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Review

A review of 3D bio-printing for bone and skin tissue engineering: a commercial approach

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ABSTRACT

The ultimate prospect of tissue engineering is to create autologous tissue grafts for future replacement therapies through utilization of cells and biomaterials simultaneously. Bio-printing is a novel technique, a growing field that is leading to the global revolution in medical sciences that has gained significant attention. Bio-printing has the potential to be used in producing human engineered tissues like bone and skin which then ultimately can be used in the clinics. In this paper, the 3D bio-printing applications of the engineered human tissues that are available (skin and bone) are reviewed. It is evident that various tissue engineering techniques have been applied in the fabrication of skin tissue; therefore, it leads to introduce tissue substitutes such as complementary, split-thickness skin graft, allografts, acellular dermal substitutes and cellularized graft-like commercial products, i.e., Dermagraft and Apligraf. Also, some bone scaffolds based on hydroxyapatite and biphasic calcium phosphate are available in the market. The technology of bio-printing has got validated for bone and skin tissue fabrication, and it is hoped that other tissues could be produced by this technique.

Introduction

Regenerative medicine holds the promise to restitute the normal function of cells, tissues or organs lost due to disease or damage via replacing or regenerating [1]. In fact, there are three solutions for patients with organ impairment, based upon the condition and severity of the destruction, they are: graft implantation, substitution and restoration. Graft implantation has comprehensively extensive lists of anticipants all around the world, for example, organ transplant waiting list updated every 15 in the USA [2]. The ultimate prospect of tissue engineering is to create autologous tissue grafts for future replacement therapies through utilization of cells and biomaterials [3, 4]. Besides, tissue engineering has been seen as an

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efficient method to assist in rescuing lives and improving the quality of life. There are many methods to produce an appropriate scaffold that cells could seed on, like foam casting, electrospinning, phase separation, decellularizing, etc.

Recently human donor organs, such as kidney [5–7], lung [8–10], heart [11–13] and liver [14–16], have been experimented to obtain decellularized extracellular matrix scaffolds (dECM) in order to clarify their potential application in regenerative medicine. However, despite the important basic science achievements in the field, clinical applications of decellularized tissues are not available yet [17]. Also, the use of dECM scaffolds for bioengineering of human scale patient-specific organs using human pluripotent stem cells (hPSCs) has been considered as a major platform for therapeutic applications [18]. Interestingly, the concept of organ printing has lately taken the center stage due to recent 3D bio-printing (3DBP) advancements [19–22].

3DBP is considered to have significant impact in tissue engineering area. Bio-printing is a growing field that is leading to a global revolution in medical sciences and has gained significant attention worldwide because of tremendous transformation it will have in the treatment of diseases [23].

Bio-printing can be defined as the simultaneous printing of living cells and biomaterials like hydrogels, bioglasses, bio-ceramics and collagen by a prescribed layer-by-layer stacking organization, using a computer-aided transfer process for fabrication of bioengineered constructs. Initially the study of cells was performed applying 2D structures; nonetheless, with the initiation of 3D printing to the engineering of tissues, it became feasible for researchers to use 3D scaffolds. Even though vascularization, controlled cell dispersion, innervation and cell deposition with high resolution, in complicated 3D tissues are still current technical challenges faced in 3DBP, however, compared with other techniques it presents many advantages such as scalability, simplicity and cost efficiency. Due to these advantages, 3DBP development and application has been increasing constantly over the past few years [24]. Also, 3DBP techniques have extensive applications in tissue engineering [25–28], transplantation clinics [23–29], drug screening, high throughput assays [30] and cancer research [31].

Since the human organs are different in terms of the size, 3DBP is an appropriate and versatile method for fabrication that asserts micrometric cell patterning for extensive biomedical engineering applications [21]. Generating the printing paths, selecting appropriate bio-inks, printing control and performing quality control after printing are major steps that assure passable print [22].

Generating the printing pathways and verifying its feasibility by designers is the first step of the bio-printing process. By selecting appropriate cells and hydrogels, loading the bio-inks into the bio-printing system is needed. The next step is sending the designed paths to the controlling system and building structures by depositing bio-inks. The bio-printed constructs are examined through a microscope. As more researches are performed implementing the techniques of 3DBP, this will ensure an enhancement of the printing resolution and quality and also the actualization of the current challenges, furnishing the capacity to print more complex 3D constructs.

Due to the advances in the additive manufacturing, some of the most well-known for bone tissue engineering, including stereo-lithography, selective laser sintering, fused deposition modeling and three-dimensional printing are reviewed [32, 33]. Moreover, some basic physical principles along with primary applications of aforementioned techniques have been reviewed beside a list of bone tissue engineering-related biomaterials [33]. Various types of bio-inks used for bone bio-printing are reviewed as well as their major challenges and future strategies [34]. The recent advancements, limitations, challenges and future strategies in bone bio-printing are summarized in recently published reports [32, 34, 35].

There are several studies about 3DBP which cover diverse tissues [36–43]; meanwhile, to the best of our there isn't any review study about bone and skin tissues bio-printing. In fact, this paper focuses on tissues that successfully passed the commercializing procedures not only by printing techniques, but also by the prior scaffold fabricating methods. The authors tried to include the skin and bone-related literature that published till preparing the paper with the "bio-printing, 3DBP, 3D printing" key words, whereas the unrelated papers in tissue engineering fields were excluded.

Our aim was to focus on studies with commonly employed cells, materials and printing methods in skin and bone bio-printing (Fig. 1).

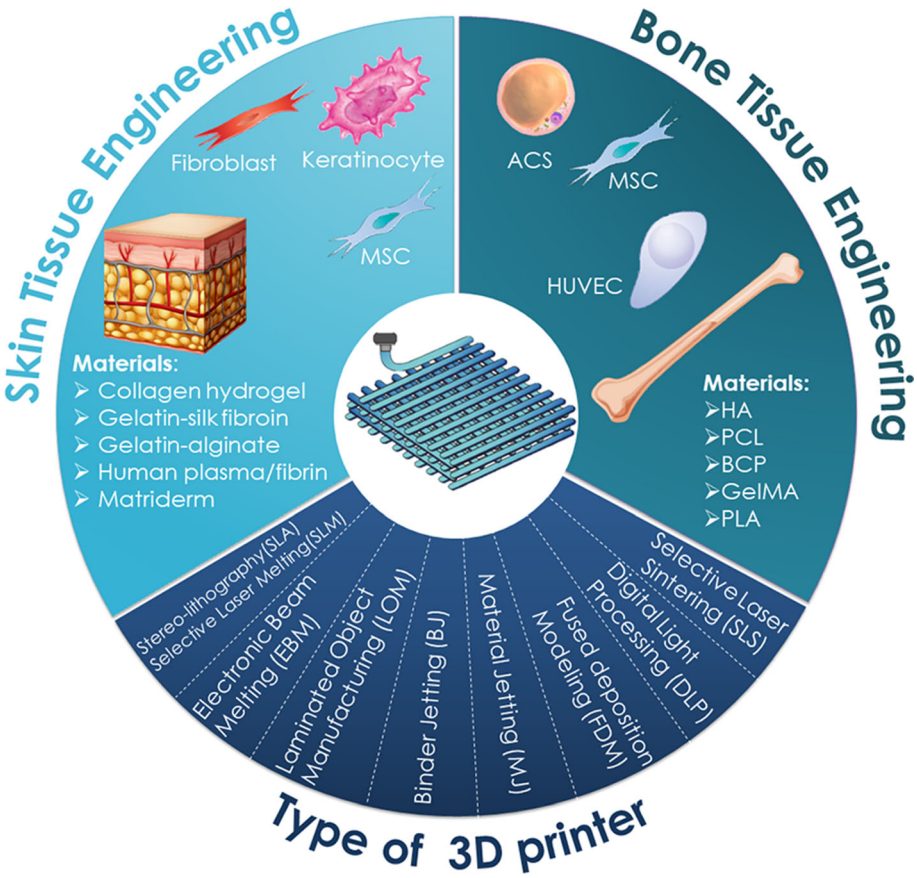

Figure 1 Various cells, materials and printing methods used in bone and skin tissue bio-printing.

Bio-inks and their performances

Among all the bio-inks used for 3DBP, there are some that are distinguished based on their merits. In some studies that refer to this issue, specific applications, new methods and spectacular properties have been reported [44–50]. In certain biomedical appliances, conductivity is of extreme importance while in scaffolds, cell support is vital [24]. In a recent study, a formidable bio-ink was designed for reconstructing cardiac tissue [51], it was produced to supply the correct conductivity and evade postponed electrical confluence in cardiac cells. This new gold nano-rod-integrated gelatin methacryloyl-based bio-ink was shown to be precisely printable, cytocompatible and boosted the performance of cardiac cells.

Nerve [52], kidney [53] and cartilage [54] rejuvenation and restoration including bionic ear [55] are other precise utilizations investigated for bio-ink improvement. Impressionable electronics for bio-electronic boundaries are also presently under comprehensive investigation [56, 57]. Also, 3DBP of commercialized tissue engineering products is a novel idea that can result in more effectiveness and lowering of costs.

Skin tissue 3D bio-printing

Many tissue fabrication techniques have been employed in the creation of skin tissues which culminate in the introduction of tissue substitutes, such as autologous split-thickness skin graft [58], allografts [59], acellular dermal substitutes and cellularized graft-like commercial products [59] such as Dermagraft and Apligraf [60]. New, bio-printing technology was utilized for skin tissue fabrication, Pourchet et al. [61] produced a two-layered (dermis and epidermis) 3D cell-printed full-thickness skin. The bio-ink was a mixture of gelatin and fibrinogen; moreover, they embedded human dermal fibroblasts in the mentioned mixture and printed to produce a dermis construct. Next stage was to generate the skin substitutes with 5 mm thickness which seeded the human epidermal keratinocytes over the dermis construct. Within 26 days of culture, natural human

skin histological-like characteristics of the 3D cell-printed skin exhibited. Interestingly, immunofluorescence results using different differentiation markers exhibited high expression of Loricrin, showing the barrier function of the skin, which is related to the stratum corneum formation. Table 1 lists the studies on skin tissue 3DBP.

Cubo et al. [62] produced a full-thickness human skin similar to one-step manufacturing one, which used 3DBP technique. A combined structure was comprised of four different elements—human fibroblasts, human plasma supplemented with fibrinogen, calcium chloride ($CaCl_2$) and human keratinocytes. Based on in vitro and in vivo evaluations, it was shown that the 3D cell-printed human skin substitute was very similar to natural human skin tissue, and extremely differentiated dermis and epidermis layers clearly were noticed. They constructed an intelligible and efficacious 3DBP technique and bio-inks that permitted the creation of a double-layer human skin, adopting human plasma and primary human fibroblasts (hFBs) and human keratinocytes (hKCs). The printed tissue was very similar to natural human skin and indistinguishable

Table 1 Summary of skin tissue 3DBP studies representing the cell types and source, growth factors, animals and the print technique used in some skin tissue engineering studies

Biomaterials/bio-ink	Cell type	Cell source	Growth factor/ biomolecules	In vivo animal model	Bio-printing technique	References
Gelatin–fibrinogen–alginate	Fibroblast, keratinocyte	Human skin	–	–	Extrusion	[61]
Human plasma/fibrin	Fibroblast, keratinocyte	Human skin	–	Nude mice	Extrusion	[62]
Gelatin methacrylamide (GelMA)	Keratinocyte	–	–	–		[63]
Collagen hydrogel	Fibroblast, keratinocyte	Human skin	Human keratinocyte growth supplement	–	Solid freeform fabrication	[64]
Gelatin–silk fibroin (SF)	Child foreskin fibroblasts (CFFs)	Human	FGF-2	Rat	Pneumatic bio-printing	[65]
Chitosan–polyelectrolyte gelatin hydrogel	Fibroblast skin cells	Human	–	–	–	[67]
Collagen hydrogel precursor	Melanocytes, fibroblast, keratinocyte	–	–	–	Extrusion	[68]
Gelatin–alginate	Bone marrow mesenchymal stem cells	Rat	–	Mouse	Extrusion	[69]
Gelatin and sodium alginate	Epidermal progenitor cells	Mice	Mouse plantar dermis and epidermal growth factor	–	Extrusion	[70]
Collagen and fibrinogen	AFS or MSC	Amniotic fluid	Thrombin	Mice	Inkjet	[73]
Collagen hydrogel/ gelatin/PCL	Fibroblast and keratinocyte	Human skin	–	–	Extrusion and inkjet	[74]
Matriderm	Fibroblast and keratinocyte	Mouse embryo human skin	Hydrocortison	Male BALB/ c-nude mice	Laser-assisted	[75]
Hydrogel fibrinogen and collagen type 1	Fibroblast and keratinocyte	Human skin	Thrombin	Porcine wound model	Inkjet (in situ)	[76]

from dermo-epidermal analogs, precedent handcrafted in their laboratory and employed successfully in the clinic. This method set up a novel technology that permitted the production of skin substitutes in reasonable amounts at shorter times. It showed decreased production cost and an improved production line by utilizing an automotive and standardized system of producing skin counterparts, thereby overcoming some of the challenges encountered by the present physical production process.

Zhao et al. [63] synthesized varying concentrations of gelatin methacryloyl (GelMA) hydrogels for a monolayer skin modernization process. GelMA hydrogels have good physical properties, and subsequently they systematically change the concentration of GelMA in order to control the adhesion, proliferation and differentiation of keratinocytes. A hydrogel scaffold was used to reach a keratinocyte suspension, which was used to develop the reconstruction of the classified and functional epitromes. The result of this study indicated that the physical and biological properties of the resultant hydrogels could be adequately controlled to meet the requirements for epidermis formation, by altering the concentration of GelMA pre-polymer solution. GelMA hydrogels supported the formation of a stratified epidermis with a certain barrier function, e.g., electrical resistance and prevention of water loss. Higher concentrations of hydrogels indicate the hardness of materials for cell adhesion and the formation of single-layer keratinocytes and cell adhesion, coupled with prolonged resistance to collagenase degradation.

Lee et al. [64] constructed a two-layer skin via a 3DBP procedure using skin dermal matrix formed by collagen. In fact, replacing the natural human skin by 3D-printed one is not impossible morphologically and biologically, while the 3D-printed one was reinforced via histological and immunofluorescence properties. In order to cover the full thickness of the transdermal and localized wound forms, this technique has a wide range of applications in skin design of toxicity investigations and wound healing. Their study illustrated that cell viability and function were affected little by proteins and printing cells in nanodroplets form. Both keratinocytes and fibroblasts enjoyed sufficiently high rate of viability in this study [66].

Xiong et al. [65] study revealed that the rate of full-thickness wound healing accelerated by utilizing from 3D-printed gelatin–silk fibroin base scaffolds. Also, incorporation of fibroblast growth factor 2 (FGF-2) could further enhance the treatment efficacy. Skin scaffolds shown to contain sulfonated moieties in order to raise scaffold hydrophilicity. The immobilized growth factor FGF-2 facilitated a sustained release kinetics, as well as being able to initiate cell proliferation and migration in vitro. Printed scaffolds exhibited favorable results in vivo. Proliferation rate in this study showed a significant raise from 40 to 75% by using FGF-2. Tissue morphology, collagen fibril assembly, blood vessel formation and the expression of various corresponding markers grew impressively. These data demonstrated that recombinant FGF-2 delivered by the scaffold could be a viable and innovative therapeutic strategy for severe skin wound.

Rutz et al. [66] introduced a versatile and cell-compatible bio-ink from a variety of amine-containing polymers and their mixtures, synthetically and naturally. It was shown that 35 formulations of bio-inks can be customized with regard to composition (additives and composites), the degree of crosslinking and polymer concentration in order to optimize structural and biological performance, while maintaining printability.

Also, Ng et al. [67] optimized a scaffold based on polyelectrolyte–gelatin–chitosan (PGC) hydrogel by 3DBP. In order to form polyelectrolytic compounds, the chitosan was modified with the different gelatin functional groups at pH of 6.5. In this work, to achieve an excellent biocompatibility with fibroblast skin cells, the PGC hydrogels were modified at room temperature for the 3DBP procedure. In fact, PGC hydrogels have a high viscosity that is suitable for the printing procedure at room temperature. The PGC hydrogels were optimized for the bio-printing of skin designs. Their scaffolds in 400 μm for three layers were representative of the outer epidermal layer and part of the dermal area. Their findings suggested the potential use of polyelectrolyte–gelatin–chitosan hydrogels for skin bio-printing applications.

Min et al. [68] developed a 3DBP procedure that there was capability of producing a thick skin with pigmentations. Multiple layers of collagen hydrogel precursors with fibroblasts were printed using sodium bicarbonate as the cross-linker. For the skin pigmentation induction on the subsequent air–liquid interface, melanocytes and keratinocytes were sequentially printed on top of the dermal layer. To

clarify the formation of distinct skin layers also to recognize the pigmentation presence, histological analysis was done. The printed skin product illustrated that final differentiation of the keratinocytes caused the formation of the stratum corneum in the dermal and epidermal layers. Moreover, the epidermal layer included melanocytes that showed the dermal–epidermal junction with freckle-like pigmentations, without the use of chemical stimuli or external ultraviolet light. For therapeutic and research purposes, explanation of 3DBP technique as a productive on-demand option is available and presented the ability of engineering ephelides production in the biomimetic skin. Additionally, Li et al. [69] designed and manufactured the gelatin/alginate scaffolds via 3D bio-printer and investigated its biocompatibility and the histocompatibility over the skin wound healing duration using bone marrow-derived mesenchymal stem cells (BMSCs).

Huang et al. [70] produced a 3D ECM mimic construct for the sweat glands regeneration. Sweat glands perform a vital thermoregulatory function in mammals; like other skin attachments, they are made up of epidermal progenitors. Also, adult epidermal progenitors could be specified to differentiate to a sweat gland cell lineage but this remains largely unexplored and whether they have low regenerative potential in response to injury is still questionable.

Additionally, in order to create a functional in vitro cell-laden 3D extracellular matrix mimics (3D-ECM), 3D printing technology was used with composite hydrogels based on gelatin and sodium alginate, due to their chemical and structural similarities to ECM components. Facilitating cell spreading and matrix formation because of the biological 3D structure could maintain cell viability. In this study, Ng et al. [71] demonstrated a bio-printing technique that can be utilized for the production of films for skin wound healing. Application of these bio-printed films could be in skin tissue engineering area.

For the first time, Rimann et al. [72] provided an all-in-one solution for the production of a skin-like soft tissue model with human primary fibroblasts and keratinocytes. The defined printing method and the advanced bio-ink were cell compatible and allowed long-term culture models to be generated. Further optimization of their model can possibly promote the full standardization of the production of 3D tissue model. Also, future advances in this technology will depend on standardizing bio-printing equipment and tailored bio-inks to support the correct functioning of cells. Reliable in vitro skin models are urgently required, especially in the cosmetic business, for testing cosmetic ingredients as required by legislation in Europe.

In a novel study, Skardal et al. [73] applied bioprinting technique for the full-thickness skin wounds treatment in nu/nu mice. They used fibrin-collagen gel filled with amniotic fluid-based stem cell (AFSs) and mesenchymal stem cells (MSCs) to print them on the wound site.

Although Kim et al. [74] invented a novel 3D cell-printing single-step process approach for human skin engineering with a functional transwell system. They established a hybrid 3D cell-printing system that facilitated the employment of extrusion and inkjet modules simultaneously. The collagen-based construct facilitated this procedure with polycaprolactone (PCL) mesh that interrupted collagen contraction during tissue maturation. Moreover, the inkjet-based disbursing unit was used to evenly distribute keratinocytes. This skin model disclosed promising biological properties that comprised of a steady fibroblast-stretched dermis and stratified epidermis layers 14 days thereon. This method also possessed 50 times lower cost and 10 times less consumption of medium than in a stereotyped culture. All in all, due to one-step procedure possibilities, authors advised their cell-printing approach for different human skin replicas engineering.

Michael et al. [75] produced a completely cellularized auxiliary skin by employing a laser-assisted bioprinting (LaBP) method. The unique aspect of LaBP is the opportunity to situate diverse types of cell in a precise three-dimensional pattern in space. They fixed fibroblasts and keratinocytes atop a sustaining matrix Matriderm in order to construct skin surrogates. These skin surrogates were later verified in vivo, using the dorsal skinfold chamber in nude mice. Full-thickness skin wounds were then implanted with the grafts, and these were completely bound to the neighboring tissue when explanted after 11 days. The printed keratinocytes established a multiple-folded epidermis with a commencement of differentiation and stratum corneum. The proliferation of the keratinocytes was principally identified in the percussive fundamental layers. Test tube controls, which were cultured at the air–liquid interface, also revealed proliferative cells, but these were somewhat situated in the entire epidermis. The presence of

E-cadherin as an indication for adherens junctions and consequently the formation of tissue could be seen in the epidermis both in vivo and in vitro. In both conditions, the printed fibroblasts partially remained above the substratal Matriderm where they formed collagen, while a part of them wandered into the Matriderm. The blood vessels were seen to develop from the base of the wound and its edges toward the printed cells. In summary, Michael et al. [75] successfully exhibited the 3D printing of a cell composite through LaBP and the successive formation of tissue in vivo. These discoveries denote the precondition for the generation of a composite tissue-like skin, comprising of various types of cells in a sophisticated 3D pattern.

In vivo skin 3DBP procedure is shown in Fig. 2.

In a different study, Binder [76] aimed at developing a prototype skin bio-printer that could act as a test bed for the core components of an in situ printing system. A movement system was constructed capable of 1.57 μm precision. The printer enjoyed a cartridge-based delivery system capable of delivering up to eight different types of cells. This study promoted the idea of utilizing bio-printing in the clinics.

In fact, skin bio-printing is a novel technique which must be brought to the clinic (Fig. 3).

After a bio-ink pre-cellularization using a novel passive blending unit method, Thayer et al. [77] produced skin analogs. This method was designed to simplify the blending steps of a cell suspension into an extremely viscous bio-ink. In this study, a bio-ink based on nano-cellulose/alginate was used. The analogs of skin tissue could be grown for up to 4 weeks. Histological results showed both tissue-specific extracellular matrix (ECM) markers deposition and cell viability.

Albanna et al. [78] described a novel model of a mobile skin bio-printing process that quickly manages comprehensive injuries on site. The biomaterials used consisted of fibrinogen from bovine plasma and thrombin from bovine plasma lyophilized powder. Immunohistochemistry for human cells showed that 3–6 weeks after printing, as well as endogenous cells, human fibroblasts and keratinocytes were present in

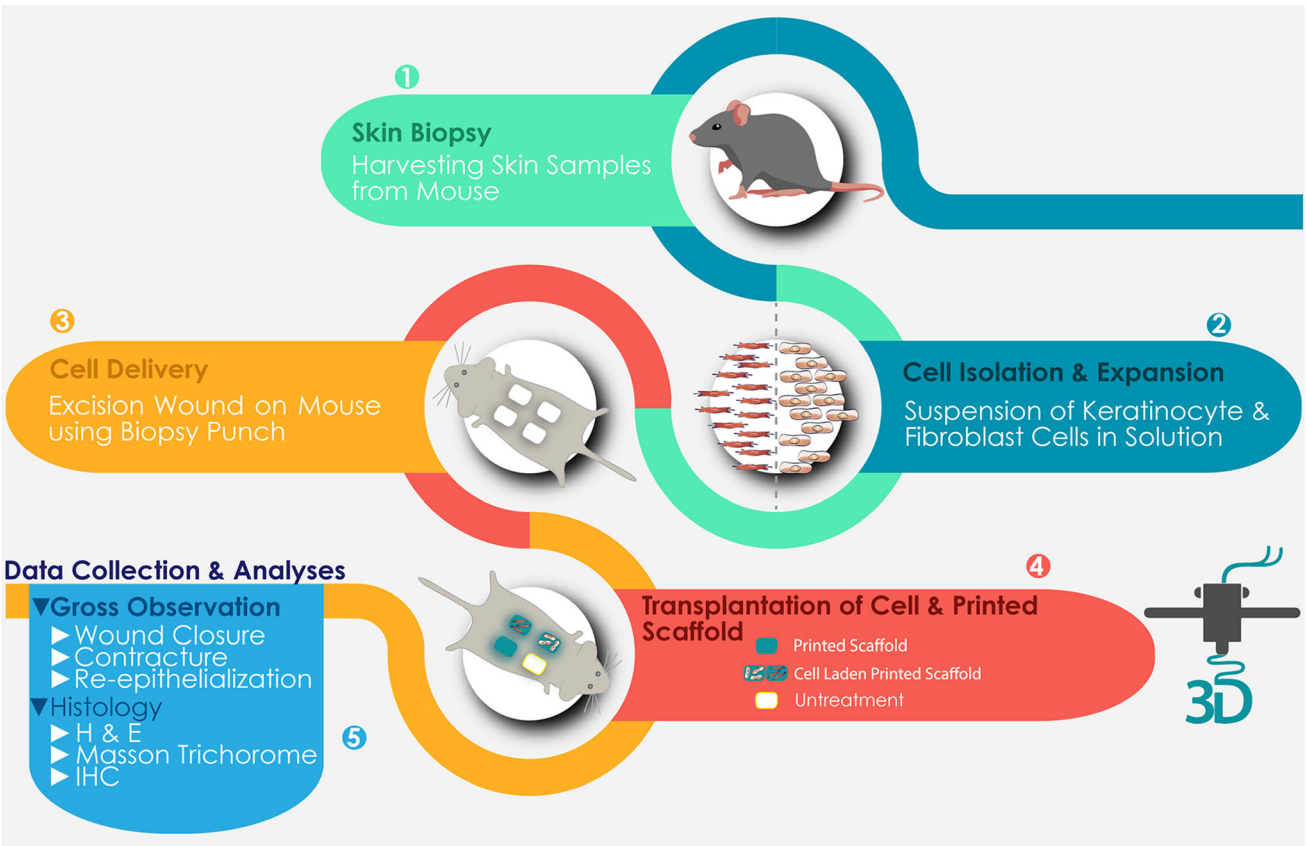

Figure 2 In vivo study procedure of printed skin scaffolds. The first step is skin biopsy. Then cell isolation and expansion is the second one. After cell delivery, cell and scaffold transplantation are necessary. Finally, data collection and analysis of procedure is expected.

Figure 3 3DBP skin procedure. Reproduced with permission from Universidad Carlos III de Madrid (UC3M) and Lawrence [139]. Based on skin wound area, the wound repair strategy is selectable. Whether printing on wound or printing on a feeder layer and assembling it on wound area is available.

the dermis and epidermis of the wound, respectively. This research discussed the proof-of-concept validation of mobile in situ skin bio-printing process with embedded imaging technology to quickly manage full-thickness wounds on site. It was observed that the treatment with autologous fibroblasts and keratinocytes, supplied immediately to targeted wound places depending on wound size and topology, consisting of improved wound healing and standard in situ skin formation.

Admane et al. [79] demonstrated that the special undulated pattern of the dermal–epidermal junction in the 3D human skin is physiologically relevant to human skin and the bio-printed skin structure was dimensionally stable compared to the serious contraction associated with the collagen-based skin structure. At the other side, extensive keratinocyte migration is observed by day 21 with the observed self-assembly of keratinocytes by full coverage of the 3D bio-printed construct's pore. Proteomics data analysis demonstrating striking resemblance of the developed 3D human skin model with a number of skin-specific pathways and required expression of proliferation and cornification markers depicting full stratification of the advanced 3D human skin model and extensive transcriptomics.

All the mentioned artificial materials are usually non-biodegradable, and subsequent removal of such

temporary wound dressings from the wound site is mandatory. Progression of biodegradable films is necessary in the skin tissue engineering field [80]. Albeit solvent casting is a simple construction technique to produce such films, requirement qualities such as mechanical strength and water transmission rate cannot easily guarded through a solvent casting technique. Hence, the bio-printing technique could be used to manipulate the ultimate tensile strength, moisture permeability and the water uptake ability of the film.

3D bio-printing of bone tissue

Bone tissue engineering has been widely studied using 3DBP. Leukers et al. [81] studied scaffolds based on hydroxyapatite by using 3D printing for engineering of bone tissue. They brought forth a special test-part in which mouse calvaria 3T3-E1 (MC3T3-E1) cells were cultured on the scaffolds and maintained under static and dynamic setups, followed by a histological examination which was performed to determine the growth of these cells. In brief, the dynamic culture process resulted in a potent population versus the static culture process. The cells were developed into the structure forming a nearly indirect communication with the hydroxyapatite (HA) granules, by creating a scaffold layout with inclined layers of 45°. This design facilitated the seeding procedure and increased cell attachment because the cells made the structure more integrated and prevented them from sliding down the structure. In a static culture, cells are deposited on the interface of the HA granules in layers, whereas in a dynamic seeding process, the cells grow within the cavities of the HA granules.

The dynamic cultured cells are significantly different from the static cultured cells. The powder-based 3D printing process developed micro-porosity of the scaffold and as a result, it enhanced the scaffold surface available for the medium flow and dissolution. Cox et al. [82] also presented the property of bone tissue scaffolds manufactured by 3D printing from a composite of HA and polyvinyl alcohol (PVOH). However, mechanical stability, microstructure and porosity of scaffolds produced by 3D printing were affected by the presence of HA: PVOH ratio precursor materials. By testing their comprehensive strengths, these constructs showed anisotropic behavior and partly failed at the interface of their interlayer bonds. This study used 3D printing, in other words, a print-based additive layer manufacturing (ALM) technique for fabricating an applicable porous scaffold adequate for the applications of the engineering of bone tissue. In brief, the characterization of precursor flow ability, using two common funnel tests, qualitatively comparable with observed printability can be assumed as an exclusive vital prerequisite since it required recoating of the build bed which finally distinguished several critical physical criteria such as mechanical strength, microstructure and porosity.

A glance at Table 2 provided reveals that there are several studies in bone tissue engineering field. Brunello et al. [83] experimented with 3D printing of powder for the purpose of the bone tissue engineering. Powder-based 3D printing is propounded as a special encouraging bone remodeling technique, as the exterior frame, interior structure, permeability and 3D-printed physical properties of bone replacements can be modified and hence used for particular purposes. 3DBP of stem cells and polymer/bioactive glass compound scaffolds for the engineering of bone tissue was accomplished by Murphy et al. [84]. They used 3DBP techniques for manufacturing of PCL/bioactive borate glass composite, as well as human adipose stem cells (ASCs) in their work, by applying a two-syringe system for fabrication of a scaffold with a bio-polymer/bio-glass composite. As a scaffold, material of this composite dissolved in an organic solvent, whereas concurrently printed cells remained suspended in the Matrigel®. They noted that the borate glass content could have an impact on the printability of composite paste, the scaffold temporal bioactivity, degradability and cell survival in the scaffold. The extrusion bio-printing technique has important features, which can produce a scaffolding structure that supports cells and provides shape and mechanical integrity. Extrusion bio-printers normally have more than one syringe, one of them dedicated to print scaffolding structures. Molten deposition of polymer and fused deposition modeling (FDM) with a polymer wire feed were the options applied for this matter, also the pore size factor is considerable because it has a potential to affect the bone growth after implantation.

Byambaa et al. [85] produced bone-like microstructure tissue constructs which contained perfusable vascular lumen by 3DBP. The bio-printed

Table 2 Summary of bone tissue 3DBP studies representing the cell types and source, growth factors, animals and the print technique used in some bone tissue engineering studies

Biomaterials/bio-ink	Cell type	Cell source	Growth factor/ biomolecules	In vivo animal model	Bio-printing technique	References
HA	MC3T3-E1, post-printing	Mouse	–	–	Fused deposition modeling 3D printer	[81]
Composite of hydroxyapatite (HA) and poly(vinyl) alcohol	–	–	–	–	Additive Layer Manufacturing (ALM)	[82]
Polycaprolactone (PCL)/bioactive borate glass composite	Human adipose stem cells (ASCs)	Human	–	–	Extrusion-based 3D bio-printing	[84]
Gelatin methacryloyl (GelMA) hydrogel	Human umbilical vein endothelial cells and hMCSCs	Human	VEGF bFGF	–	Extrusion-based direct-writing bio-printing	[85]
PLA-based scaffold conjugated with nHA	hMSCs, post-printing	Human	VEGF	–	Fused deposition modeling 3D printer	[87]
Poly(ethylene glycol) dimethacrylate (PEGDMA) peptides with nanoparticles of bioactive glass (BG) and hydroxyapatite (HA)	MSCs	Human	–	–	Thermal inkjet bio-printing	[88]
PCL polymer and a sacrificial Pluronic F127 hydrogel composite hydrogel gelatin/fibrinogen/HA/Glycerol	Cells encapsulated human AFSCs,	Human	–	Rat	Integrated tissue-organ printer (ITOP)	[89]
Biphasic calcium phosphate (BCP) (with a composition of hydroxyapatite (HA) and b-tricalcium phosphate (b-TCP)	MSCs encapsulated	Human	VEGF	Rat	Direct-write assembly (robocasting) technique	[90]
PCL/alginate	MC3T3-E1 cells, post-printing	Mouse	–	–	Fused deposition modeling 3D printer	[92]
Alginate–PVA–HA hydrogel	Cell encapsulation MC3T3	Mouse	–	–	Selective laser sintering process	[93]
Tricalcium phosphate (TCP), hydroxyapatite (HA), bio-oss (BO), or decellularized bone matrix (DCB).	Adipose-derived stromal/stem cells	Human	bFGF	–	Fused deposition modeling (FDM) process	[94]
Poly(ε-caprolactone) scaffolds modified with hydroxyapatite and poly(propylene fumarate)	Rabbit bone marrow stem cells BMSC	Rabbit	–	Rabbit femur defects	–	[95]

constructs were used as biomimetic in vitro matrices to co-culture human umbilical vein endothelial cells (hUVECs) together with human mesenchymal stem cells (hMSCs) in a naturally derived hydrogel. A central cylinder with %5 GelMA hydrogel and low methacryloyl substitution was printed. For the purpose of osteogenesis induction and synthesizing hydrogel formulations with a chemically conjugated vascular endothelial growth factor (VEGF) to promote vascular spreading, cell-laden GelMA cylindrical parts loaded with silicate nano-platelets were applied, the engineered construct could support cell survival and proliferation during in vitro maturation.

Kim and Kim [86] examined a combination of 3D printing, electrospinning and physical punching process techniques to provide a composite of PCL/alginate construct along nano-fibrous content also modified mechanical strength. This was achieved by sandwiching layers of micro-sized PCL structures between electrospun layers of PCL/alginate and punching the final scaffold to produce micro-sized pores moving through the stack of 3D-printed and electrospun materials. Interestingly, PCL/alginate composite scaffolds against pure PCL scaffolds showed a considerable 7 days increased cell viability, calcium deposition and alkaline phosphatase (ALP) activity at 14 days and a high increase in water absorption capacity due to the improved hydrophilicity contributed by the content of alginate scaffold.

PLA-based scaffold employing an integrated precipitation modeling 3D printer has been developed by Holmes et al. [87]. To support reconstruction of the ossified bone, like vascular cell growth, scaffolds were designed with highly interconnected 3D microvascular-mimicking channels. The constructed scaffolds were also chemically conjugated with nano-hydroxyapatite (nHA) to induce osteodifferentiation of seeded hMSCs. SEM imaging illustrated printing of vertical micro-channels having both a 500 and 250 mm radius, surrounded by a porous bone matrix.

Gao et al. [88] applied inkjet 3DBP to co-print an acrylated polyethylene glycol (PEG) hydrogel with acetylated peptides. Composite hydrogel filled with hMSCs applied to initiate simultaneous photo-polymerization of the hydrogel during printing following exposure to ultraviolet light. The constructed scaffold demonstrated high biocompatibility with a cell viability of 87.9 ± 5.3% 24 h after printing. Mentioned constructs containing hMSCs were cultured for 21 days in both osteogenic and chondrogenic media. Osteogenic and chondrogenic gene expressions were noticed to be highly enhanced from day 7–21, as well as a major collagen and extracellular matrix deposition was observed.

Kang et al. [89] developed an interwoven scaffold which was containing cell-laden hydrogels, PCL polymer and a sacrificial pluronic F127 hydrogel used as a multi-head bio-printer. The Pluronic F127 has been included in several other composite constructs to facilitate the development of provisional structural support or vascular channels.

Wang et al. [90] constructed a 3D-printed bio-ceramic scaffold with phage nano-fibers to dominate obstacle of bone tissue formation. The 3D-printed scaffold contained biphasic calcium phosphate (BCP) with a composition of HA and b-tri-calcium phosphate (b-TCP) at a mass ratio of 60/40. Uniform structure along interconnected macroscale and microscale pores on the columns of the scaffold are features of the mentioned construct. To achieve modification of scaffold osteogenesis and also its vascularization, nano-fiber phages loaded with Arg-Gly-Asp (RGD) were combined with chitosan and adhered to the construct pores through electrostatic interactions. After implantation of this construct in an animal model, it was observed that the host cells interfered with the scaffold and established a vasculature, with MSCs undergoing osteogenesis. Even though the host cells had their survival within the cell-laden construct impaired; however, they slowly formed the vasculature. Costantini et al. [91] constructed a 3D-printed biomimetic hydrogel scaffold containing different combinations of GelMA, chondroitin sulfate amino ethyl methacrylate (CS-AEMA) and hyaluronic acid methacrylate (HAMA). By applying of two coaxial-needle bio-printing system, they reached cell high density, increased cell viability, high printing resolution and post-printing.

Kim et al. [92] manufactured a SF/HA composite of hydrogel, made by hyaluronic acid-dopamine and also with surface modification of HA nanoparticles, managed to facilitate distribution of the HA content. The hydrogel composite demonstrated excellent cell proliferation, an in vivo analysis required to entirely investigate its bone tissue engineering potential.

Bendtsen et al. [93] created a modern formulation of a scaffold made of alginate/PVA/HA hydrogel. This scaffold had the appropriate rheological property for 3D printing of MC3T3 cells. Nyberg et al. [94] printed a 3D porous PCL scaffold applying a FDM process. To functionalize them, mineral additives were mixed in that had been widely utilized commercially and clinically: TCP, HA, Bio-oss (BO) and decellularized bone matrix (DCB). In order to investigate properties of osteoconductivity, each scaffold composites were seeded with an adipose-derived stromal/stem cells in vitro and their differentiation into osteoblasts was evaluated. The content of calcium—normalized to DNA—was especially elevated in PCL-TCP, PCL-BO and PCL-DCB groups relative to PCL only.

Buyuksungur et al. [95] printed 3D PCL scaffolds adapted with HA and poly-propylene fumarate (PPF). In order to produce a mechanically strong implant with uniform pore size and porosity, governable surface hydrophilicity and osteoconductivity, cylindrical disks of PCL were printed by FDM and modified with nHA and PPF. The cytotoxicity, irritation and inflammation analyses showed that the scaffolds were biocompatible. Also, PCL/nHA and PCL/nHA/PPF scaffolds were implanted in the rabbit's femurs for in vivo testing, with and without seeding of rabbit BMSCs and evaluated after 4 and 8 weeks by histological test, micro-CT and mechanical test. As determined by bone mineral density and micro-CT, scaffolds that were seeded by BMSC demonstrated progress in bone tissue regeneration. After eight weeks of implantation, the values obtained from mechanical analysis were remarkably better than those of the healthy rabbit femur and demonstrated a high capacity for patient-specific bone defect.

In addition to these researches, at present time many researchers are attracted to the study of bone 3DBP [96–113]. The 3DBP bone transplantation procedure is shown in Fig. 4. Based on this figure, a computer-aided design of bone graft is an initial phase for fabricating of bone grafts procedure.

Instances of successful 3D printing for bone application are that of the 3D printing of bone scaffolds with hybrid biomaterials. Oladapo et al. [114] designed a new hybrid material bone implant, by combination of polylactic acid (PLA) matrix-reinforced with carbohydrate particles (cHA) using the additive manufacturing (AM) technology. A software application was used for digital surfacing in the mass proportions of 100/0, 95/5, 90/10 and 80/20 for application in bone tissue engineering, seeking higher proposition strength of PLA. As it is evident, biomimetic application can produce high-strength biomechanical implants with appropriate mechanical features. The combination of polymers leads to a rise in diversity of components and applications of biomaterials increased.

In another additive manufacturing technique for scaffold fabricating, Zhao et al. [115] constructed bionic porous titanium scaffolds by the selective laser melting (SLM) procedure. In those studies, different bionic bone scaffolds were manufactured by computer-aided design (CAD). This structure with novel porosity was plotted by using parameterization modeling. At all stages of construction from the design phase of the evaluation of the scaffold porous structures, the parametric modeling of porous titanium bone scaffold with competent mechanical and biological virtues was obtained. Meanwhile, in another study, Lai et al. [116] created a novel porous poly(lactide-co-glycolide) (PLGA)/TCP/Mg (PTM) scaffolds using low temperature, rapid prototyping (LT-RP) technology with the formulation of Mg powder, PLGA and β-TCP. The release of Mg ions was studied, and physical characterization of PTM scaffold in vitro assay was performed. The PTM scaffolds were implanted in a rabbit model for evaluation of the osteogenic and angiogenic properties of

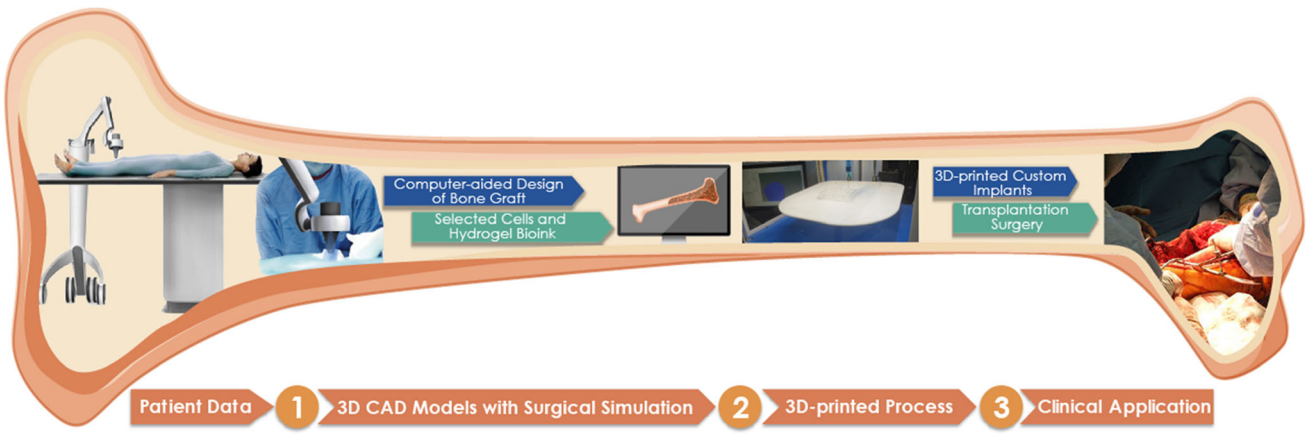

Figure 4 3DBP bone transplantation procedure. Patients suffering from bone disorder, supposed to data gathering by computer-aided instruments such as MRI. Provided bone graft design will be transmitted to a bone scaffold by selecting appropriate cells and growth factors in order to produce a well printable bio-ink. After completion of printing procedure, transplantation surgery is the final step.

the implant. Their results proved that the PTM scaffold had designed in the bio-mimic the structure and modified mechanical properties. Ultimately it was confirmed that the PTM scaffolds are desirable composite biomaterials for solving challenging bone defect that would have great excellent property for its clinical usage.

Roopavath et al. [117] prepared a 3D-printed hydrogels by using an extrusion-based 3D printing technology. The material of this hydrogel is based on HA that had been approved clinically. SEM and Micro-CT results provided revealed that the scaffold enjoys from a better rate of porosity. Mechanical tests were employed to evaluate the porosity effects on the compressive properties of 3D-printed structures. Eventually printed HA hydrogel made of a patient-specific bone graft was tested in a series of studies in patients. The results confirmed the promising potential of this 3D-printed material in manufacturing a bio-mimic porous structure-based anatomical bone models and preoperative 3D planning.

3D bio-printing challenges

The 3DBP has created a huge impact in the tissue analysis field and is turning into a practical strong tool to produce tissues of human body.

The main challenge of 3DBP is the need for in vivo vascularization in order to provide the cells with adequate nutrition, growth factors, oxygen and remove carbon dioxide and wastes. Of course, the future developments of bio-printing can also potentially overcome these vascularization challenges [118]. In vivo, capillaries are mostly located at a 100 mm distance from a majority of cells in order to enable enough diffusion for the cells to survive [119]. For greater distances, like in thick tissues in printed organs, supplementary modes for diffusion may be required. To surpass this huddle, Hutmacher et al. [120] suggested an artificial vascular system.

Also, the bio-printing process is not currently automated and plenty of manual operations separated in various steps may result in slow processing speed, thereby increasing the prospect for mistakes and errors [21]. In order to form a highly mimetic tissue or organ on a macroscale, bio-printed cells should proliferate. When selecting cells, two main factors are considered: how the bio-printed cells can imitate the physiological state of cells in vivo and how much the bio-printed cells can perform their in vivo functions under optimized microenvironments [22]. Artificial tissues are seeded by either printing functional primary cells with supporting cells [75, 121–126] or printing progenitors or stem cells for further differentiation [127–132]. Direct printing of primary cells can rapidly increase the complexness of bio-printing.

Prospective market

3DBP is presently increasing greatly toward a large industry as a result of its variation and potential implementations. 3DBP market size is hoped to obtain a $10.8 billion worth in 2021 from a $2.2 billion stance in 2012 [133]. Presently, many companies engage in 3DBP production, for the purpose of tissue engineering applications [134].

Furthermore, in 2014, a bio-printed human liver tissue, named exVive3D^{TM} Liver, which was manufactured for drug toxicity evaluation, was introduced [135]. However, the product provided for in vitro drug screening, the successful development of a commercially available liver tissue, is still pending [24]. Microfluidic systems [136] and layer-by-layer assembly [137] will have an effect on the bio-fabrication of microstructures in the future. It is inevitable that advances in bio-fabrication will also profit related fields such as imaging and diagnostic applications too [24]. It is predicted that the progressive trend of 3DBP methods' prevalence will lead to in situ bio-printing developing, which could be considered as an upward procedure from benchside to the bedside [78, 138].

Conclusion

In this paper, the different procedures of 3DBP of skin and bone tissues, results, advantages and disadvantages have been reviewed with details. This review emphasizes on the 3D bio-printed skin as a novel technology that provides the scaffold using biomaterials such as gelatin, fibrinogen, GelMA, chitosan and collagen. In this technology, applying cells, such as fibroblast, keratinocyte, melanocyte and HUVEC by growth factors like FGF-2, thrombin and hydrocortisone into a 3D environment, provides a similar setting close to the natural skin tissue. Skin

constructs can be beneficial for patients, whom interfere with extensive burns and full-thickness skin wounds. Skin bio-printer can decrease healing time and less pain, and this technology has the potential of creating the fully functional skin constructs.

For bone tissue 3D printing, materials such as HA, PVOH, PCL, GelMA, PLA and PLGA were used by utilization of various cell types such as human adipose stem cells (ASCs), HUVEC and hMSCs. This fabricating process could involve powder-based 3D printing and extrusion bio-printing.

The bio-printing technology is a growing field that is leading to a global revolution in the medical sciences and has gained significant attention worldwide. However, bio-printing technology has been adopted for skin and bone tissue fabrication and it is hoped that other tissues could be produced by this technique.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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