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Review Article

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Application Progress of Digital Science Based on Three-Dimensional Printing Technology in Orthopaedic Trauma

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Abstract

In recent years, the application of three-dimensional (3D) printing technology in orthopedics has become ever more in-depth, from simple teaching models, surgical guides, and implants to biological 3D printers, all showing the advanced aspects of 3D printing technology. Among them biological 3D printing, which combines 3D printing technology with tissue engineering and stem cell technology, has become the main research areas in 3D printing technology research, with precise control of the shape and internal structure of the scaffold and printing biomaterials and the inclusion of stem cells and/or other cells into the scaffold to provide 3D biological functions. This article summarizes results of 3D printing technology applied at different levels.

Keywords: Three-dimensional; Orthopaedic trauma; Biological 3D printing

Introduction

Three-Dimensional (3D) printing technology, known as rapid prototyping technology or additive manufacturing technology, involves the generation of a 3D solid model through the guidance of digital files converted into a 3D digital model to subsequently build the 3D solid model [1,2]. Three-dimensional printing technology is expected to be used to generate artificial bones with biological activity by virtue of their refined structure, good mechanical properties, and strong material simulation. In recent years, the medical application of 3D printing technology in orthopedics has also been developing rapidly and many major research and application results have been achieved. This article summarizes application results of 3D printing technology from different levels.

Application of 3D Printed Models in Orthopedic Trauma

In recent years, with the development of 3D printing technology, its applications in the medical field, particularly for artificial bones, prostheses, models, and orthodontic devices, have gradually become widespread. The digital medical 3D printing technology includes a variety of rapid prototyping and manufacturing technologies, which reconstruct the relevant 3D model from the accurate data of the human anatomical structure in the relevant medical image. At present, the 1:1 physical model manufactured by 3D printing technology is playing an increasingly powerful role in clinical teaching. The technology includes education, visualization, preoperative planning, program exercises, simulation, custom medical implant design, and tissue engineering [3,4] (Figure 1).

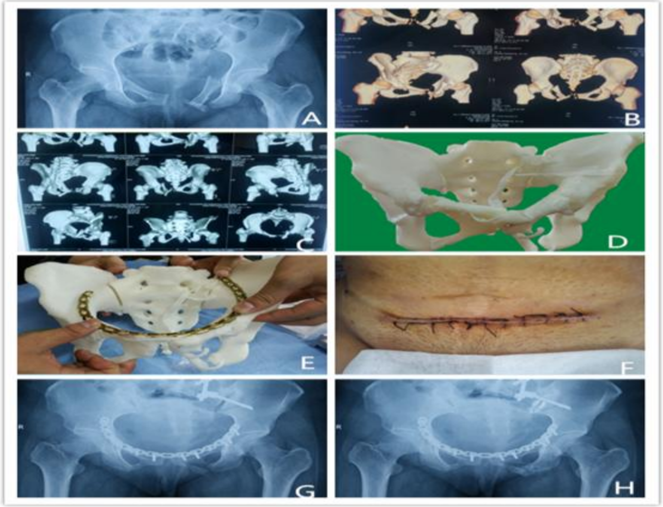

Figure 1: Application of 3D printed orthopedic models in trauma orthopedics. Patient information: Female, 23 years old, multiple injuries from car accident, Tile type B2 fracture of pelvis. A: Preoperative X-ray films; B: Preoperative THREE-DIMENSIONAL reconstruction; C: preoperative CT film; D: preoperative 3D printing model; E: Prebend the steel plate according to 3D model before surgery; F: Postoperative X-ray film.

In the printing of auxiliary materials for orthopedic surgery, the personalized osteotomy technology based on 3D printing has obvious advantages in the accuracy of osteotomy guidance. Prior to surgery, reference can be made to the anatomical landmark points on the patient's bone 3D model to plan the lower limb force line and rotation axis. At the same time, combined with the experience of the surgeon, a personalized osteotomy plan can be determined. The personalized extramedullary osteotomy guide plate designed and printed based on the osteotomy plan not only ensures an accurate osteotomy, but also simplifies the operation steps, which can further ensure the safety and postoperative results of knee replacement surgery [5-8].

Application of a 3D Printed Guide Plate in Orthopedic Surgery

Three-dimensionally printed orthopedic surgical guides are of great significance in the medical field, and they can improve surgical efficiency and accuracy. Such orthopedic surgical guides are mainly based on patient medical imaging data, including Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) scan results, and the use of digital software to reconstruct a 3D model of the region of interest [9,10]. Consequently, on the basis of specific clinical requirements and surgical approach, a navigation device with a guiding function is designed, and the fitting of the 3D reverse guide plate and the guiding device is established [11,12]. Finally, the 3D printing method and printing materials are determined according to the clinical needs, and the guide plate is printed and subsequently applied in the operation [13,14] (Figure 2).

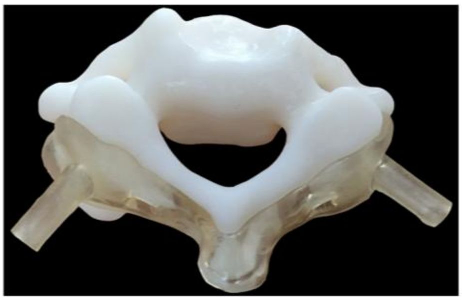

Figure 2: Implant nail guide plate with 3D printing. Photo provided by Anhui Zhongjian 3D Co., LTD.

At present, there are many types of orthopedic surgical guides in clinical practice. Osteotomy and nail guides among guides are used more frequently, as well as some other series of guides [15]. Different surgical guides have different clinical uses. The osteotomy guide plate is mainly applied in guiding the precise osteotomy of the operation. When considering Total Knee Arthroplasty (TKA) as such an example, traditional arthroplasty is mainly performed based on preoperative imaging data and intraoperative osteotomy guides. Therefore, it is normally difficult to achieve a precise intraoperative osteotomy. By contrast, when using a three-dimensionally printed personalized osteotomy guide plate, precise preoperative planning can be performed, which significantly reduces the difficulty of the intraoperative osteotomy. Bandyopadhyay et al. [16] compared 27 cases with three-dimensionally printed personalized osteotomy guides and 32 cases with traditional osteotomy methods during the operation. The operation time, intraoperative bleeding, and postoperative drainage were determined and the postoperative lower limb strength was measured. The line method proved that the application of a three-dimensionally printed personalized osteotomy guide plate in TKA can significantly shorten the operation time, reduce perioperative bleeding, and facilitate perioperative blood management. Feng et al. [17] when comparing three-dimensionally printed osteotomy guide plate-assisted TKA with traditional TKA treatment to treat knee valgus deformity found that the three-dimensionally printed osteotomy guide plate-assisted TKA shortened the operation time, reduced the amount of bleeding, and obtained greater precision.

The nail guide plate provides help for precise nail placement during the operation. In thoracic and cervical spine surgery, there are strict requirements for the nail placement and angle. When there is a significant deviation, it may affect the nerves and technical near the cervical spine. Wu et al. [18] performed thoracic and cervical pedicle screw implantations on 19 patients with three-dimensionally printed individual nail guide plates. Of the 64 pedicle screws, 62 were completely inside the pedicle, with an accuracy rate of 96.8 %, and the use of three-dimensionally printed nail guides to assist surgery can improve the safety of nail placement, significantly shorten the operation time, and reduce the radiation exposure of doctors and patients. Zhong et al. [19] compared the accuracy of postoperative nail placement between the three-dimensionally printed guide plate group and the free-handed group during spinal deformity surgery, and believed that the use of three-dimensionally printed nail channel guides could provide greater nail placement accuracy for severe spinal deformities. Currently, many domestic and foreign scientists are studying and exploring new types of three-dimensionally printed orthopedic surgical guides **(Table 1).** In the future, the clinical application and significance of three-dimensionally printed orthopedic surgical guides will definitely increase.

Table 1: Studies on surface modification of a three-dimensionally printed multi-cavity titanium alloy metal support (Ti_6Al_4V).

Modification method	Research group	Experimental result
Plasma spraying	Li Y, Yang W, Guo Z, et al. **[20]**	Three-dimensionally printed porous titanium alloy scaffolds heavily coated with polydopamine/Hyaluronic Acid (HA) improved osteogenesis and bone integration
Micro-arc oxidation	Gorgin KZ, Hedayati R, Pouran B, et al. **[21]**	Three-dimensionally printed porous titanium alloy scaffolds produced with calcium/ phosphorus coating on the surface, and the mechanical properties remained unchanged.
Anodizing	Qin J, Yang D, Masher S, et al. **[22]**	HA coating was formed on the surface of the modified scaffold, which promoted the osteogenic differentiation of osteoblasts
Polydopamine coating	Li Y, Li Y, Yang L, et al. **[23]**	Three-dimensionally printed porous titanium alloy scaffolds heavily coated with polydopamine/HA improved osteogenesis and bone integration
Electrochemical deposition	Teng FY, Tai IC, Ho ML, et al. **[24]**	Three-dimensionally printed porous titanium alloy scaffold coated with a Ca/P layer was able to release bone morphogenetic protein 2 slowly. The modified scaffold promoted bone and blood vessel growth.

Application of Three-Dimensionally Printed Implants in Orthopedics

A bone defect caused by various diseases is the most common problem in orthopedic departments. In the clinical treatment of bone defects, the use of autologous/allogeneic bone grafts is recognized as the gold standard method for bone defect treatment. However, due to the lack of bone sources, pain, and other immune response limitations **[25],** artificial bone synthesis materials with excellent performance are needed. To achieve an excellent performance, a bone repair material must meet the requirements of: 1. Display good biocompatibility; 2. Have good biological activity; 3. have suitable biomechanical strength. At present, medical bone repair materials mainly include metal materials, bioceramics, and medical polymers. Medical metal materials mainly include titanium alloy, cobalt-nickel-molybdenum alloy, and stainless steel among others. Because of their good biocompatibility, non-cytotoxicity, and great strength, metallic materials are widely used in clinical practice. In recent years, because of the emergence of 3D printing technologies that use metal powder as materials (including selective laser melting technology and selective electron beam melting), cost consumption has been reduced, and the printing process molding speed has been effectively increased. At the same time, 3D printing technology can also precisely control the porosity of the product and the shape of the void geometry to manufacture complex specific components **[21].** However, due to its "stress shielding" phenomenon, the possibility of reducing the bone healing rate limits the clinical use of this material.

Medical bioceramic materials mainly include hydroxyapatite, calcium phosphate, and bioglass among others. Although the biocompatibility and biological activity of medical bioceramic materials are good and they can meet the basic requirements of bone repair implant materials, they are unsuitable for the long-term mechanical strength and stability of implant materials due to their poor strength, toughness, and easy fracture **[22].** Medical polymer materials currently mainly include polymethyl methacrylate and ultra-molecular-weight polyethylene. They have mechanical strength close to that of bone tissue and strong plasticity, but it lack any biological activity. They cannot promote bone regeneration when implanted in the body or form an osseous bond with surrounding tissues. Polyether Ether Ketone (PEEK) is used more frequently in clinical practice to introduce medical polymer materials. PEEK has good biomechanical strength, corrosion resistance, and X-ray permeability, displays no immune rejection, and has other excellent properties. This material has many properties similar to metal implants (mechanical properties, corrosion resistance) **[23],** and reduces the stress shielding caused by the high elastic modulus of metal materials, thus preventing metal implants from becoming loose. Its X-ray permeability helps surgeons observe the fracture site and avoids the occurrence of fracture nonunion. However, PEEK material is of limited clinical use due to its surface hydrophobicity and a lack of bone conduction and osseointegration capabilities **[24].**

Application of 3D Bioprinting in Basic Orthopedics Research

Since ancient times, the most difficult problem of orthopedic trauma has been a bone defect or nonunion. At present, autologous bone transplantation is the main clinical treatment for bone defects, which has a good biological match with the bone recipient area. Therefore, the bone defect can be repaired well, but the amount of bone that can be collected is limited and is accompanied by new trauma. Therefore, when a bone defect is large, it is difficult to meet the clinical needs. Biological 3D printing is the precise and personalized shaping of cells and extracellular matrix at specific locations to create tissue structures with specific biological functions. At present, stereolithographic, inkjet, and extrusion printing are the three mainstream printing methods **[25].** For these three printing methods, the preparation of bio-ink has become the current limitation. The currently used bio-inks are mainly cell-containing hydrogels, microcarriers, and Decellularized Extracellular Matrix (dECM), but more effective tissue decellularization methods are needed to reduce the cost of bio-inks and prevent the damage of dECM structures **(Figure 3).**

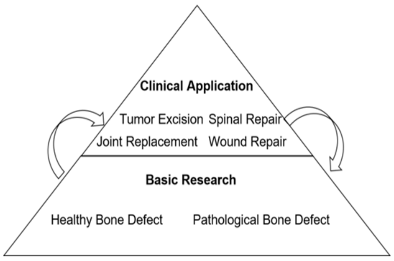

Figure 3: The interrelationship between basic research and clinical application.

At present, relevant research focuses on bone or cartilage repair, because compared to other tissues of the human body, their structure is relatively fixed, which is highly suitable for repair using scaffolds, and bone or cartilage is convenient to control pores and implant cells **[26].** Due to the diversity of bone and cartilage tissues, in the research of their repair, the selection and production methods of respective biomaterials are not the same **[27] (Figure 4).**

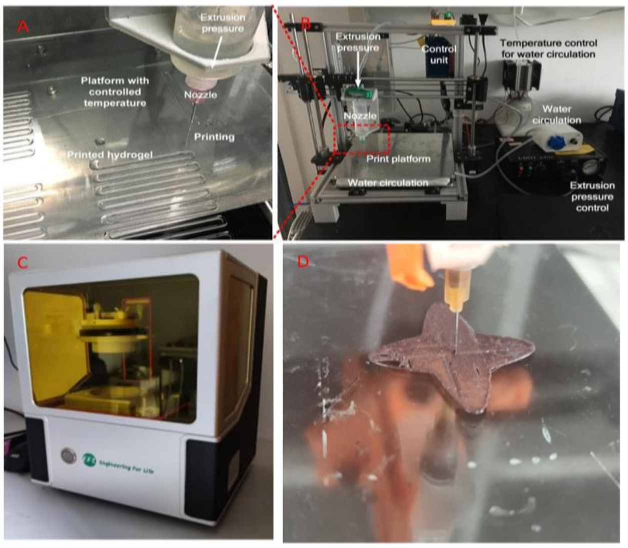

Figure 4: A, B: Biological 3D printer developed by our research group. (10.1049/mnl.2018.5076; copyright 2018 John Wiley and Sons); C: Photocurable biological 3D printer; D: Extruded biological 3D printer

Bone tissue printing

Bone tissue is a compound with a limited self-healing ability, and is composed of relatively fine-structured organic matter and inorganic matter **[28-30]**. Some natural and/or synthetic bone substitutes with good biocompatibility have been developed to promote bone regeneration and as substitutes for autologous or allogeneic bone grafts. Weitz et al. **[31]** used photo-crosslinked microfluidic control to prepare microspheres. The microgel provides a good growth microenvironment for bone marrow stromal stem cells to achieve injectable bone tissue regeneration. Luiz et al. **[32]** developed a collagen hydrogel containing Human Mesenchymal Stem Cells (hMSCs) and promoted protein-induced collagen fiber mineralization by adding soluble Ca^{2+}, PO_4^{3-}, and nucleation inhibitor-osteopontin to simulate the natural intra- and extra-fiber nano-mineralization profile of bone. This proved that the constructed microenvironment itself is sufficient to stimulate the osteogenic differentiation of hMSCs, and it can also form capillaries supported by hMSCs in vivo and in vitro. Inspired by the natural mineralization process in bones and coral reefs, Sung et al. [33] reported a new type of material system. In this system, the piezoelectric stent generates proportional charges under external mechanical load stimulation and uses these charges as signals to induce mineralization by the deposition of mineral ions from the surrounding medium onto the stent, thereby enhancing the mechanical properties of the load part to achieve self-hardening. Alireza et al. [34] used double bonds and dopamine-modified sodium alginate to prepare adhesive hydrogels and modified them with RGD polypeptides to further enhance the gel biocompatibility. The gel can realize light-induced chemical cross-linking, thereby filling complex bone defect wounds and providing good interface adhesion. Lee et al. [35] used the extrusion method to obtain Exosome Mimics (EMs) from Human Mesenchymal Stem Cells (hMSCs). They devised an alternative strategy to produce exosome-associated vesicles, which resulted in a higher yield and improved regeneration ability when hMSC-EMs were applied together with injectable chitosan hydrogel to unhealed mouse skull defects, showing excellent bone repair performance. There remain many unresolved problems regarding the cytocompatibility and osteoinduction of bio-three-dimensionally printed materials. Further research on the optimal combination of cells and osteogenic factors is necessary to achieve complete bone regeneration.

Cartilage tissue printing

Cartilage damage caused by osteoarthritis and joint damage is the main cause of pain and disability. Cartilage lacks a blood supply and has no self-healing ability. Clinically, microfractures, osteochondral transplantation, and autologous chondrocyte implantation are generally used to repair cartilage damage. Microfracture is the main method to obtain bone marrow stem cells for articular cartilage repair. However, this invasive treatment cannot regenerate hyaline cartilage. Bio 3D printing is particularly suitable for cartilage repair in specific regions, including cartilage tissue in the craniofacial area and ear cartilage among others. Compared with traditional tissue engineering, bio 3D printing can meet the requirements of these complex cartilage geometric structures. Zhou et al. [36] prepared a composite photocrosslinked hydrogel from Gelatin Methacrylate (GelMA) and Human Anti Mouse Antibody (HAMA) using 3D printing technology to achieve precise control of the external 3D shape and internal pore structure. Additionally, by using freeze-drying technology, they further improved the mechanical properties and prolonged the degradation time. Experimental results showed that the combination of scaffold and chondrocytes successfully regenerates mature cartilage with a typical lacuna structure and cartilage-specific extracellular matrix. This research provides a series of optimized scaffold manufacturing strategies to precisely control the scaffold structure, degradation rate, and mechanical properties, providing a new type of natural biodegradable scaffold for cartilage regeneration. Su et al. [37] used suspension 3D printing technology to print cell microspheres to create cartilage-like tissue. The results showed that the stem cells in the cartilage-like tissue produced by this method differentiate into chondrocytes and exhibit cartilage-like behavior. Compared with the traditional culture method, the extracellular matrix deposition in the printed tissue structure was significantly improved. Therefore, this type of cartilage manufacturing method contributes to the further clinical development of cartilage replacement and regeneration. Chan et al. [38] synthesized a light-curable bio-ink material: glycidyl methacrylate-modified silk fibroin (Sil-MA). Studies have shown that Sil-MA has mechanical properties that match natural cartilage, excellent cell-carrying Digital Light Processing (DLP) printing properties, and biological properties that promote cartilage formation. A. P. Duarte [39] changed the hardness of electrospun fibers by the degree of crosslinking of Methacrylic Hyaluronic Acid (MeHA), which proved that the softer MeHA fiber network is easily deformed and densified under cell traction, whereas with the harder MeHA fiber network it is easier to invade the meniscus tissue. When the scaffold was implanted under the skin, the harder MeHA fiber network displayed greater cell invasion and more collagen deposition after 4 weeks, thus promoting cartilage tissue repair. Therefore, the mechanics and deformability of the fiber network may change the interaction between the scaffold and cells and the level of cell invasion, providing important design parameters for the design of cartilage tissue repair scaffolds. Fan J et al. [40] prepared GelMA/nano clay hydrogel (Gel-nano) to continuously release Small extracellular vesicle. Gel-nano-sEV has the ability to stimulate cartilage formation and heal cartilage defects, and can be applied in a broad field in the treatment of cartilage defects.

At present, cartilage tissue engineering cannot simulate natural cartilage in terms of a layered structure, ECM synthesis, or mechanical properties, and the mechanical properties are poor. Improving printing resolution is essential for printing cartilage joints with complex anatomical structures. When performing multi-layer printing, the cross-linking and curing after extrusion is very important to ensure the printing accuracy and maintain the printing shape. In addition, it is necessary to further optimize cell sources and bioactive factors to promote cartilage tissue healing [41,42].

Summary

With the continuous improvement of 3D printing technology and the emergence of new bio-inks, 3D printing technology will be ever more able to meet the needs of various different clinical levels, and will be of greater benefit to general health [43-45]. Although 3D printing technology has many advantages, it still faces many challenges due to the limitations of its own technological development. These include the physical and chemical properties of the printing materials, biocompatibility, and acquisition cost prices among others, and these will affect their clinical promotion and application. In the future, 3D printing technology will make major breakthroughs in materials science and biology, and will surely solve key problems in clinical applications, making 3D printing technology an important tool in clinical diagnosis and treatment [46,47]. Therefore, 3D printing technology will become a development trend of future medical treatment, particularly in orthopedics, and has broad application prospects.

Author Contributions

CS and YW designed and wrote the paper, and contributed equally to this work: ideas, development or design of methodology. QJ reviewed summary of related publications, checked the correctness of the cited article. SF and JZ supervised, reviewed, and edited the manuscript. All authors read and approved the final manuscript.

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