalangeal (MTP) joints affected; Group B, with midfoot joints affected; and Group C, with ankle joint involvement.

2.3. Therapeutic Approach

S53P4 Bioactive Glass is reported to have bacteriostatic, osteostimulative, and osteointegrative properties. The biochemical processes that follow application into and interaction with tissue lead to alkalization of the environment, which has an inhibitory effect on bacterial growth. Additionally, the ions released stimulate bone growth and remodeling through molecular mechanisms. The material has gained approval by relevant major European institutions (the European Medicines Agency (EMA)) [13,17,18].

For the treatment of the cases described in this report, S53P4 BAG in the form of granules (Bonalive® granules, Bonalive Biomaterials Ltd, Turku, Finland), mixed with autologous venous blood before application, and in the form of putty (Bonalive® putty, Bonalive Biomaterials, Turku, Finland), was used where appropriate.

Patients received surgical care led by a single surgeon experienced in diabetic foot pathology. The procedure was single-phase in isolated pathologies and multi-phase in the presence of concomitant foot pathologies. The operation consisted of the resection of affected joint and bone, irrigation, and lavage of the affected site. Application of BAG was then performed, and consequent primary wound closure by layer was performed. Where appropriate, the procedure was performed with the addition of external fixator device positioning.

Prolonged antibiotic treatment leading up to and after the operative treatment was prescribed based on clinical signs, and laboratory follow-up was conducted based on clinician judgement and/or upon consultation with experienced infectious disease specialists.

2.4. Follow-Up and Outcome Measures

Participants were monitored as outpatients. A laboratory inflammatory marker control was conducted, as well as a control X-ray of the foot. When appropriate, an external fixation device used was removed. During follow-up, clinical examinations and radiographs were performed as well as laboratory testing, where appropriate, to assess the efficacy of treatment and need for reoperation or presence of complications. The primary outcome was the reoccurrence of septic osteoarthritis or osteitis in the affected joint and the need for amputation at the time of follow-up, which was 2–26 months (average 11 months; standard deviation $\pm$ 8.4). Our secondary outcomes included 30-day readmission and reoperation rates.

2.5. Data Analysis

The data are presented as absolute values per category with percentage for categorical variables. For continuous variables, data are presented as means with standard deviation. The outcomes are presented as binary variables. The calculations of the descriptive statistics measures used were performed using SPSS (IBM, Version 25 for Macintosh, Armonk, NY, USA). No hypothesis testing was performed due to the modality of the report.

This report was prepared in accordance with the Declaration of Helsinki. As the cases reported were retrospectively included and analyzed, the diagnostic and treatment process was unaffected by this case study. All patients received optimal standard care. Included patients provided written informed consent for the procedures performed.

3. Results

Table 1 presents the basic population characteristics overall and by group according to the site of affection. Characteristics were noted in the outpatient clinic upon admission, including type of diabetes mellitus, presence of Charcot neuroarthropathy, and history of other significant extremity amputation. Additionally, other diseases were documented such as arterial hypertension, hyperlipidemia, and chronic kidney disease. Upon suspicion of significant peripheral artery disease, an angiological assessment was performed prior to surgery to exclude major macrocirculatory issues.

Table 1. Patient population: demographic information and characteristics.

Patient Characteristics	Overall (*n* = 16)	Group A—MTP Joints (*n* = 8)	Group B—Midfoot (*n* = 4)	Group C—Ankle (*n* = 4)
Sex (male/female)	15/1	8/0	4/0	3/1
Age (mean ± SD)	61.0 8.85	62.3 8.50	55.8 9.54	63.8 9.03
Diabetes mellitus (type I/II)	2/14	1/7	1/3	0/4
Charcot neuroarthropathy (*n*; %)	10 62.5%	4 50.0%	3 75%	3 75%
Arterial hypertension (*n*; %)	13 81.3%	6 75.0%	3 75%	4 100%
Hyperlipidemia (*n*; %)	7 43.8%	4 50.0%	3 75.0%	0 0%
Chronic kidney disease (*n*; %)	1 6.3%	1 12.5%	0 0%	0 0%
Previous or other foot surgery/amputation (*n*; %)	5 35.3%	1 12.5%	3 75.0%	1 25.0%

MTP—metatarsophalangeal; SD—standard deviation.

All cases were observed over the follow-up period. Upon follow-up, detailed clinical examination and X-ray studies were performed as well as laboratory testing as per clinical assessment of the clinician conducting the follow-up. During follow-up, pre- and intraoperatively obtained microbiological results were reviewed. Table 2 displays the most frequently isolated microorganisms.

Table 2. Microbiological results of intraoperatively obtained bone samples and adjacent soft tissue samples.

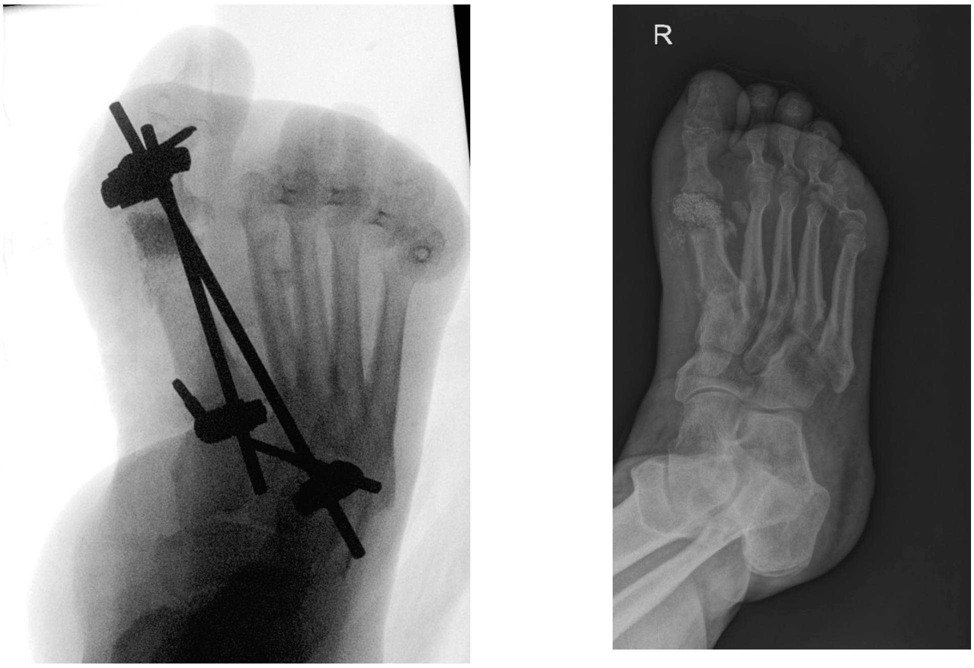
Bacteria Isolated	Overall (*n* = 16)	Group A—MTP Joints (*n* = 8)	Group B—Midfoot (*n* = 4)	Group C—Ankle (*n* = 4)
Staphylococcus aureus	5	3	1	1
MRSA	1	1	0	0
Other Staphylococci	6	3	2	1
Pseudomonas aeruginosa	3	1	1	1
Corynebacterium spp.	6	3	0	3
Enterobacterium cloacae	6	2	2	2
Enterococcus faecalis	4	3	0	1
Anaerobic bacteria	7	5	1	1

MRSA—methicillin-resistant *Staphylococcus aureus*.

No patient suffered recidivant infection or complication due to material insertion (such as a hypersensitivity reaction) requiring surgical treatment within the first 30-day follow-up period post-operation. Out of the cases included, one patient suffered a complication involving the affected joint during the follow-up period. The other patients did not suffer any recidive of osteomyelitis that would require reoperation during the follow-up period.

3.1. Metatarsophalangeal Joints

Out of the eight cases included in this group, four were reported to have Charcot neuroarthropathy, and all had clinically and radiologically suspected osteoarthritis. Table 1 shows their detailed characteristics, including significant concomitant diseases documented. For seven patients, the affected site was the first MTP joint, while one patient suffered from osteoarthritis of the lesser (fourth and fifth) MTP joint. Figure 1 demonstrates the intraoperative placement of BAG as well as a small fixator, and the extent of bone defect, remodeling, and osteointegration after three months. Two procedures performed for the treatment of the first MTP joint were single-phase with resection and application of BAG, while five were multiple-phase procedures, with the utilization of antibiotic gentamycin beads (Septopal® Chain, Zimmer Biomet Deutschland GmbH, Freiburg im Breisgau, Germany) in three cases. An external fixator device was used in all seven cases involving the first MTP joint, with removal scheduled after approximately three months. The procedure performed for lesser MTP joint osteoarthritis was single-phase with resection and BAG application, without the use of an external fixator device. All patients received a prolonged antibiotic regime of at least six weeks, with an initial treatment of approximately two weeks of intravenous antibiotic therapy in-hospital. None required revision during the 30-day period postoperation, suffered early complications, or required amputation during the follow-up period. The patient with affected fourth and fifth MTP joints had no early complications and achieved healing; however, as the follow-up period in this case was the shortest (only two months), late complications could not be definitively assessed.

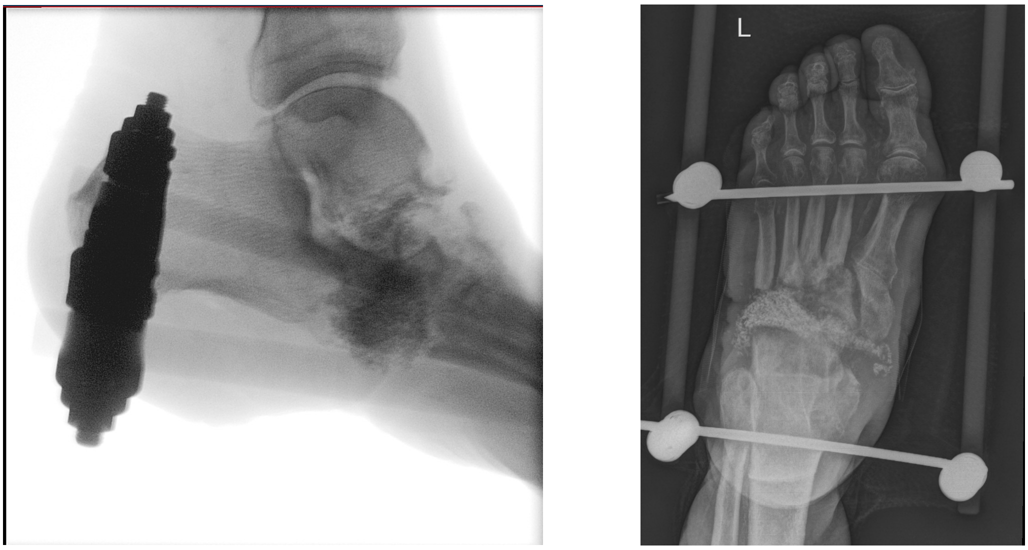


(**a**) (**b**)

Figure 1. (**a**) Intraoperative X-ray—resection of 1st metatarsophalangeal joint, placement of bioactive glass granules, and placement of external fixation device. Image captured intraoperatively with diascopy using Siemens Cios Alpha® (Siemens, Munich, Germany) (average exposition parameters: 50 kV, 0.05 mAs, and 5 fps); (**b**) patient three months after resection of 1st metatarsophalangeal joint and bioactive glass insertion. Image captured with Philips Digital Diagnost® (Philips, Amsterdam, The Netherlands) (exposure parameters: 70 kV and 2 mAs).

3.2. Midfoot

Out of the four cases in this group, three were reported to have Charcot neuroarthropathy and all had confirmed septic osteoarthritis. Table 1 shows their detailed characteristics, including significant concomitant diseases documented. In three cases, the procedure was single-phase with resection of affected midfoot bones, debridement of soft tissue, and placement of BAG granules; in one case, the procedure was two-phase, involving the placement of antibiotic beads and, in the second phase, BAG was applied instead of antibiotic beads. Figure 2 displays an example of a single-phase procedure with extensive resection of the midfoot bones due to osteitis. At least three weeks of intravenous antibiotic treatment was received in the perioperative phase. In three cases, an external fixator was used. None required revision during the 30-day period postoperation or suffered early complications. Additionally, no late complications in terms of recurring osteomyelitis or septic osteoarthritis requiring operative management were observed.



(**a**) (**b**)

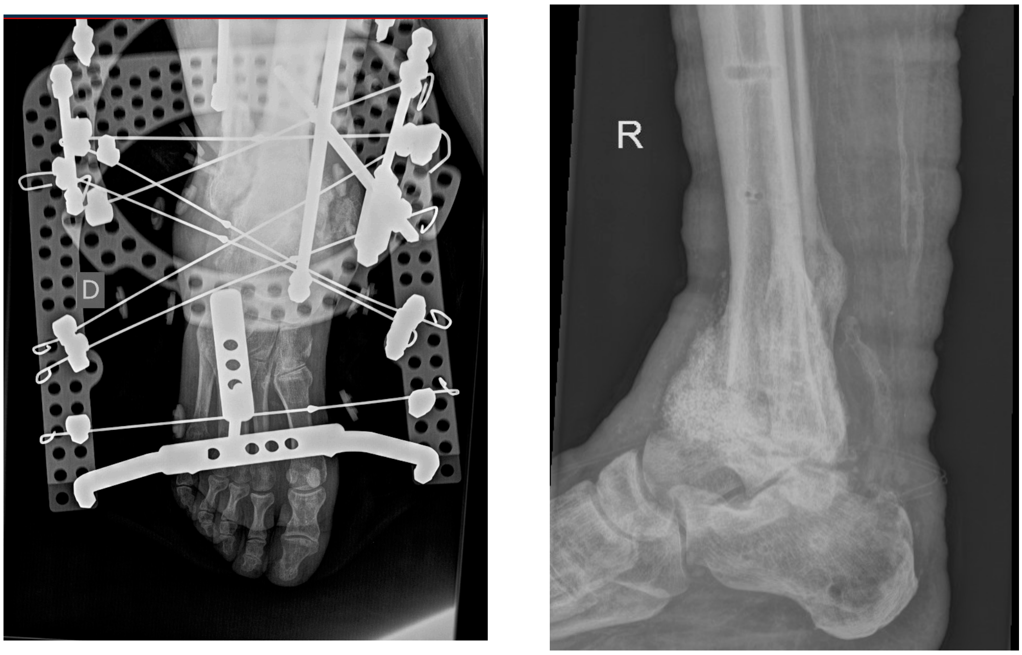
Figure 2. (**a**) Intraoperative X-ray—resection of cuboid bone, base of 4th and 5th metatarsal bones as well as head of talus due to osteitis, placement of bioactive glass granules, and an external fixator. Image captured intraoperatively with diascopy using Siemens Cios Alpha® (Siemens, Munich, Germany) (average exposition parameters: 52 kV, 0.03 mAs, and 7.5 fps); (**b**) patient three months after resection and bioactive glass insertion. Image captured with Philips Digital Diagnost® (Philips, Amsterdam, The Netherlands) (exposure parameters: 63 kV and 2 mAs).

3.3. Ankle

Out of the four cases presented in this group, three were reported to suffer from Charcot neuroarthropathy and all had confirmed septic osteoarthritis. Table 1 shows their detailed characteristics, including significant concomitant diseases documented. For two patients, the procedure was single-phase, with resection of the affected bone and joint and insertion of BAG in the form of granules and putty. One patient received multiphase surgical treatment and, in the ending phases, the application of BAG into the talocrural and subtalar joint and an external fixator. In all patients, an external fixator device was used; in two cases, an Ilizarov round fixator was used. Figure 3 demonstrates the use of an Ilizarov fixator and intraoperative placement of BAG granules and putty as well as the extent of osteointegration in the talocrural joint after eight months.

The same three patients received at least six weeks of concomitant antibiotic therapy. The mentioned three patients suffered no early or late complications.

The fourth patient suffered late complications. The patient suffered from Charcot neuroarthropathy. Initially, septic osteoarthritis of the ankle was treated in two phases. First, resection of the ankle joint was performed with placement of a gentamycin bead chain as well as placement of an external fixator. After three weeks, the gentamycin bead chain was replaced with BAG granules and putty. According to the antibiogram, they received intravenous antibiotic treatment for three weeks and additionally another six weeks perorally. They were discharged one month after surgery and checked up every month for three months. However, for the next three months, the patient skipped planned checkups. Seven months after surgery, they came back with a fistula at the lateral ankle side. They rejected hospitalization and were urgently admitted four months later with signs of systemic infection and *Staphylococcus aureus* sepsis. Lifesaving supramalleolar amputation was performed. Subsequently, the patient was treated in a surgical intensive care unit. After stabilization and resolution of systemic infection, a below-knee amputation was performed with primary closure of the stump, the postoperative wound being without signs of infection and healing as per primary intention.



(**a**) (**b**)

Figure 3. (**a**) Patient after insertion of bioactive glass granules and putty (malleolus) with an Ilizarov external fixation device. Image captured with Siemens Polydoros SX80® (Siemens, Munich, Germany); (**b**) patient after removal of Ilizarov external fixation device (eight months after insertion of bioactive glass granules and putty). Image captured with Philips Digital Diagnost® (Philips, Amsterdam, The Netherlands) (exposure parameters: 68 kv and 4 mAs).

4. Discussion

The benefits of the use of bioactive glass in infections of bones and joints have been described in several studies, including larger-scale systematic reviews [19,20]. A review by Bigoni et al. assessing eight clinical studies exploring the use of BAG in the setting of osteomyelitis found BAG to be an appropriate material for use in the setting of osteomyelitis with varying location, causation, and therapeutic strategies employed before its application. Notably, the review reported promising results despite variance in the stages of procedure and indication, location, and other aspects of the underlying pathology [19]. A systematic review was performed by van Vugt et al. including 15 studies that aimed to evaluate different options of bone graft substitutes (including S53P4 BAG) and their clinical applications and efficacy. The review found promising results in terms of treatment of bone and joint infection as well as the role of bone graft substitutes in promoting bone growth. Due to the differences in study design and risk of bias, as well as the inclusion of different bone graft substitutes into consideration, the review did not yield generalizable results or conclusions in terms of BAG use [20]. However, none of the systematic reviews focused on diabetic foot pathology.

The use of BAG in the context of diabetic foot, and particularly in patients with Charcot neuroarthropathy, has seldom been described in previous reports in the literature. However, two previous observational retrospective studies focusing on patients with diabetic foot pathologies complicated with infections have reported beneficial results with BAG.

De Giglio et al. reported 44 patients with diabetes mellitus and diabetic foot pathology, of which 22 received standard treatment with surgical debridement and 22 also received an application of BAG. The group who received the intervention had a higher rate of osteomyelitis resolution and needed less antibiotic therapy. Three patients in the control group required reoperation, while none in the intervention group did, and one patient less required major amputation in the intervention group. Additionally, no systemic side effects of BAG application were observed [14]. Their study also presented more locations of diabetic foot osteomyelitis and osteoarthritis; however, no particular focus was placed on Charcot neuroarthropathy.

Iacopi et al. observed healing in 80% of the included 10 patients with diabetic foot osteomyelitis and osteoarthritis in different joints of the foot in the follow-up period of six weeks, with one patient requiring reoperation. As a secondary outcome, they reported a mean healing time of 34 days. The study reported no early hypersensitivity reactions, which is similar to that in our study, and one patient required surgical revision and amputation due to recidivant infection [13].

Additionally, our previous retrospective observational study with controls, performed in 2019 at the University Medical Centre Ljubljana, conducted on a population of 22 patients total, found potential benefits of using a single-stage procedure employing S53P4 BAG in comparison with a two-stage procedure utilizing a gentamycin antibiotic chain. All patients in the intervention group receiving BAG achieved complete remission of osteomyelitis and osteoarthritis, while complications were observed in the control group [8]. A notable difference from this report is that the listed study included fewer patients who received the intervention, as well as the fact that in this case series, patients with Charcot neuroarthropathy were also included, and the intervention was applied in different joints of the foot; the 2019 study primarily focused on the first metatarsophalangeal joint and first ray preservation.

A case series of six patients with diabetic foot bone and joint infection by Rodriguez et al. reported no residual infection after 24 months of follow-up. Healing and osteointegration was achieved in four patients; however, half suffered from postoperative complications, with two requiring reoperation due to vascular or soft tissue issues [16].

A case report by Godoy-Santos et al. detailed the multimodal treatment of a patient with Charcot arthropathy, including surgical debridement of the metatarsal bases, midfoot bones, and plantar calcanear prominence and BAG application. Here, the authors reported no recidivant osteomyelitis or septic osteoarthritis. Of note, an appropriate range of motion and osteointegration of the inserted material were reported [15]. Another case report, published by Panunzi et al., detailed particular benefits in treating osteomyelitis limited to the forefoot but caused by multidrug resistant bacteria, reporting success in preventing bone and soft tissue infection recurrence with a conservative therapeutic approach [21]. In our case series, microbiology isolates in patients with a successful recovery have also included multi-drug-resistant bacteria. This clinical finding, combined with in-vitro results, suggests that the material does not induce drug resistance [17], opening the possibility of using such materials as a beneficial therapeutic approach in resilient infections. However, to the best of our knowledge, no other published study or paper has focused on the use of BAG in Charcot neuroarthropathy.

The therapy of complicated infections of the diabetic foot remains a challenge. The International Working Group on the Diabetic Foot (IWGDF) provides guidance on options for conservative management and the necessity of a surgical consultation. Patients who are clinically stabile, are not systemically affected by infection, are not suffering from severe complications (such as widespread gangrene, gas gangrene, or compartment syndrome), and can be treated with an appropriate antibiotic do not necessarily require immediate surgical treatment. As per IWGDF guidelines, such patients can be treated with antibiotics for up to six weeks with regular reevaluation of the efficacy of treatment, and in case improvement is not noted within two to four weeks of optimal treatment, the therapeutic approach (surgical approach or substitution of antibiotic treatment) might have to be adjusted. The guidelines recommend consultation with a surgeon in cases of moderate to severe infection and complications [22]. If surgical treatment is employed, intraoperatively acquired samples can be used for guidance regarding appropriate choice of antibiotic as well as differentiation between contamination and significant infection. However, delayed surgical treatment in complicated infections or in the presence of necrotic tissue can cause additional exacerbation [22,23]. Treatment is complex, and there is a lack of clear consensus or evidence on strategies and advantages of surgical treatment. Of additional concern is the finding that while we may be under the impression that treatment strategies are rapidly improving, a recent systematic review and meta-analysis by Liu et al. showed that reamputation rates in patients with diabetes mellitus have not significantly decreased in the last 20 years, calling such beliefs into question [10].

In this retrospective case series, we detailed our experience with the use of S53P4 BAG in patients with septic osteoarthritis and osteomyelitis of the diabetic foot and complications related to Charcot neuroarthropathy in diabetes mellitus types I and II. We noted one case of recurrent septic osteoarthritis and osteomyelitis as well as delayed systemic infection. In others, limb preservation and conservation of function were noted. Additionally, early unplanned readmission and reoperation were avoided in all cases. No significant early complications were thus observed. In the follow-up period, good results were observed, without great divergence from other available reports in the literature focusing on this particular pathology.

The strengths of this series include the relatively large number of cases included. Additionally, the heterogenicity of cases demonstrates a wide array of potential scenarios in which this novel therapeutic approach can be considered, and the number of cases allowed for stratification according to affected site. Because the included patients were treated at a tertiary healthcare center, a large variety of diagnostic, therapeutic, and follow-up options were available, as well as experienced healthcare personnel, to ensure optimal management. This case series reports several therapeutic applications of BAG in the diabetic foot, where available evidence in the literature is scarce.

The limitation of our study is the diversity of the location of osteoarthritis and osteomyelitis in the included patients, in addition to the fact that the study was observational and not randomized.

According to our observations and previous reports in the literature, BAG use is promising in the surgical treatment of septic osteoarthritis and osteomyelitis, including diabetic foot infections, where management and preservation of limb integrity and function in the face of complication risks resulting in amputation remain a challenge. Because the available reports in literature are scarce and with the grade of evidence generally being lower, larger, prospective, controlled studies are necessary to further analyze the safety and efficacy of the treatment. Additionally, this treatment approach would need to be sufficiently examined in comparison with standard treatment approaches and other bone substitution alternatives.

5. Conclusions

The case series of 16 patients we presented shows a wide array of potential applications for the use of S53P4 Bioactive Glass that appear promising in diabetic foot surgery pertaining to septic osteoarthritis and osteomyelitis and in several cases in complications of Charcot arthropathy.

Bioactive glass was used in the preservation surgery of diabetic foot pathologies in osteomyelitis- or septic-osteoarthritis-affected metatarsophalangeal joints, midfoot, and ankle joints. The treatment strategy applied was conservative, with the aim of limb integrity and functionality preservation. There have been other studies showing promising results in the treatment of osteomyelitis in diabetic foot; however, further systematic research is warranted to clarify the specific indications and treatment protocol that would ensure the maximum efficacy of BAG use in diabetic foot patients.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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