Three Dimensional Printed Bone Implants in the Clinic

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Abstract: Implants are being continuously developed to achieve personalized therapy. With the advent of 3-dimensional (3D) printing, it is becoming possible to produce customized precisely fitting implants that can be derived from 3D images fed into 3D printers. In addition, it is possible to combine various materials, such as ceramics, to render these constructs osteoconductive or growth factors to make them osteoinductive. Constructs can be seeded with cells to engineer bone tissue. Alternatively, it is possible to load cells into the biomaterial to form so called bioink and print them together to from 3D bioprinted constructs that are characterized by having more homogenous cell distribution in their matrix. To date, 3D printing was applied in the clinic mostly for surgical training and for planning of surgery, with limited use in producing 3D implants for clinical application. Few examples exist so far, which include mostly the 3D printed implants applied in maxillofacial surgery and in orthopedic surgery, which are discussed in this report. Wider clinical application of 3D printing will help the adoption of 3D printers as essential tools in the clinics in future and thus, contribute to realization of personalized medicine.

Key Words: 3D printing, bioprinting, personalized medicine, tissue engineering

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Bone defects may result from congenital disorders, or they may follow trauma, disease, or surgical resection. They need reconstruction to resume function and restore shape. The gold standard of reconstructing bone defects has been the use of bone grafts.[1] However, these suffer from limited availability, donor-site morbidity, and associated risks.[2] Bone substitute materials were thus developed to reconstruct bone defects but they suffer from limited success due to failure to integrate and remodel, infection,[3] inflammation, and pain.[4] With the advent of tissue engineering, it was hoped that living grafts can be made in the laboratory by using cell-seeded scaffolds.[5] However, it was difficult to produce scaffolds with controlled structure and homogenous cell distribution.[6] The technique of three-dimensional (3D) printing was originally invented in 1986[7] and was later used to produce scaffolds with controlled structure.[8] Furthermore, cells mixed with a biomaterial to form bioink for 3D bioprinting in which cells can homogeneously be distributed in the resulting constructs.[9] In the reconstruction procedures of complex craniomaxillofacial (CMF) skeleton, with irregular defects, it is difficult to adapt available implants, and thus, the fabrication of patient-tailored devices is needed. With the use of 3D printing, the production of customized implants becomes achievable. Although the technology has been proved in many studies in vitro[10–16] and in vivo[17–19] employing various types of biomaterials, its translation to the clinic has not advanced with the same pace because of many reasons, including the lack of efficacy and complicated approval procedures.

EVOLUTION OF 3D PRINTING

3D Printing

For 3D printing, various types of biomaterials were used including metals and polymers. To render 3D constructs osteoconductive,[20] ceramics such as hydroxyapatite,[19,21–23] tricalcium phosphate (TCP),[17,24] biphasic calcium phosphate,[18,24,25] nano-silicate,[26] silica, and bioactive glass[27] were used. The use of biodegradable materials alleviated the problems and risks associated with the use of biostable materials such as infection, cold sensitivity, interference with imaging, risk of pseudomigration, problem in the growing skulls of children, and restriction of growth.[28,29] In addition, biodegradable materials can be combined with growth factors,[30] cells, and drugs. The 3D biodegradable materials may be produced at the point of care in future because it can be a less demanding fabrication process as compared to 3D printing of metals.

3D Bioprinting

For bioprinting, gels are usually used to contain cells in a pregel liquid with subsequent gelation achieved by using crosslinking methods which can be chemical,[10,31–34] physical,[7,10,26,35] or combination of them, depending on the type of the material. However, using hydrogels[23,25,32,36,37] allows for fabricating of constructs with only limited number of layers, as the weight building up may lead to collapse of the structure. Thus, various support and reinforcement methods were employed such as the use of bioceramics,[32,38] nanofibers in the structure[39,40] (Fig. 1), struts,[42] or external polymeric frames or other temporary support.[17] Most 3D bioprinted biodegradable constructs last for only few weeks which may limit their application in the clinic. For example, gelatine methacryloyl constructs last for a maximum of 3 weeks on average because they are degraded.[26] Cell-laden silk fibroin gelatin constructs were unstable after 21 days. When modified with methacrylic anhydride, hyaluronic acid was found to last for almost 38 days[43] (Fig. 2). When bone-marrow-derived stem-cell-laden TCP-containing

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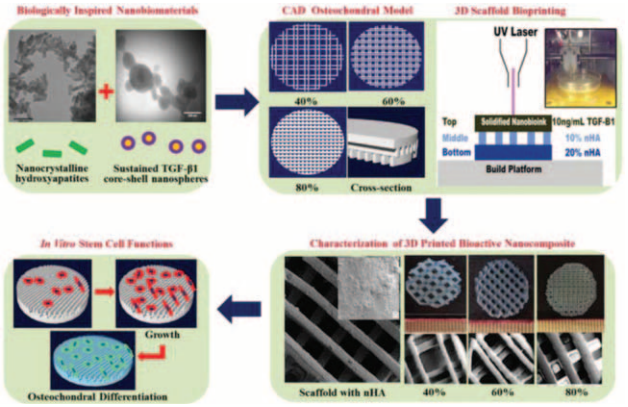

FIGURE 1. 3D printed composite osteochondral construct. Nanomaterials for human mesenchymal stem cell (hMSC) differentiation to osteogenic (using nano-hydroxyapatite, nHAp) and chondrogenic (using transforming growth factor-beta 1, TGF-β1 loaded polylactide-co-glycolide, PLGA nanospheres) cells. Computer-assisted design (CAD) model of porous construct. The construct was 3D printed via table-top SL. In vitro hMSC studies are also shown. Reproduced with permission from Castro et al.[41]

alginate constructs were studied, they were found to completely degrade within 6 weeks.[33]

TRANSLATION TO THE CLINIC

Most of translational studies that were performed so far have focused on the use of 3D printing for surgical planning rather than for producing therapeutic devices for surgical implantation (prostheses and implants).[44] Nevertheless, they demonstrated the usefulness of using 3D printing in improving understanding anatomy and the pattern of treated fractures.[45] Most commonly, 3D printing was applied in the area of CMF and in orthopedics.[44] However, efficacy and effectiveness studies as well as long-term trials on the use of 3D implants are needed.[44] These studies are essential to carry out to enhance the translation of this promising technology into standard clinical practice.

Orthopedics

There are few reports on the use of 3D printed implants in orthopedic surgery, but their clinical indications are expanding. In hip replacement, preplanned custom-made hip implant was possible

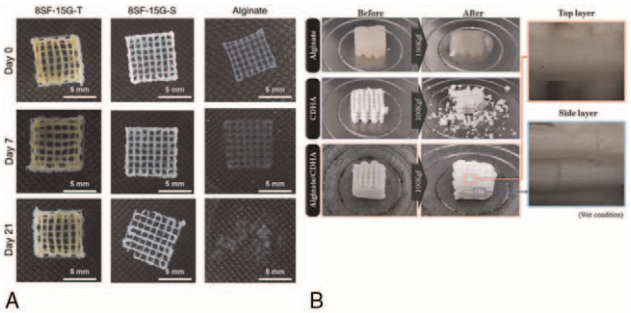

FIGURE 2. (A) Images showing long-term stability of 8% w/v silk-fibroin and 15 wt% of gelatin crosslinked with tyrosine (8SF–15G–T), or crosslinked with sonication (8SF–15G–S), as well as alginate (control) constructs in culture media. Reproduced with permission from Das et al.[10] (B) Images showing the results of compression tests compared to their appearance before testing. Constructs made of alginate, calcium-deficient hydroxyl apatite (CDHA), and CDHA/alginate core/shell scaffolds are shown. Reproduced with permission from Raja and Yun.[32]

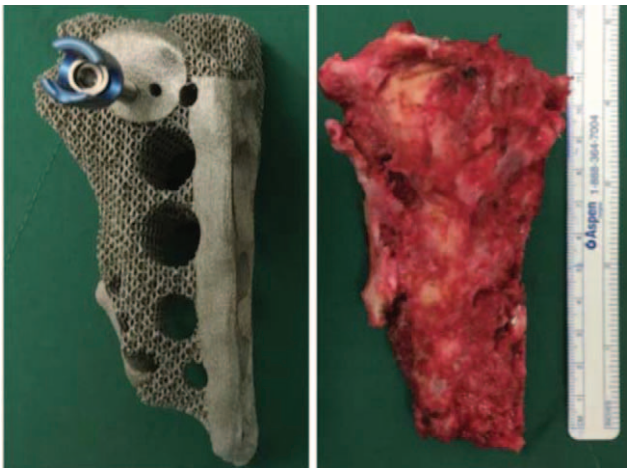

FIGURE 3. Image of 3D-printed custom made hemisacral porous construct made of titanium (A) resembling the shape and size of en-bloc resected left sacrum (B). Reproduced with permission from Kim et al.[47]

to develop and apply in a young patient with hip deformity while she was in her twenties because it was difficult to have standard hip implants work in her case.[46] This application represents an important step toward adopting clinical translation of 3D printing. Recently, 3D printed custom-made metallic implant was used for the reconstruction of sacral bone following hemisacral resection (Fig. 3).[48] In spinal surgery currently, 3D implants were used but long-term clinical results and evidence of positive clinical outcomes are required to be able to recommend the technology for use by clinicians.[49] Currently, there is an active prospective randomized clinical trial with the objective of comparing the use of either 3D printed implant to bone grafting and evaluating their surgical efficacy in the treatment of bone defects. It is estimated to complete the study by December 31, 2021 (Clinical trial # NCT03166917).

Oral Surgery

In a randomized controlled trial, 3D printed poly-ε-caprolactone (PCL) scaffolds were implanted into tooth extraction sockets and compared with test groups where no implants were used. After 6 months, there was significantly less resorption of the vertical ridge in treated group. However, micro-computed tomography (micro-CT) and histology of trephined specimens showed mineralized bone formation in both test and control groups (Fig. 4).[50] Despite encouraging results of this study, another report did not advise

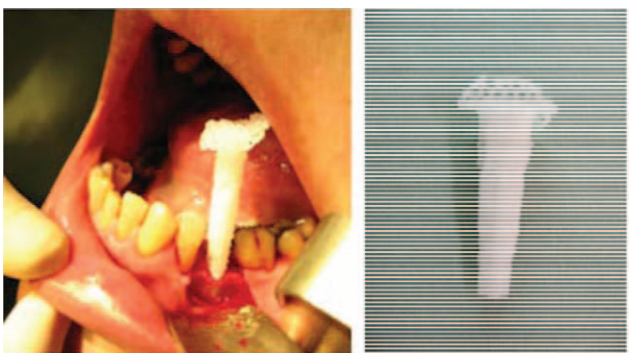

FIGURE 4. Poly-e-caprolactone (PCL) scaffold was trimmed off and used to fit into the socket of tooth extraction (A). Prefabricated 3D printed implant is shown in (B). Reproduced with permission from Goh et al.[50]

the use of PCL.[51] In this report, 3D printed PCL was used to treat large labial bone defect in the jaw of 1 patient. The CT-derived image was used as basis for 3D-printing of PCL constructs. Following 13 months, there was implant exposure and fragments of the implant had to be removed. Two weeks later, there was larger wound dehiscence and the whole implant was removed. It seems that PCL may not be a suitable polymer as it takes long time to degrade and resorb (the molecular weight of the polymer remained unchanged at 14 months postoperatively). There was only minimal evidence of bone repair.[51]

Maxillofacial Surgery

The first customized jaw implant was prepared by using laser melting technique of titanium particles. It was used to treat a jaw having progressive osteomyelitis that involved almost all of the jawbone. In the first postoperative day, the patient resumed normal speaking and swallowing. The implant also restored the patient's facial aesthetics.[52] In a recent study, Ahn et al[53] reported, for the first time on the treatment of alveolar a cleft defect with a patient-customized 3D-printed cell-seeded construct. In this report, a 10-year-old child having unilateral irregular cleft alveolus and oronasal fistula was operated on. A custom-made 3D printed construct made of PCL was used to treat the defect. The construct was subsequently seeded with bone marrow stromal cells taken from iliac crest of the patient. Seeding and implantation took place at the same surgical setting and no cell expansion step was needed, but only incubation for 20 minutes. After 6 months postoperatively, new bone formation in the treated defect was found to occupy ~45% of the total volume of the defect. Bone mineral density of the newly formed bone was found to be ~75% of that of the surrounding bone.

Another report involved a patient with rare disease of van Buchem which is associated with extensive bone thickening especially of the cranial bone.[54] She has lost her vision and started to develop impairment of motor coordination. It was anticipated that other essential brain functions will also be affected and will eventually die. Thus, surgery was indicated and a 3D printed cranial vault was used to reconstruct the skull. Three months postoperatively, the patient has fully regained her vision, and she had no more complaints.

CHALLENGES

Challenges with the use of 3D metallic implants remain mostly related to validation and approval of procedures to allow their wider clinical applications. As regards bioprinted constructs, cytocompatible materials, which can preserve their mechanical properties and shape for longer times enough to support bone healing, are needed. The other challenge related to 3D bioprinted constructs is the size limitation. So far, the size of produced bone constructs using 3D bioprinting is only few centimeters[17] and means to develop larger implants are needed. Lack of vascularization of implanted 3D constructs is another limitation[8,55] which may lead to death of cells in the construct because cells usually live on diffusion not farther than 200 μm from the circulation.[56] Vascularized 3D bioprinted bone constructs having endothelial cell lined network to mimic blood vessels were recently produced[26] to prove principle and need to be tested in vivo. In future, further developments should lead to the integration of implants with the native tissues following their implantation. In vivo and subsequent clinical studies are awaited to prove such integration and demonstrate how the challenge of vascularization can be overcome. In addition, 3D printed implants have to undergo complete testing and clinical trials to prove their safety and efficacy before they can be approved by regulatory bodies even if they are made of previously approved and used materials. The process can be costly and take time and this affects the timing when these products will become available for wider use in the clinics.

FUTURE

In future, exosomes can be used with cells or even instead of cells. It was recently claimed that the same effect that transplanted cells may have can be achieved by using their exosomes as shown, for example, in the heart.[57] There is growing evidence coming from animal studies.[58,59] In bone tissue, the application of exosomes or secretome is being applied to treat bone defects.[60,61] This will allow the avoidance of a second surgical procedure as well as associated complications and risks. In addition, it will lead to avoidance of the use of allogeneic cells and their problems. The technology can potentially be scaled up and be used as off-shelf therapy.

Nevertheless, in future, it would be great to have 3D bioprinting in the clinics. In addition, 3D printing can take place at the point of care and the procedure can employ new devices such as hand-held printers.[62] This will have a place in treating osteochondral defects, where debridement is needed and final shape of the defect cannot be determined preoperatively. Using bioprinting, it is also possible to build gradient of cells that may enable the reconstruction of osteochondral tissue. The bioprinters will become ultimately essential surgical tools in the hospitals. In addition, more advanced 4-dimensional (4D) printing is developing in which 3D bioprinting is employed to produce constructs with dynamic properties, that is, they can change their shape in a controlled predetermined fashion by the action of stimuli responsive materials that make their matrix or by the action of contained cells or by both.[63–65] The future will also involve the merging of 3D bioprinting with bioactuators and micro- and biorobotics. These will be helpful in the delivery of therapy, regenerative medicine, and making surgical procedures less traumatic (minimally invasive). The addition of sensors, cell fate tracking technologies, and data communication will complete the cycle of proper integrated therapy and open doors for wider integration of more disciplines to shape the future personalized medicine.

CONCLUSION

The 3D printing has been developed and it contributed to the development of training and surgical planning. The 3D printing has advanced to 3D bioprinting in which cells are included in the constructs, offering new possibilities to produce living implants. However, clinical application of 3D surgical implants has been so far very limited due to various challenges including approval procedures. It is important to develop personalized constructs especially for the treatment of complex CMF skeleton and it is envisioned that 3D printers will become essential tools in the clinics.

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