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Review Article

Bioprinting of Skin Tissues: From Concept to Clinical Applications

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ABSTRACT

3D bioprinting, with its vast potential in therapeutic uses, has evolved into a forefront technique for creating skin tissues. This article delves into a thorough analysis of various aspects of bioprinting skin tissues, including strategies, bioinks, clinical applications, challenges, and future outlooks. Different bioprinting strategies, such as laser-assisted, inkjet-based, and extrusion-based techniques, are explored, each offering unique advantages in crafting complex, lifelike skin structures. The composition and cell-friendly nature of collagen-based bioinks are discussed, underlining their significance in establishing a conducive microenvironment for cell survival and tissue development. Clinical applications, particularly in providing personalized treatments for wound healing using bioprinted skin tissue, are examined. The article also investigates the potential uses of tailored and in vitro bioprinted skin models. Challenges, including achieving optimal printability, vascularization, and innervation of various skin components during the bioprinting process, are addressed. Lastly, the article looks forward to future developments, such as transforming regenerative medicine and merging skin bioprinting with other bioprinting technologies.

INTRODUCTION

Additive manufacturing includes a set of advanced technologies that directly create three-dimensional (3D) material objects from computer-aided design (CAD) data. Currently, additive manufacturing methods are used to make 3d structures using thermoplastic polymers, metals, and ceramics (Vanaei et al., 2021). 3D bioprinting is an advanced technology that allows the creation of biological structures with a hierarchical architecture, where it use rapid prototyping or additive manufacturing methodologies to produce biofunctional substances in a sequential layer-by-layer, specifically including the printing and arrangement of cells or other biological objects (Matai et al., 2019). This technology enables the automatic seeding of cells on a structure or tissue with a wide range of biomaterials according to the intended application of the end-product. The field of 3D bioprinting holds great promise for a variety of medical research needs, including but not limited to regenerative medicine, and the creation of functional organ replacement (Vanaei et al., 2021).

Various study investigates the application of 3D bioprinting technology in producing biological tissue for various areas, including the skin, heart, bone and cartilage, and other organs. In skin tissue engineering, 3D bioprinting is primarily utilized for autologous skin transplantation, a technique widely employed in clinical practice. Due to the skin's direct exposure to the external environment, its intrinsic capacity for complete regeneration after injury is limited. To overcome this challenge, 3D bioprinting techniques are being employed to create functional skin substitutes with enhanced precision and resolution (Weng et al., 2021).

Bioprinting Strategies for Skin Tissues

Skin tissue bioprinting generally involves four steps (Figure 1). Firstly, pre-processing, which includes selecting the cell types, bioinks, additional biomaterials, and CAD design, Next is 3D

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bioprinting, followed by post-processing, which includes cell proliferation, tissue remodelling, and maturation after the printing of skin constructs. Lastly, the cell functionality will be assessed using biochemical and physiological characterization of the printed skin tissue (Yan et al., 2018).

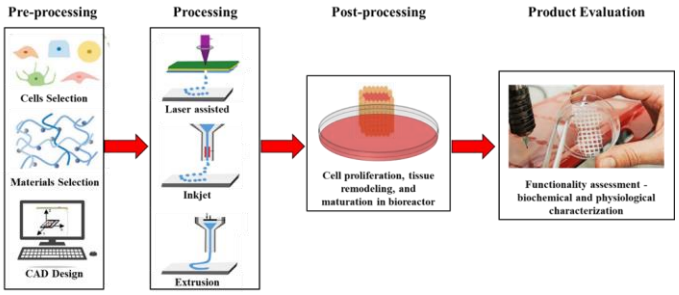

Fig 1 Steps involve in 3D bioprinting of skin.

There are several bioprinting techniques that can be used to fabricate a bioprinted skin tissue, these include laser-assisted bioprinting, droplet-based or inkjet-based bioprinting, and extrusion-based bioprinting. The advantages and disadvantages of these type of 3D bioprinting are summarized in Table 1. Laser-assisted bioprinting use the lasers focused on an absorbing substrate to generate pressures that propel cell-containing materials onto a collector substrate (Guillemot et al., 2010; Gu et al., 2020). This technology is a nozzle-free technology, which eliminates issues like nozzle clogging and contamination that are common in conventional nozzle-based bioprinting methods and can fabricate a tissue construct with high resolution, high cell density and viability. A skin substitute with fibroblast and keratinocyte cells embedded in collagen hydrogel is successfully fabricated via laser-assisted 3D bioprinting (Koch et al., 2012). The bioprinted skin substitute closely resembled the natural skin cell localization and gap junction formation.

Table 1 Advantages and disadvantages of various type of 3D bioprinting (Murphy & Atala, 2014)

Type of 3D Bioprinting	Advantages	Disadvantages
Laser assisted	Non-contacting process Nozzle free High precision High concentration and high viability of cells	Limited printable materials High cost Time-consuming
Inkjet-based	Widely used High printing speed High resolution High cell viability Low cost	Thermal and mechanical stress to cells Limited printable materials Low cell concentration
Extrusion-based	Widely used Good compatibility with materials	Limited printing accuracy The need for gelation and shear thinning properties of materials

In addition, droplet-based or inkjet-based bioprinting is a technique in which bioinks are dispensed as droplets through a nozzle. It allows for precise positioning of individual droplets, enabling the creation of complex structures. There are two types of inkjet bioprinting which are continuous-inkjet bioprinting and drop-on-demand inkjet bioprinting. Continuous-inkjet bioprinting depends on the bioink solution's innate tendency to flow through a nozzle under pressure to eventually shatter into continuous droplets as a result of Rayleigh instability (Zhang et al., 2023). Continous-inkjet bioprinting generate droplet at a relatively faster rate, whereas drop-on demand inkjet bioprinting generate droplets when required (Vijayavenkataraman et al., 2018; Gudapati et al., 2016). Drop-on demand inkjet bioprinting use thermal or a piezoelectric or an electrostatic actuator to generate a pressure pulse. This method offers advantages such as high resolution, versatility in printable biomaterials, and the ability to print cell-laden droplets (Ng et al., 2017). A vascularized skin model was successfully fabricated via a modified 3D bioprinting system where they combine inkjet and extrusion bioprinting (Kim et al., 2017). After 14 days, the bioprinted skin model with a functional transwell system displayed positive biological traits, such as a stabilized fibroblast-stretched dermis and stratified epidermis layers.

Extrusion-based bioprinters use pneumatic or mechanical (piston or screw) dispensing systems to extrude continuous beads of cell-laden bioink. The benefits of this method include cost-friendly, rapid printing speed, scalability, and the ability to print a diverse spectrum of bioinks such as hydrogels, polymers, micro-carriers, decellularized ECM, and cell aggregates (Antezana et al., 2022). Apart from that, this versatile extrusion-based bioprinting can be combined with other bioengineering technologies to fabricate a skin tissue model, for example, with coaxial bioprinting, multi-material bioprinting and microfabrication technologies (Kim et al., 2017; Kim et al., 2021; Lian et al., 2022; Murphy & Atala, 2014). Ahn et al successfully construct a full-thickness skin model with a uniform and stratified epidermal layer using sacrificial gelatin-assisted extrusion bioprinting (Ahn et al., 2023).

Bioinks for Skin Bioprinting

Bioink is defined as a solution of a biomaterial or a mixture of several biomaterials in the hydrogel form, usually encapsulating the desired cell types (Gungor-Ozkerimet al., 2018). Bioinks are essential in the creation of functional skin tissue constructions using 3D bioprinting technology. Bioinks are materials that can be used to print 3D structures layer by layer. They comprise living cells and biomaterials that act as structural supports while promoting cell development and differentiation. Bioinks are utilized in skin tissue engineering to generate skin constructs that resemble the native anatomy and physiology of skin and surrounding tissues (Gungor-Ozkerim et al., 2018). Choosing a correct biomaterials and cells type for bioink preparation is crucial to successfully bioprinting a skin model.

Natural polymers and synthetic polymers are the most common biomaterials used in 3D bioprinting. In skin bioprinting, natural polymers existed in natural extracellular matrix (ECM) or extracted from marine organisms and natural substances such as gelatin, collagen, alginate, chitosan and fibrin, have been widely used due to its high-water content which mimic the native ECM (Scognamiglio et al., 2020). Due to their excellent biocompatibility, biodegradability, low immunogenicity and ability to imitate native ECM, they are

preferable bioink materials for skin 3D bioprinting (Zhang et al., 2023). Apart from that, polysaccharides such as alginate, chitosan, and pectin also extensively utilized in bioinks due to their capacity to produce hydrogels and offer a favorable environment for cell development and differentiation (Xu et al., 2020). On the other hand, synthetic polymer has remarkable advantages which are controllable mechanical properties and structure stability (Bedell et al., 2020). However, it is more commonly used to create artificial bone and cartilage than artificial skin, especially nonbiodegradable synthetic polymer such as polyethylene glycol (PEG) (Zhu et al., 2011). Synthetic polymers are frequently modified and combined with natural polymers to improve their qualities (Zhang et al., 2023).

Prior on determining the type of cells use to bioprint a skin, the skin anatomy and structure has to be understood. Skin is stratified into layers of epidermis, dermis and subcutaneous tissue (Figure 2). The epidermis is the most outer layer of the skin where keratinocytes is the primary cells of this layer. Melanocytes are aligned at the basement membrane of the epidermis to separate the epidermis from the dermis. Dermis, primarily made of collagen and fibroblast is the thickest layer of the skin. The fat cell or lipocytes made the subcutaneous tissue layer can buffer impact force, store energy and secrete bioactive substances (Brüggen et al., 2020). The main option for skin tissue engineering is to use fibroblasts and keratinocytes, either separately or in combination, to reassemble the epidermis and dermis (Daikuara et al., 2022). These types of cells have performed well in in-vitro tests, but for in-vivo use, the host immune response must be taken into consideration (Jain et al., 2022). It is challenging to collect cells from the injured host autologously, and the clinical use is constrained by the high cell demand and prolonged culture period of time. To address this problem, stem cells such as mesenchymal cells (MSCs), adipose-derived stem cells (ADSCs) and induced pluripotent stem cells (iPSCs) are take into consideration and have been applied into skin tissue engineering (Mazini et al., 2020).

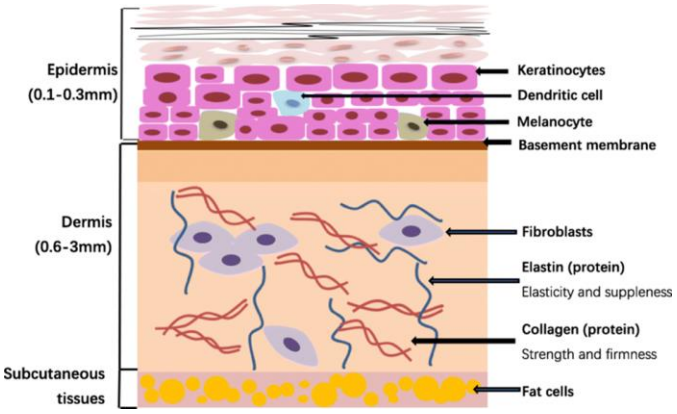

Fig 2 Schematic diagram of skin structure (adapted from Zhang et al., 2011)

Clinical Applications of Bioprinted Skin Tissues

3D bioprinted skin tissue holds significant promise for various clinical applications, particularly in the field of regenerative medicine and wound care. 3D bioprinted skin tissues are being highlighted as the new gold standard for alternative models to animal testing, as well as for full-thickness wound healing (Kang et al., 2022). One notable application involves custom therapies for wound healing and skin regeneration (Shopova et al., 2023). 3D bioprinting facilitates the creation of skin that closely resembles the complex composition of human skin. Additionally, this technology enables the inclusion of specialized cells and bioactive compounds, thereby improving the effectiveness of the healing process. In a recent systematic review on 3D printing for wound healing, it was found that 3D bioprinting enables precise cell and material distribution, facilitating customized skin shapes. This enables the effective and dependable production of bionic skin substitutes, meeting clinical and industrial requirements (Tabriz & Douroumis, 2022).

Next, the utilization of a proficiently 3D bioprinted skin model can serve as an effective in vitro model for various purposes, including pharmaceutical development, drug delivery system testing, and drug screening (Yan et al., 2018). Olejnik et al., state that 3D-printed skin models allow researchers to mimic the complex structure and function of human skin (Olejnik et al., 2021). This advancement enables the study of different diseases, the evaluation of treatment choices, and the creation of personalized medicine approaches. Therefore, these models provide a more reliable method of assessing the safety and efficacy of products. Possible uses in dermatology include examining the pathophysiological causes of skin diseases and testing new biological treatments (TNF, IL-17, and IL-23) for diseases like vitiligo, psoriasis, and atopic dermatitis (Lee et al., 2014; Hou et al., 2017; Tarassoli et al., 2018).

Finally, the customization potential of 3D-printed skin holds promise for skin transplants, providing a readily available solution that can be tailored to fit the patient's needs, potentially reducing rejection risks, and allowing for rapid and scalable production (Varkey et al., 2019). This has the potential to revolutionize burn care by offering tailored solutions and improving outcomes for patients with severe burns.

Challenges in Skin Bioprinting

With the advancements in 3D bioprinting of skin tissues, clinicians and researchers have encountered several limitations that needed to be addressed for achieving accurate models. The challenges of printability, vascularization, and innervation have emerged as crucial technical challenges. Firstly, ensuring perfect printability involves considering the biocompatibility and mechanical strength of the bioink used. Researchers have faced difficulties in selecting materials that are both biocompatible and mechanically strong for human applications (Zhang et al., 2023). High-resolution cell deposition techniques have been used to mimic skin architecture, but cell placement in the correct layers and structures is still a challenge, affecting the quality and functionality of the printed skin tissue (Augustine, 2018).

Vascularization is another significant limitation in the 3D bioprinting of skin tissues. Researchers have investigated strategies such as incorporating vascular cells and growth factors into bioinks to promote angiogenesis (Daikuara et al., 2022). However, the development of proper methods to achieve fully vascularized skin tissue is still an ongoing area of research. Furthermore, innervation, which involves incorporating sensory perception in 3D bioprinted skin tissue, has also been studied by researchers (Olejnik et al., 2021). Factors such as material selection and printing parameters have been identified as influential in achieving proper innervation.

While the reviewed journals and papers present promising results, it is important to note that the field of 3D bioprinting for skin tissues is still in development. Finding suitable materials for printing, vascularization, and innervation remains a critical concern that needs to be addressed for further advancements in this area.

Future Perspectives and Advancements

With recent advancements in bioprinting techniques and materials, the potential for fabricating skin tissues with enhanced functionality and complexity has grown. Among these advances is the development of patient-specific skin grafts and tissue constructs that are tailored to individual needs. Personalized treatments truly have the potential to transform regenerative medicine for burn victims, chronic wound patients, and people with genetic skin disorders (Yu et al., 2019). In fact, Chen et al. (2020) demonstrated a noninvasive in vivo 3D bioprinting technology based on near-infrared photopolymerization, allowing the printing of tissue constructs without surgical implantation, which could greatly benefit patients more holistically.

Another promising bioprinting prospect is the ability to incorporate skin bioprinting with other organ bioprinting technologies. For instance, this incorporation involves integrating bioinks with multiple cell types in epidermal and dermal skin layers, including keratinocytes, fibroblasts, and endothelial cells. Moreover, utilising new scaffold-free bioprinting methods along with the previous technique enables the fabrication of more complex and functional skin tissue constructs (Yu et al., 2016).

Additionally, Gupta and Negi also discussed the combination of biofabrication techniques such as microfluidics and organ-on-a-chip systems that show promise in mimicking the microvasculature and dynamic microenvironment of the skin (Gupta and Negi, 2022). Therefore, by understanding the current landscape and future directions of bioprinting for skin tissue engineering, researchers can shape the future perspectives of skin bioprinting and contribute to the development of innovative solutions in regenerative medicine.

CONCLUSION

In conclusion, laser-aided, droplet-based or inkjet-based, and extrusion-based bioprinting are the most prevalent methods for skin tissue fabrication. Laser-assisted bioprinting prints high-density cell suspensions and bioinks with a wide viscosity range nozzle-free. Due to its low cost, ease of use, and low cell injury risk, inkjet bioprinting, especially microvalve-based bioprinting, can create biomimetic skin equivalents. Extrusion bioprinting, the basic approach, creates bioinks efficiently and effectively. These bioprinting methods help generate various skin tissues. Furthermore, bioinks replicating the extracellular matrix (ECM) are used in tissue engineering to mimic skin's innate structure and physiology. Natural collagen and polysaccharides like alginate and chitosan are great bioink materials due to their biocompatibility and ability to mimic native skin tissue's ECM. Moreover, 3D-printed skin with specialised cells and bioactive substances can be used to create custom wound healing and skin regeneration therapies. This method allows exact cell and material distribution, making possible bionic skin substitutes for clinical and industrial use. 3D-printed skin's personalization and rapid, scalable production make it a promising skin transplant solution. These advances could revolutionise burn care and improve outcomes for severe burn victims. In addition, printing, vascularization, and innervation materials are still a major issue that must be addressed for this field to advance. Besides, bioprinting techniques and materials are able to produce skin tissues with more functionality and complexity. Vascular networks, innervation, and immune system components make skin models more physiologically relevant. Bioprinting allows for complex skin tissues, patient-specific grafts, and interaction with other bioprinting technologies, which advances regenerative medicine.

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