ORIGINAL ARTICLE

Bali Medical Journal (*Bali MedJ)* 2021, Volume 10, Number 1: 122-125
P-ISSN.2089-1180, E-ISSN: 2302-2914

Bali Medical Journal
www.BaliMedicalJournal.org
Published by Bali Medical Journal

The future of three-dimensional skin graft: a mini-review

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Received: 2021-02-04
Accepted: 2021-03-16
Published: 2021-04-01

ABSTRACT

Over the last few years, the development of three-dimensional (3D) skin bioprinting has increased rapidly. The concept of bioprinting involves a computer in designing using conventional 3D printing. 3D bioprinting can produce tissue structures such as skin and have the opportunity to substitute autografts, which are still the gold standard today. Network construction in bioprinting requires stages in the network structure design, selection of cell and biomaterial raw materials, and the molding process. The use of keratinocytes and fibroblasts is used as the main raw material in the manufacture of the dermis and epidermis layers. The biomimetic technique will combine these raw materials with other biomaterials (hydrogel, collagen, fibrin, gelatin, alginate, chitosan, and chitin) and growth factors (hydrocortisone, thrombin, and FGF-2) so that the physiological condition of the skin can be created. Currently, 3D bioprinting research continues to develop in response to the various shortcomings and challenges faced. The purpose of this review is to discuss the current use of 3D bioprinting technology, the principles of this technology and the prospects for 3D skin bioprinting in the future.

Keywords: three dimensional, bioprinting, skin.
Cite This Article: Santoso, Z.A. 2021. The future of three-dimensional skin graft: a mini-review. *Bali Medical Journal* 10(1): 122-125. DOI: 10.15562/bmj.v10i1.2242

INTRODUCTION

In 1986, Charles Hull invented 3D lithography for the first time, then followed 30 years later with an invention of 3D fabrication technology in the form of 3D bioprinting.[1] Bioprinting has received great attention globally because it can bring medical science to a global revolution.[2] The working principle of bioprinting is in the form of conventional 3D printing that uses computer-assisted design (CAD) with a high degree of flexibility to form specially designed network structures through a deposition process biomaterials, living cells, and growth factors that have been designed beforehand.[3] Bioprinting has the opportunity to replace the gold standard autografts currently in use because bioprinting allows biomimicry like never before.[4,5] Bioprinting on the skin can cause replication in blood vessels by forming hollow channels, depositing a thin layer of melanocytes, and on the dermal cells can form a microenvironment that triggers hair.[4,6] The benefits of bioprinting in patients with extensive burns and thick skin wounds are full. It can shorten healing time, minimize pain, and improve cosmetic aspects' outcomes with skin molding that resembles real skin.[2,4,7] At present, the management of wounds in patients has used various biomaterials such as scaffold formats, fabrication techniques, crosstalks material,s and bioactive factors.[8] The advances in biology, medical science, manufacturing and materials have caused skin bioprinting to have great potential to be developed to produce better wound repair despite the many challenges in its application.[4] The purpose of this review is to discuss current uses of 3D bioprinting technology, the principles of bioprinting technology and the prospects for 3D skin bioprinting in the future.

PRINCIPLES OF 3D BIOPRINTING SKIN

Until now, there is no genuine leather that can be fully imitated by bioprinting leather in terms of its biochemistry, morphology or function.[5,6,9] The bioprinting stages sequence is by making an image of the tissue structure to be imitated, selecting suitable cells and biomaterials, and continuing with the printing of the previously constructed tissue (Figure 1).[3]

The most common biomaterials used in the printing process of the dermis and epidermal layers are keratinocytes and fibroblasts.[4,9–11] Meanwhile, to improve the construction of tissue printing functionally, human umbilical vein stem cells or endothelial cells, melanocyte cells, and cultured fibroblasts and keratinocytes with specific cells were used.[2,9] Examples include the combination of endothelial cell culture with fibroblasts and melanocyte with keratinocyte cell culture to construct pigmented and vascular sites.[8] Besides combining specific cell combinations, cell culture can also be done separately or without a combination, for example, hair follicle cell culture, skin stem cells, and sebaceous gland cells for newly grown skin.[8,12]

In artificial skin, a biomimetic approach is carried out by utilizing various natural and synthetic materials such as hydrogel, collagen, fibrin, gelatin, alginate, chitosan and chitin so that later it can form skin that resembles the physiological conditions of natural skin.[8,9,13–16] In order to increase the

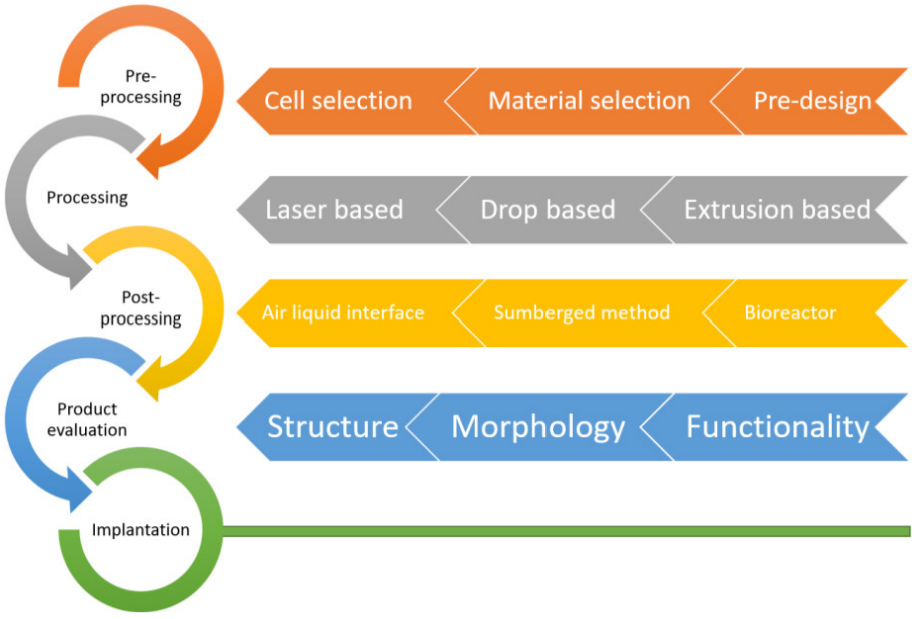

Figure 1. Schematic of the overall 3D bioprinting process for human skin

similarity of natural skin structure, in the bioprinting process, several growth factors are also added, such as hydrocortisone, thrombin and FGF-2, which have an impact on increasing the engineering of skin tissue significantly.(2,8,14)

The main pre-designed approach used to reconstruct skin structures and guide the imprinting process is computer-assisted imaging (computed tomography, magnetic resonance imaging) techniques.[3,9,10,17] Sutula carried out an increase in skin graft efficiency meshing in 2020 by determining the optimization of the graft meshing pattern for samples subjected to biaxial extensions of up to 150%, thus forming an expansion ratio of 1: 2: 25. Although three prospective unit-cell solutions were proposed to increase the skin graft pattern's efficiency, these studies' results did not meet the criteria for experimental validity.[17]

Bioprinting techniques also have many instrumentation approaches, such as inkjet or laser-assisted bioprinting and microextrusion.[3,9] The electrohydrodynamic bioprinting (EHD) technique also has the potential and high resolution that has been further explored to produce skin construction in drip mode. In order to produce a better leather engineering model through the 3D bioprinter technique, it is necessary to understand the working principles and physics of each printing process.[9]

After the skin construction has been printed, the method usually used is the static culture in a petri dish; for example, the ALI method is used for epidermal ripening. The submerged method is used for dermal ripening, but this method is also not always suitable for large-scale production.[9,18] Another method used to ripen post-construction skin is a bioreactor with a perfusion system and a stirred flask to allow cell proliferation to form tissue in the artificial skin.[9]

In the process of characterizing the dermal compartment, measurement of the duration of MTT staining, histology and immune staining, and life-death staining can be used, with indicators of skin cell survival and ECM production levels. The dermal layer of the artificial skin, precisely in the blood vessels, can show the vascular system's development in human skin grafted for artificial skin construction.[9] The reconstructed artificial skin tissue's ultrastructural image can be seen from the immunohistochemical technique followed by observation under an electron microscope. There are indicators used to compare it with normal epidermal tissue, namely localization of epidermal differentiation markers and molecular and functional barrier features to determine the stratification method. It is necessary to understand the artificial skin's mechanical properties to know in more detail the relationship between the biomechanical and molecular aspects of the skin.[9,18,19] The bioprinting process must achieve good structural and functional integrity to resemble real skin to be able to heal wounds, but this process also allows for the printing of keratinocytes, fibroblasts, and stem cells using biocompatible "ink".[6,20]

In 2017, there are BioMask products published by Seol et al. These products have great potential in functional and aesthetic aspects for the recovery of facial skin that has been injured with fast recovery times. The wound healing and skin reconstruction effect of the product comes from the reprinted elastic PU polymer. In in vivo studies, 3D bioprinting methods have been used for skin transplantation in immunodeficient mouse models.[11]

CURRENT AND FUTURE PERSPECTIVES

Some limitations and challenges need to be overcome, although skin bioprinting has many advantages in creating skin functions equivalent to normal skin.[8,9,21] Some of the disadvantages of skin bioprinting in the biological aspect are scar tissue, vascularisation failure, difficulty in integration with the wound bed and lack of functionality.[8,20] Various cell types and cell numbers can overcome weaknesses in the form of lack of skin functionality.[22,23] According to studies, cells located far from capillaries (more than 200 μm) will experience internal mass transfer limitations to be more prone to hypoxia and apoptosis.[24] In overcoming this problem, stem cells can be used, but there is a risk of long-term side effects, so this alternative still needs to be considered and investigated further.[25] The use of stem cells can even be used for skin that is not injured by causing skin replacement resulting in the restoration of skin pigmentation, regeneration of the epidermis (hair, sebaceous and sweat glands), vascular, and subcutaneous tissue.[7]

Artificial skin, which mostly uses collagen type I, has a weakness in skin shrinkage. However, the combination of collagen with a mesh polymer such as PCL can be an alternative solution. However, this solution is also followed by the disadvantage of a long PCL

degradation time, which inhibits skin implantation.[9] Obstacles in scar tissue can be overcome by regulating the expression of the growth factor TGF-β which plays a role in scar tissue formation in adult individuals.[8] Meanwhile, the aspects of vascular and sensory receptor failure in the construction skin still do not have an alternative solution and become a challenge in the future.[22,23] Other obstacles related to bioprinting, such as regulations and ethics, also need to be overcome.[9]

So far, large skin construction in patients with more than 50% skin loss remains a major challenge, although several in vivo studies show skin bioprinting's success in small wounds.[8,11] This is due to differences in the wound's size and depth, which will impact the speed and quality of skin regeneration from the engineered material.[8] Also, aspects of cost, production volume, storage mechanisms, and storage space availability also need to be considered in the plan to implement 3D bioprinting in hospitals.[6,8,26]

3D skin tissue is a potential pathway with promising cosmetic aspects. Therefore, a small-scale study is needed to determine the short and medium-term clinical effects of this technology before being applied to reconstructive surgery patients.[6,9,20] In the future, 3D bioprinting also needs to be developed in a portable form to become one of the management options for patients who require skin reconstruction in remote areas or emergency conditions.[27]

CONCLUSION

In realizing the construction of artificial skin physiologically similar to natural skin, skin bioprinting has great potential. However, there are still limitations in the application aspect to make artificial leather constructions that resemble real leather, for example, the lack of printers and software for printing access. Therefore, multidisciplinary cooperation is needed to improve the quality of 3D bioprinting.

DISCLOSURE

Author contribution

The author contributed to the drafting and writing of this manuscript .

Funding

None.

Ethical statement

None.

Conflict of interest

The author declared there was no conflict of interest in the writing of this manuscript.

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