

A Comparative Analysis of PMMA Versus CaP Titanium-Enhanced Implants for Cranioplasty After Decompressive Craniectomy

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Research Article

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Abstract

Objective

Numerous materials used for cranioplasty (CP) after decompressive craniectomy (DC) have been investigated to meet certain demanded key features, such as stability, surgical applicability, and biocompatibility. We aimed to evaluate the feasibility and safety of biocompatible calcium-phosphate (CaP) titanium-enhanced implants for CP compared to polymethylmethacrylate (PMMA) implants.

Methods

The medical records of all patients who underwent CP between January 1st, 2015, and January 1st, 2022, were reviewed. Demographic, clinical, and diagnostic data were collected before and after the CP.

Results

82 consecutive patients with a mean age of 52 years (range 22–72 years) who received either a PMMA (43) or CaP (39) cranial implant after DC were included in our study. Indications for DC were equally distributed in both groups, including middle cerebral artery infarction (35 cases), traumatic brain injury (24 cases), subarachnoid hemorrhage (15 cases), intracerebral hemorrhage (3 cases). Time from DC to CP was similar in both groups 143.8 ± 17.46 days (PMMA) versus 98.46 ± 10.37 days (CaP). The mean follow-up period was 34.9 ± 27.1 months. 13 procedure-related complications occurred in patients with PMMA, 6 in those with CaP implants ($p = 0.126$). Revision surgery with implant removal was necessary for 9 patients with PMMA implants, one in those with CaP implants. The probability of implant removal was significantly higher in the PMMA implant group ($p = 0.039$).

Conclusions

In the present study, a titanium-enhanced biocompatible CaP implant proved superior to a PMMA implant in terms of surgical site infection. This supports the idea of the biocompatible implant material with its ability for tissue integration.

Introduction

Cranioplasty (CP) after decompressive craniectomy (DC) is a neurosurgical procedure to repair resulting skull defects. Defect reconstruction was historically considered for cosmetic reasons [23]. More recent studies suggest a beneficial role for the patient's functional and neurological outcome [27, 30]. Both motor and cognitive function improve after CP due to cerebrospinal fluid hydrodynamics and cerebral blood flow changes [11, 15, 23]. Although the surgical procedure is relatively straightforward, it is associated with substantial cost and morbidity [38]. Complications include post-operative bleeding,

seizures, meningitis, surgical site infection (SSI), and bone flap resorption (BFR) [5, 9, 31, 37]. Uncertainty persists regarding the implications of the timing of CP in terms of complication rates and potential benefits [2, 3, 35, 39]. Materials for reconstruction of cranial defect ideally provide osteoinductive and osteoconductive properties to promote structural and functional restoration [25]. Autologous bone flap reinsertion is common after hemicraniectomy. Storage of the bone flap between craniectomy and CP is performed either intracorporeally (e.g., the patient's abdomen) or extracorporeally (i.e., by tissue banking) [21]. However, the benefits of autografting, including low cost, precise matching, and immunologic tolerance, are offset by the high risk of SSI and BFR [14, 16, 19, 20, 32, 33]. Alloplastic materials, such as polymethylmethacrylate (PMMA), polyetheretherketone (PEEK), polyethylene, titanium, and injectable/moldable calcium phosphate-based bone cement have been used as alternatives [4, 34, 36, 40]. Risk factors for SSI, implant exposure, and graft removal after alloplastic CP include inaccurate matching and poor bone and soft tissue integration [1, 22]. A large systematic review addressing alloplastics in CP reconstruction in 3591 adult patients found that PMMA implants had a higher infection rate (PMMA: 7.95%, all others: 6.05%), while PEEK was associated with a higher local complication rate (17.19%, all others 12.23%) and the highest ultimate graft failure rate (PEEK: 8.60%, all others: 5.52%) [24]. The stringency of data on the safety and complication rates of various materials used in CP is limited by a large diversity of study methods, clinical settings, and reported outcomes [36]. Nonetheless, studies agree that the failure risk of autografts is higher than that of allografts [14, 19, 20, 32, 33, 36].

With the developments of 3D virtual planning and computer-aided design and manufacturing based on individually computed tomography (CT), precisely-fitted patient-specific alloplastic implants are now available for reconstruction of the bony defect [25, 34]. By incorporating innovative osteointegrative, osteoconductive and osteoinductive biomaterials, these custom implants may alleviate the shortcomings mentioned above. A novel bioactive calcium phosphate (CaP) titanium-enhanced cranial implant by OssDsign (Uppsala, Sweden) has been shown to induce bone healing demonstrated by gene expression analyses and histology in patients with cranial defects [12]. These custom bioactive implants show potential for overcoming current issues with alloplastic implants, leading to improved patient care and outcomes.

Our study evaluates the feasibility and safety of biocompatible CaP titanium-enhanced implants for cranioplasty compared to alloplastic PMMA implants in CP.

Patients And Methods

Patients: All patients who received either a PMMA or a CaP cranial implant between January 1st, 2015, and January 1st, 2022, were included in our study. As standard of care, (SOC) patients subjected to CP before 2019 received PMMA implants and CaP implants from January 2020 onward. SOC remained unchanged. To account for difference in follow-up time, we performed a subgroup analysis of 20 patients from each group with a given one-year follow-up. Demographic, clinical, and diagnostic data were collected before and after the cranioplasty. Early (< 72 h) postoperative CT scans were used to evaluate the implant fit and occurrence of complications. Hemorrhage, CSF fistulas, seizures, implant loosening,

wound healing disorders and early SSI were defined as post-operative complications. Compromised implant fitment and failure of implant integrity were defined as intraoperative complications. Patients were either re-evaluated on an outpatient visit, or their relatives were contacted by phone to obtain an assessment of the evolution of the neurological status and potential complications after cranioplasty as a part of the clinical routine.

Implants for cranioplasty: All implants were designed from high-resolution (1.0-mm-thick slices) CT scans and returned to the surgeon for approval before production.

Mosaic-designed CaP titanium-enhanced were manufactured using a molding technique as described previously (OssDsign, Uppsala, Sweden) [13]. They are constructed by an inner titanium mesh to enhance stability and coated by a biocompatible CaP shell.

A porous fine-grained PMMA material characterizes the PMMA implants (Zimmer Biomet, Warsaw, USA). The porous structure has been designed to allow fibrovascular ingrowth and bony attachment, while its rigidity equals the skull bone [26] (Fig. 1).

Surgical procedure: Under general anesthesia, prophylactic antibiotics were administered 30 min before skin incision. The skin flap was elevated through previous incision lines, followed by dural exposure and baring of the bony edges of the skull defect to fit the implant. Dural tack-up sutures reduced the epidural space. The implant was fixed using 1.5-mm titanium screws and mini plates (Promedics, Düsseldorf, Germany). The temporal muscle was attached to a reconstructed temporal line through pre-formed holes. As a standard of care, a subgaleal drain was placed. The wound was closed in layers using single button sutures. All patients underwent standard postoperative care.

Statistics: Data analysis was performed using GraphPad Prism version 8.4.2 for macOS, GraphPad Software, La Jolla California USA, www.graphpad.com. Unpaired categorical and binary variables were analysed in contingency tables using Chi-Square and Fisher's exact test. Findings were reported as mean or mean \pm SD/SEM. Results with $p < 0.05$ were considered statistically significant.

Ethical approval: Patients were given written information about the procedures. Data analysis was performed retrospectively and anonymously. The ethical review board has been consulted. According to the local laws of Rhineland Palatinate, Germany (Landeskrankenhausgesetz §37) no formal approval and informed consent is necessary for such kind of retrospective analysis.

Results

Baseline characteristics: We included 82 consecutive patients who received either a PMMA or CaP cranial implant after decompressive craniectomy (DC). Forty-three consecutive patients received a PMMA implant between January 1st, 2015, and December 31st, 2018. Further, thirty-nine consecutive patients received a CaP cranial implant between January 1st, 2020, and January 1st, 2022. DC was performed mainly due to malignant medial infarction (MMI) (PMMA: 47%, CaP: 23%), traumatic brain injury (TBI)

(PMMA: 35%, CaP: 26%), subarachnoid hemorrhage (SAH) (PMMA: 12%, CaP: 38%), or intracerebral hemorrhage (ICH) (PMMA: 5%, CaP: 13%). There was no difference in sex (PMMA: 14 female (33%), 29 male (67%); CaP: 20 female (51%), 19 male (49%); $p = 0.067$) and age (PMMA: 51.23 ± 11.2 years; CaP: 53.03 ± 12.38 years; $p = 0.81$) in both groups. Similar numbers of patients received DC of either the left or right hemisphere. Time from DC to CP was comparable in both groups 143.8 ± 17.46 days (PMMA) and 98.46 ± 10.37 days (CaP) ($p=0.102$) (Table 1). Patients requiring persistent ventricular drainage due to hydrocephalus occurred equally in both groups PMMA: 14 (32.6%), CaP: 14 (35.9%); $p=0.818$). Patients with a ventricular-peritoneal shunt were not prone to higher numbers of infection or surgical complications.

Surgical procedure: There were no intraoperative complications related to the implant itself in both groups. Matching of the CaP implants proved to be superior as they retain partial modelability. A post-operative scan showed the near perfect fit of the implant without detectable offset or gaps (Figure 1).

Post-surgical complications: The mean follow-up period was 49.3 ± 22.8 months for the PMMA and 8.1 ± 4.9 months for the CaP implant group. After CP, procedure-related complications occurred in thirteen patients with PMMA implants (5 patients with epidural hematoma, 5 with seizures, 1 with early SSI and 1 with insufficient matching implant, one with CSF fistula) and in six patients with CaP implants (4 patients with hemorrhage, 2 with hemorrhage and seizures). (Figure 2A) SSI occurred immediately after surgery in 7 patients within one 1 year and 1 during the second year after CP with PMMA. No surgical site infection occurred after CP with CaP ($p=0.0025$), After PMMA implant CP, revision surgery with implant removal was necessary for nine patients (21.9%; $p=0.0157$). One patient with a CaP implant necessitated revision surgery with explanation due to skin atrophy developed by pathological head posture. No bacterial growth was detected on the implant itself. There was no statistically significant difference in the occurrence of post-surgical complications in both groups (68.4% versus 31.6%; $p = 0.126$). However, the PMMA implants were removed significantly more often than CaP implants ($p = 0.039$) (Figure 2B).

Subgroup analysis: 35 patients that received either a PMMA or CaP implant after DC were included in our subgroup analysis. 20 consecutive patients between January 1st, 2017 and December 31st, 2018 received a PMMA implant. Further 15 consecutive patients received a bioactive CaP implant between January 1st, 2020 and December 31st, 2020. DC was performed due to MMI (PMMA: 64%, CaP: 27.0%), SAH (PMMA: 14%, CaP: 47%), ICH (PMMA: 14%, CaP: 13%) or TBI (PMMA: 8%, CaP: 13%). During a follow-up of 12 months 8 procedure-related complications occurred in patients with PMMA implants (3 patients with hemorrhage, 3 with seizures, 1 CSF fistula, 1 implant dislocation), 3 in those with CaP (2 patients with hemorrhage, 1 seizure). Revision surgery with implant removal was required in 5 patients with PMMA, none in in those with ceramic implants within 1 year after CP surgery ($p<0.00365$).

Implant integration: After explantation, less integration was macroscopically observed in PMMA implants than CaP implants. Integration in bioactive implants was pronounced with the surrounding tissue rendering the implant hard to separate from the elated skin necessitating sharp dissection. The CaP implants showed an outstanding anatomical matching in the osteoclastic defect in this series due to their

computer-assisted design and partial modelability (Figure 3). MRI images 6 month after implantation showed good integration and vascularization of the covering skin flap (Supp. Figure 1).

Discussion

The present study provides evidence that implants with osteoconductive and osteoinductive properties can reduce the risk of SSI and the rate of explantations after CP compared to allogenic materials (PMMA). There was no difference in surgery-related complications between the two implant types in our study.

The optimal timing of CP to minimize complications has yet to be established. Some favor early (within 12 weeks) and ultra-early (within 4 weeks) CP [11, 19, 23]. Early CP has been associated with lower infection rates and lower probability of developing hydrocephalus, although some authors reported that timing had no influence and have observed similar SSI numbers [17, 23]. In our study, CP was performed at 122.2 ± 96.37 days after DC. The time span did not differ between both groups. Continued research will show if the timing of CP should be adapted to the chosen implant material.

Titanium-enhanced biocompatible CaP implants comprise a ceramic compound containing monetite, β -calcium pyrophosphate (PPi), β -tricalcium phosphate, and brushite [13]. These ceramics have chemical resemblance to the osteoconductive and osteoinductive elements in native bone. While osteointegration has been defined as load-bearing integration without loosening, osteoconduction facilitates bone growth on a particular surface [29] and osteoinduction encompasses processes leading to the differentiation of undifferentiated osteoprogenitor cells to osteoblasts [22, 25].

Gene expression analysis in bioactive CaP implants has detected osteoblastic activity and bone formation at nine months after CP [12, 13]. In large animal models, bioactive ceramics are better promoters of bone formation, remodeling, and osteointegration than titanium implants [13]. We found that the integration of the bioactive ceramic implant as seen in one patient after explantation proved superior to PMMA implants. This observation adds proof to the previously published *in vitro* and animal data. Only one patient required explantation of the bioactive ceramic implant. Osteointegration is also observed with PMMA in animal models [6]. However, it is much less pronounced and matter of ongoing research using different porosities and additives such as strontium containing borate bioactive glass to improve upon this property [6, 10].

Much is yet to be learned about the safety and efficacy of bioactive CaP, among others, as CP implant materials. Despite the early paucity in literature, PEEK CP seems to be associated with lower post-operative complication rates compared to autografts, and with lower implant failure rates compared with titanium mesh implants [28, 34]. Previous studies indicate that infection and complication rates in CP with bone cement are substantially higher, while titanium-based implants impair follow-up imaging, and that ceramics and PMMA have similar complication profiles but differences in cost and availability [18]. We observed no statistically significant difference in postsurgical complications such as hemorrhage, CSF fistulas and seizures. However, the necessity for explanation of PMMA implants was higher in the

entire cohort, as well as in a subgroup analysis with a given 1 year follow-up. As there is currently no other published literature comparing bioactive CaP implants with alloplastic materials, it remains to be seen how these implants will ultimately reduce complication and implant failure rates and improve clinical outcomes [26]. Prospective clinical trials in this field are difficult to establish due to a tremendous variability of techniques and applied materials. However prospective registries (e.g. German Cranial Reconstruction Registry) bear the potential of longitudinal multicentric analyses with homogenous datasets [14, 31].

In contrast to alloplastic implants, surgical dissection of ceramic implants was much difficult due to substantial integration with the surrounding tissue [12, 13]. Extensive adhesions necessitated sharp dissection from the covering skin flap. This seems to further support the potential for improved implant stability and reduced probability of dislocation. It is also of note that despite contamination of the atrophic skin dehiscence, no bacterial contamination was found on the underlying ceramic implant. Implant-associated infections involve biofilms that are challenging to eradicate [8]. Despite biofilm-active antibiotic therapy, implant removal is necessary in most cases [7]. It is possible that antimicrobial treatment will be more effective in bioactive implants. Strong osteointegrative properties also relate to vascularization and soft tissue coverage, and an excellent soft tissue coverage due to robust osteointegration, promotion of vascularization, and tissue ingrowth via multiple interconnected spaces should facilitate improved wound healing, prevention of atrophy, and, with them reduced risk of SSI [13].

There was no difference in rates of post-surgical complications such as epidural hematoma or seizures. This is not unexpected, as the main osteointegrative, osteoconductive and osteoinductive advantages of the novel bioactive compound come to bear over time without immediate impact on the post-surgical course [12, 13]. As always, caution is a prime requirement when drawing conclusions from results in small patient groups. Further research will show if these promising results can be confirmed. Although follow-up in the present study was adequate, late implant-associated infections are known [14, 19]. More extended follow-up periods should determine whether bioactive CaP implants retain their advantages regarding infection and clarify the treatment strategies.

Conclusion

In our study, bioactive CaP implants showed lower rates of SSI requiring explantation. Vigorous osteointegration may be a key factor in implant durability and improved wound healing capability.

Declarations

Funding: No funding has been received in favor of this study.

Conflict of interest/competing interests: The authors declare that there is no conflict of interest regarding the publication of this paper.

Availability of data and material: All data are available from the corresponding author on reasonable request.

Code availability: Not applicable.

Ethical approval: The ethical review board has been consulted. According to the local laws (Landeskrankenhausgesetz §34) no formal approval and informed consent is necessary for such kind of retrospective analysis.

Consent to participate: Not applicable

Consent for publication: Not applicable

Authors' contribution:

DW: Data acquisition, data analysis, manuscript writing

HK: Data analysis, manuscript writing, literature review

MO: Data acquisition

MJ: Data acquisition

FR: Project supervision, manuscript editing

NK: Project supervision, data analysis, manuscript writing, literature review

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Tables

Table 1: Baseline demographics and patients characteristics

	PMMA	CaP
Study population (No of patients)	43	39
Mean age (SD)	51.2 (11.2)	53.0 (12.4; p=0.815)
Sex (p)		
Female	15	22 (p = 0.067)
Male	28	17 (p = 0.067)
Diagnosis (nb of patients (%))		
MCA infarction	20 (47)	9 (23)
SAH	5 (12)	15 (38)
TBI	15 (35)	10 (26)
ICH	2 (5)	5 (13)
Others	1 (2)	
Side of decompression		
Right	25	18
Left	18	21
Time to CP in days (SEM)		
	143.8 (17.46)	98.5 (10.37)

Figures

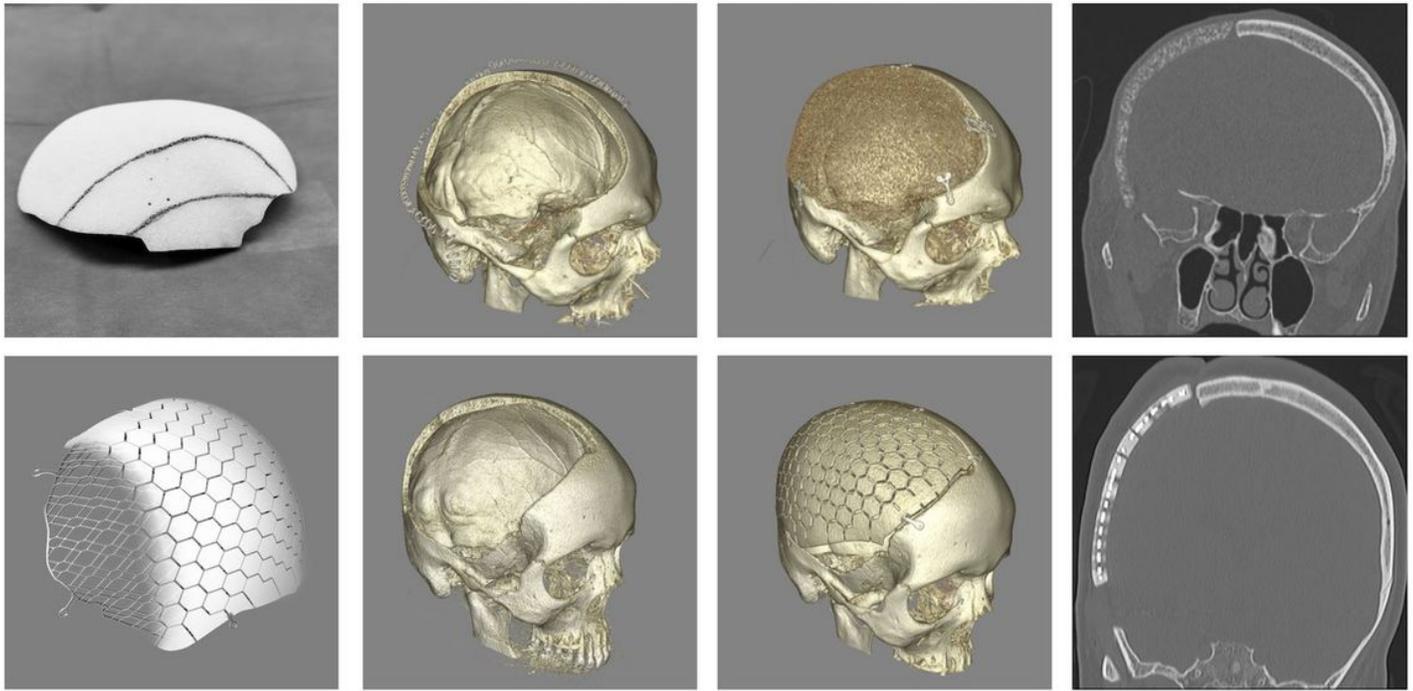


Figure 1

PMMA implant (A) and bioactive CaP implant (B) Ceramic implants provided a superior matching of the craniectomy defect.

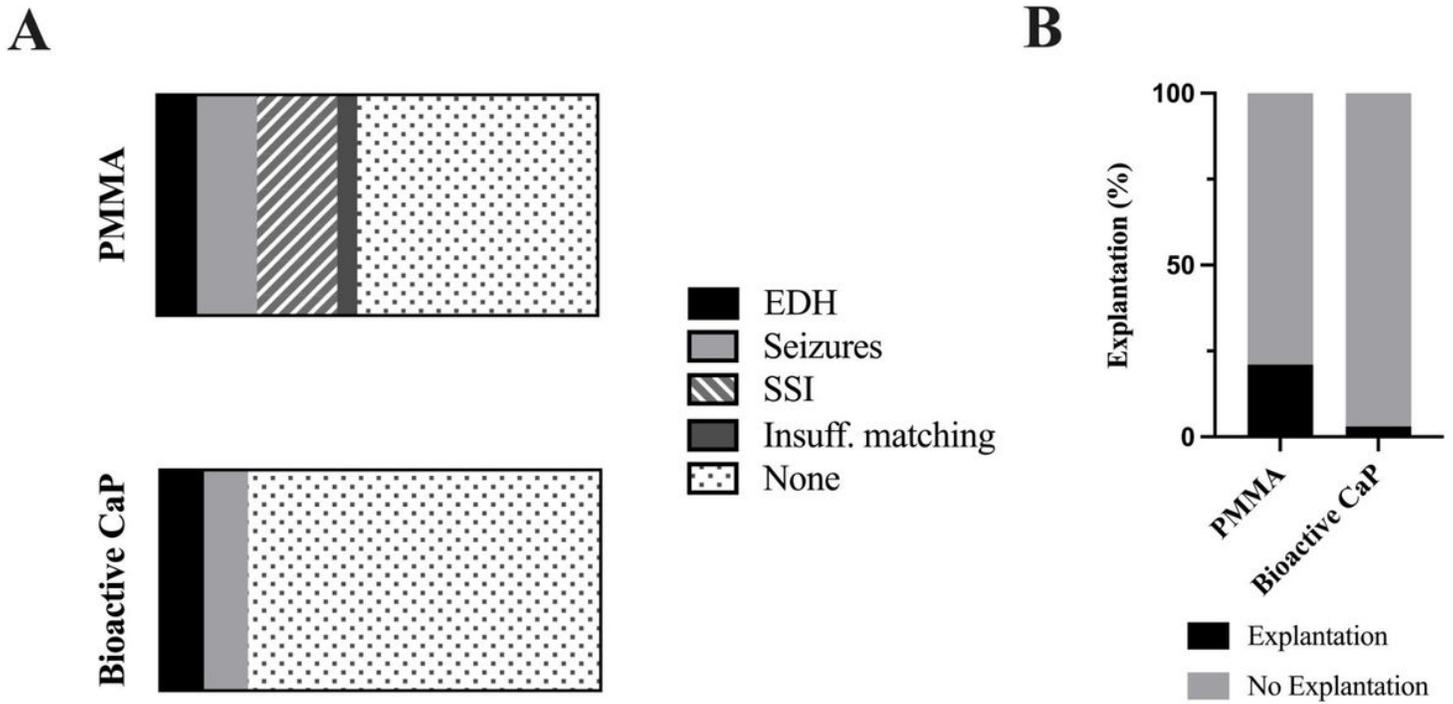


Figure 2

Post-surgical complications after cranioplasty (A). Implant explantations due to SSI during follow-up (B).

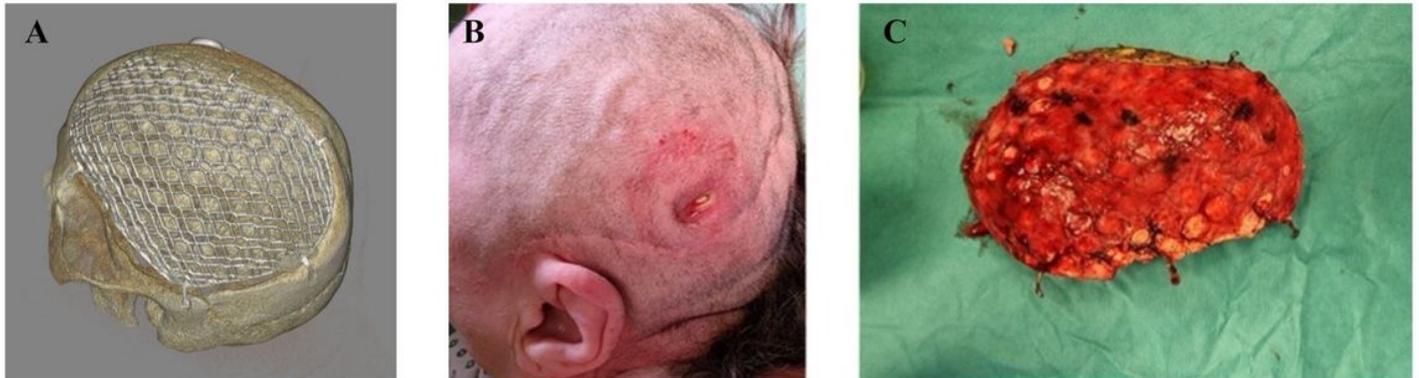


Figure 3

CT scans (A) prior to the explantation of a bioactive ceramic implant due to contaminated atrophic skin lesion from pathological head posture leading (B). No bacterial infection was detected on the implant itself. The implant showed signs of strong osteointegration with the surrounding tissue (C).

Supplementary Files

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