Editorial

Emerging applications of 3D printed microporous prosthesis in nonunion repair: mechanisms and therapeutic potential

Erika Denour[1,2]^, Samantha Lewis Eyen[1,3]

[1]College of Dental Medicine, Columbia University, New York, NY, USA; [2]Department of Molecular Pharmacology, Physiology, and Biotechnology, Brown University, Providence, RI, USA; [3]College of Engineering, The Ohio State University, Columbus, OH, USA

Correspondence to: Erika Denour, MS. College of Dental Medicine, Columbia University, New York, NY, USA; Department of Molecular Pharmacology, Physiology, and Biotechnology, Brown University, Providence, RI, USA. Email: ed2902@cumc.columbia.edu.

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Despite the exceptional regenerative capacity of bone, non-healing fractures result in continuous pain, functional limitation, and psychosocial concerns. These fractures, termed nonunion, can result in long-term bone defects (1). The Food and Drug Administration (FDA) defines nonunion as a fracture persisting for at least nine months with no evidence of healing for three months (2). As a persistent clinical issue, it is estimated that over 2.2 million bone graft surgeries are performed globally to repair non-healing bone defects (3). While a variety of classifications exist for such fractures, the Weber and Cech system is the most accepted; it categorizes nonunions by radiological response and bone quality into viable and non-viable nonunions determined by biologic activity (1). As successful management depends highly on the type of nonunion and the ability to stabilize the fracture, permanent failure of healing bone and internal fixation present unique clinical challenges for surgeons (1).

To complicate treatment planning further, no evidence-based consensus on the management of nonunion fractures currently exists. Traditional repair methods for such fractures include distraction osteogenesis (Ilizarov technique), Masquelet's induced membrane technique (MIMT), vascularized fibular graft, and the use of titanium mesh. While these methods have been regarded as the gold standard for many years, they each present unique disadvantages (4). Additionally, many of these treatments rely on bone-bone fusion with repair through bilateral bone integration (5). However, post-surgical sites vulnerable to load-bearing can severely compromise successful long-term bone-bone fusion in such cases (6,7). While the Ilizarov method has been considered an optimal treatment, drawbacks of the technique present clinical complications due to the long healing process which relies on patient immobility (5).

Bone grafting is commonly utilized in conjunction with these treatments to stimulate bone healing in large bone defects. Autologous bone-grafting sourced from the iliac crest has been recognized for its superior osteoconductive, osteoinductive, and osteogenic properties. However, this technique is time-consuming and subject to donor site morbidity, leading to clinical failure if the osteogenic elements fail to survive transplantation (8).

MIMT has been effective in managing difficult cases with large bone defects, utilizing a two-step approach. The injured bone is stabilized with a fixation device and subsequently filled with a polymethyl methacrylate (PMMA) spacer, stimulating the formation of a foreign-body membrane.

^ ORCID: 0000-0001-7648-6850.

After the PMMA spacer is removed in the second surgical phase, morselized bone is grafted into the compartment (9). Unfortunately, MIMT often requires multiple surgical interventions due to frequent donor-site morbidity (6,7). Additionally, the method necessitates sourcing a large amount of bone grafting materials in a titanium mesh susceptible to postoperative complications (6,7).

While some authors propose scaffold-based methods for repair of large bone defects, these techniques are also limited by a lack of standardized protocols and the need for autogenous or allogeneic bone grafting material (1). Recently, researchers suggested using 3D printed implant alloy Ti6Al4V for repairing bone defects, as the porous design of the alloy promotes osseointegration. Zhang *et al.* proposed an implant-bone interface fusion through an electron beam melting method in an animal model attempting to evade the limitations of traditional gold standard techniques (3). This methodology utilized a one stage approach to implant-bone fusion, as bone generated bilaterally across the porous implant with promising results (3). The authors noted radiographic evidence of bone growth through the porous implant and a mineralized callus bridging the implant's outer surface. Histology substantiated the growth of bone into the porous implant, yielding implant-bone interface fusion as opposed to growth through the implant resulting in bone-bone fusion (3).

Thus, the porous nature of 3D printed implants offers a valuable and effective option for the treatment and reconstruction of humeral bone defects due to their ability to compensate for deficiencies of these conventional treatment options. Most recently, Qiu *et al.* expanded on the animal model initially proposed by Zhang *et al.* in their article "Novel application of 3D printed microporous prosthesis to repair humeral nonunion with segmental bone defects: a case report" (4). Qiu *et al.* presented the use of a 3D printed Ti6Al4V microporous prosthesis in the treatment of a 9.5 cm humerus shaft bone defect following internal fixation failure in a middle-inferior humerus fracture (4).

Accounting for approximately 5–8% of fractures (10), humeral shaft fractures are subject to nonunion in approximately 10% of patients regardless of treatment type (11). The authors propose a technique that allows for enhanced mechanical strength to support the rehabilitation of a patient-specific defect with the advantages of early mobilization and weight-bearing capability (4). In this specific case, the large bone defect was localized in the mid and distal humerus, requiring bone reconstruction in both cylindrical and flat portions of the defect, respectively. The 3D printed prosthesis provides a customized approach to addressing the patient's unique anatomical morphology while promoting a favorable biomechanical environment for bone trabeculae growth.

Two months following an open reduction and internal fixation attempting to repair the 9.5 cm humerus defect, radiographs revealed a humeral nonunion (4). Clinical examination nine months postoperatively revealed two broken screws at the distal end of the humerus, insufficient bone mass mid-humerus, and osteosclerosis at the fractured site. Internal fixation removal and debridement of nonviable bone and fibrous tissue occurred in the first stage of treatment, along with the placement of two external fixation screws on the humeral condyle and two on the proximal end. The PMMA cement spacer placed into the defect region approximated the original shape of the bone while allowing membrane formation and bone regeneration over the course of six weeks.

The 3D printed Ti6Al4v prosthesis was designed as a "prosthesis-intramedullary nail lateral plate" integrated implant with a homogeneous porous structure with 70% porosity. This medical-grade titanium alloy offers a comparatively lower elastic modulus, capable of more effectively transferring stress at the interface (12). The Ti6Al4v prosthesis was implanted into the induced membrane during the second stage of surgical treatment, following a three-month rehabilitation period after the first stage of surgery. At this time, the external fixation and cement spacer were removed with no signs of postoperative complications. To ensure long term prosthetic stability, screws were inserted into the lateral plates following tissue debridement of the fracture.

During the first two postoperative months, rehabilitation included partial weight training of the affected limb. Full weight-bearing physical training was encouraged after this period. Prosthesis integration and limb reconstruction were monitored with periodic radiographs and CT scans, revealing callus formation at the sites of implant-bone interface at 7- and 18-month follow up. Radiographic interpretation indicated a progressive narrowing of the space between the distal prosthesis and the bone, confirming osteogenesis. Additionally, the patient reported restored upper limb function with no postoperative complications. Post-surgical outcomes were further evaluated using the Mayo Elbow Performance Score (85 points) and the Disabilities of the Arm, Shoulder, and Hand (17.5 points) assessments (4).

One clear advantage to utilizing the 3D printed prosthesis method proposed by Qiu *et al.* is the ability for the patient to resume weight-bearing exercises shortly after surgical treatment. On the second day after surgery, the patient began rehabilitation exercises that promoted osseointegration at the bone-implant interface due to axial stress stimulation (4). The personalized treatment approach implemented in this case study offers a promising strategy in the treatment of humeral nonunion fractures and also contributes more broadly to the future of individualized medicine. With further research and surgical refinement, this strategy may be applied more broadly to different surgical sites, types of defects, and clinical criteria. Similar 3D prosthetic strategies are used to treat other anatomic locations which appear clinically useful in addressing bony defects with irregular morphology. Hou *et al.* recently treated five patients with segmental irregularly shaped femur defects greater than 8 cm due to trauma or infection with a customized 3D printed titanium implant (13). Results demonstrated local osteogenesis at the implant-bone interface with sufficient osseointegration without bone grafting. Factors contributing to osseointegration include appropriate pore size and the ratio of prosthesis size to previous bone configuration. Additionally, osteogenic, osteoinductive, and vascular properties of the induced membrane should be considered (13).

Gaillard *et al.* recently utilized an induced-membrane technique for two-stage surgical repair of a refractory humeral nonunion (10). The authors discussed that the induced-membrane technique supports bone healing by stimulation of the following well established growth factors: bone morphogenetic protein 2, transforming growth factor beta, vascular endothelial growth factor, Von Willebrand factor, interleukin-6, interleukin-8, collagen type 1, stroma-derived factor-I, angiotensin-2, fibroblast growth factor 2, and prostaglandin E2 (10). Similarly, future research can focus on analyzing the benefits of adding growth factors to the microporous structure of 3D printed implants to assess osteoinductive potential.

Surgical treatment of nonunion fractures requires meticulous surgical technique and considerable preoperative planning. Given the custom nature of 3D printed implants, further research is necessary to establish long term quality control measures for the use of 3D printed prosthetics in nonunion repair. Qiu *et al.* noted the need for long term follow-up to accurately assess postoperative complications as one limitation of their case study (4). While bone ingrowth was observed in the contact area between the bone stump and prosthesis, the authors suggest that long term follow-up should include assessment of bone in growth in the middle portion of the prosthesis (4). Additionally, the authors noted that the personalization of fabricating a 3D printed prosthesis focuses more on bone defect morphology rather than internal structure, suggesting that future development of 3D printed prosthetics should focus on replicating biomechanical properties of original bone (4). While the use of patient-specific 3D printed implants provides a more personalized approach to treating nonunion fractures, widespread application of these methods is limited due to expensive equipment costs which may not be feasible for all surgeons and institutions (14). Additionally, regulatory impediments regarding regulation and implementation pose one of the greatest barriers to the widespread use of 3D printed prosthetics. The European Union classifies 3D printed prosthetics into the EU Medical Device Directive annex XIII. Some researchers have established in-house regulatory guidelines for the development pathway of using 3D printed prosthetics in semi-urgent situations (12,15).

Due to the emerging clinical interest in using 3D printed prosthetics in the United States, the FDA has developed guidance for technical considerations of additive manufacturing of medical devices (16). While frequently referred to as "customized," these prosthetics do not qualify for the Special Custom Device Exemption Act which permits the use of custom-made devices for patients with rare and unique pathology contraindicating gold standard treatment (12). The FDA concluded that 3D printed implants are required to meet the same regulatory standards as traditionally manufactured implants. The guidelines require detailed documentation of chemical specification of additive manufacturing starting material, including particle size and viscosity, as well as certificates of analysis for all materials utilized (16). Additionally, the FDA mandates adequate documentation of machine calibration and maintenance parameters. The report emphasizes that all post-processing steps should be documented, as well as potential effects of the post-processing on the 3D printed materials. For example, techniques such as Hot Isostatic Pressing have the potential to reduce metal porosity, yield strength, and elastic modulus while increasing fatigue life of the material (16). Some authors suggest validating design safety by demonstrating patient and prosthesis compatibility using 3D modeling software for virtual surgery (17).

Despite the extensive regulatory requirements, several large-scale 3D printed orthopedic implants have been approved by the FDA in recent years (18). For example,

Additive Orthopaedics recently received approval for the Bone Wedge System, a porous titanium wedge that provides an alternative to bone grafting for cotton osteotomy procedures (19). Likewise, Stryker's Spine Division also received approval for the use of Tritanium C Anterior Cervical Cage, a highly porous 3D printed titanium material designed for bone ingrowth and biological fixation in cervical spine surgery (18). Some researchers focus on dental applications of patient-specific maxillofacial implant prototypes using metal fused filament fabrication (20). Similar to other authors, Shaikh *et el*. Note that limited regulatory information for manufacturing AM-printed Ti6Al4V implants acts as a barrier to widespread use of such prosthetics in oral and maxillofacial surgery (20). While further research is necessary to establish well-designed standardized protocols for the use of 3D printed implants in nonunion fracture surgery, Qiu *et al.* propose a clinically viable approach that highlights the potential of 3D printed implants in the reconstruction of bone defects.

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