World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Next-generation 3D-printed bioengineered skin grafts: From experimental validation to clinical implementation

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World Journal of Biology Pharmacy and Health Sciences, 2025, 23(01), 369-380

Publication history: Received on 12 June 2025; revised on 19 July 2025; accepted on 21 July 2025

Article DOI: https://doi.org/10.30574/wjbphs.2025.23.1.0694

Abstract

Bioengineering Three-dimensional (3D) bioprinting has revolutionized tissue engineering by enabling the 3D printing of bioengineered skin grafts with a tissue architecture similar to that of native skin. These grafts, composed of layered cellular constructs containing keratinocytes, fibroblasts, and bioactive hydrogels, have indeed provided an alternative to traditional autografts and allografts, addressing the issues of donor source morbidity and immune rejection. The article provides a detailed overview of the achievements observed by 3D-printed skin grafts on their way to clinical use. Similar to experimental models, the viability of cells is high, differentiation is robust, and cells can be integrated with preclinical models without loss of functionality, with only minor improvements in vascularization and appendage engraftment. Regulation, scale, and graft durability, however, are some of the challenges to clinical translation. The critical outcomes were the practical wound-healing effects on animals and a pilot clinical trial, particularly in the treatment of burns and chronic wounds. The development direction emphasizes progress in the in situ bioprinting method and the improvement of graft optimisation according to Artificial Intelligence and patient-specific grafts as one way to increase the rates of treatment success. The article highlights the future of 3D-printed skin grafts as a revolutionary development in regenerative medicine. It facilitates interdisciplinary cooperation and standardisation of procedures, as well as the level of responsibility and access, to reduce the gap between laboratory innovations and clinical standards.

Keywords: 3D Bioprinting; Bioengineered Skin; Skin Grafts; Tissue Engineering; Clinical Translation

1. Introduction

1.1. Background on Skin Grafts and Current Limitations

Skin grafting is the primary form of reconstructive surgery used to treat extensive skin loss resulting from burns, chronic wounds, and other injuries. Conventional methods contain autografts, allografts and xenografts. Autografts are harvested from the patient's similar skin; therefore, they are considered the gold standard due to their immunocompatibility but are restricted by donor site morbidity, which includes, but is not limited to, pain, scarring, and the risk of infection (Kagan et al., 2013). Made from human cadavers, allografts (temporary coverings used to limit adverse effects) and porcine-derived xenografts have disastrous effects, such as immune rejection and disease transmission, which must be treated with immunosuppressive medication or monitored continuously (Halim et al., 2010). Such methods may not necessarily satisfy the needs of extensive or complicated reconstruction, especially in cases of burn victims with limited donor sites. Therefore, it is essential to develop new models that address gaps where existing techniques prove inadequate.

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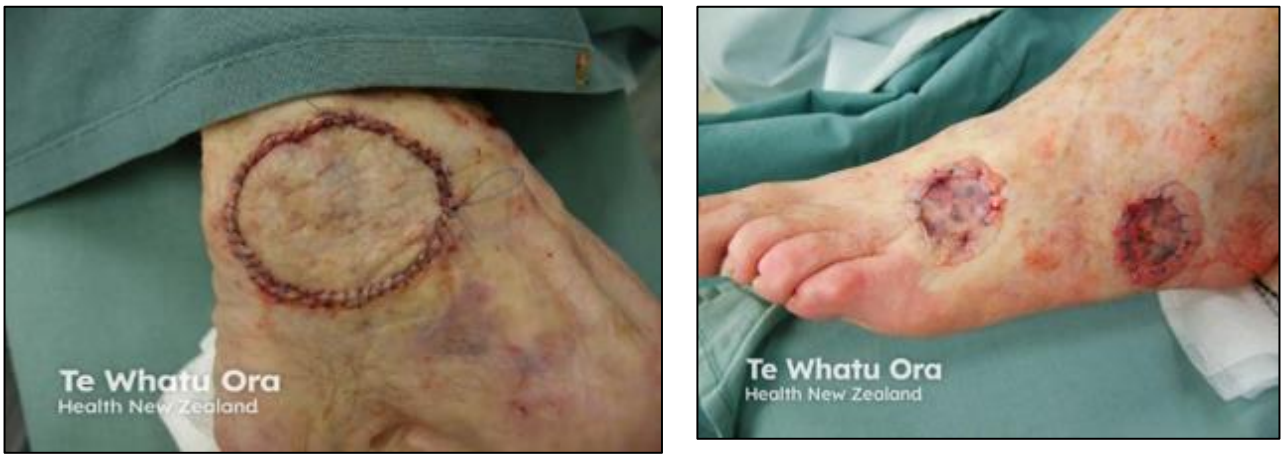
The shortcomings of conventional grafts make using something more sophisticated in such fields as burns and wounds (chronic visceral), diabetic ulcers, and other reconstructive surgeries a necessity. Chronic wounds affect the health of millions of people worldwide, and those that facilitate a quick healing process while reducing complications are needed (Sen, 2019). In the same light, burn injuries, the second major morbidity cause, require grafts to reconstruct function and aesthetics using biocompatible grafts (Rowan et al., 2015). Grafts today cannot usually regenerate vital skin structures, including appendages or blood vessels, which makes the morula outcome suboptimal and potentially results in scarring or other adverse effects due to graft failure. The challenges highlight the necessity of bioengineered skin substitutes that enable overcoming the limitations on availability, hypothetically reduce the risks of immunological complications, and enhance the functionality of restoration, thereby paving the way for the emergence of new revolutionary technologies in regenerative medicine, such as 3D bioprinting.



(a) (b)

Adapted from https://dermnetnz.org/imagedetail/20013-skin-graft

Figure 1 (a) A full-thickness skin graft on the wrist immediately after skin cancer excision (b) Partial-thickness skin grafts after skin cancer excisions

1.2. Emergence of 3D Bioprinting in Tissue Engineering

Cutting-edge 3D bioprinting is a form of tissue engineering that involves the computer-directed layering of cell combinations, biomaterials, and bioactive molecules to produce complex tissue with highly controlled cellular architecture (Murphy and Atala, 2014). The workflow combines the concept of additive manufacturing. It applies inkjet, extrusion, or a laser-based bioprinting approach to layer bio-inks in a prescribed stack, following the 3D architecture and functional complexity of native tissues. In contrast to other tissue engineering methods that rely on manual processes, such as scaffold cell seeding, 3D bioprinting offers the possibility of high-resolution positioning of multiple cell types and materials, with accurate recreations of the tissue microenvironment. This accuracy is essential in developing working tissues because it enables one to integrate cellular and extracellular components depending on computationally informed models obtained through medical imaging or histological data (Groll et al., 2016).

The benefits of a 3D bioprinting method compared to the standard tissue engineering approach are multiple, especially in skin tissue reconstitution. This has created an architectural control that is not possible with traditional methods, as it can produce multilayered skin constructs with clear stratification between the epidermal, dermal, and vascular compartments (Ng et al., 2016). It makes the use of patient-specific cells more feasible by reducing immunogenicity and allowing the production of scalable grafts (with wound size and shape). In skin regeneration, 3D bioprinting neutralises the drawbacks of traditional grafts, as it allows for the incorporation of vascular networks and skin appendages to enhance accelerated healing and restoration of function (Vijayavenkataraman et al., 2016). These abilities make 3D bioprinting a potentially game-changing process, having the capacity to reinvent wound treatment and reconstructive procedures that create biologically pertinent, tuneable skin fac-similes.

Objectives of the Article

This article aims to review experimental advancements in 3D-printed bioengineered skin grafts, focusing on innovations in bioink formulations, multilayered constructs, and preclinical outcomes. It evaluates critical challenges in clinical translation, including regulatory hurdles, scalability, and long-term graft functionality, to identify barriers to

practical application. Finally, it proposes a roadmap for clinical implementation, outlining strategies for standardized manufacturing, clinical trial design, and integration into medical practice, aiming to bridge the gap between laboratory innovation and transformative wound care solutions.

Scope and Structure of the Article

This article explores 3D-printed bioengineered skin grafts, covering their development from experimental validation to clinical application. It reviews bioprinting technologies, preclinical outcomes, and regulatory challenges, while proposing a roadmap for medical integration. Structured across introduction, fundamentals, experimental validation, clinical translation, challenges, case studies, and discussion, it aims to guide advancements in regenerative medicine.

2. Fundamentals of 3D Bioprinting for Skin Grafts

The fabrication of skin grafts is being transformed by three-dimensional (3D) bioprinting, which enables the deposition of bioinks (biomaterial suspensions) containing cells, biomaterials, and growth factors to form fully functional tissue constructs. This section explains the fundamental elements of skin bioprinting, including advanced printing systems, bioink formulations, and bioink structural design that resembles the composition of native skin layers, as well as ideal processing parameters. By combining the vascular and cellular networks, 3D bioprinting circumvents the drawbacks of traditionally used grafts, providing a solution that enables wound healing and reconstruction, thereby paving the way for clinical applications in regenerative medicine.

2.1. Bioprinting Technologies

Bioprinting, such as inkjet-based bioprinting, utilises inkjet printing, where bio-ink is ejected by thermal or piezoelectric actuation to create a high-resolution deposit of cells (e.g., keratinocytes and fibroblasts) for a skin graft (Murphy and Atala, 2014). The positioning is accurate, and it is excellent for depositing thin layers of epidermal material; however, it utilizes low-viscosity bio-ink, which raises concerns about cell injury due to shear stress. Small-scale wound repair and in vitro skin models have been employed in drug testing applications. In extrusion-based bioprinting, pneumatic or mechanical circuits are used to deposit viscous bioink, and more complex, multilayered skin constructs (including dermal and vasculature) can be built (Ng et al., 2016). Being able to process high-cell-density bio-inks, it is well-suited to complex, thick grafts, although it may require slowed printing speeds to scale.

Laser-induced forward transfer-based laser-assisted bioprinting (LAB) is used to print cells with a precision of less than a micrometre; thus, mechanical disturbance to the cells and their viability is minimized (Koch et al., 2010). The method is helpful in the development of complex skin structures, including vascular networks and is very expensive, making it unavailable to most people. Bioprinting is also enhanced by emerging technologies such as stereolithography and microfluidics integrated systems. Stereolithography enables the reproducible layer-by-layer polymerization of bio-inks to fabricate high-resolution, biochemically relevant tissue models in a short period. In contrast, microfluidics allows for the dynamic mixing of bioinks to produce gradient tissue constructs (Mandrycky et al., 2016). These advancements have made it expected that they will have greater control over skin graft complexity, allowing them to use it in burn care and also in dealing with chronic wounds.

2.2. Bioinks for Skin Tissue Engineering

The combination of hydrogels, extracellular matrix components (ECM) and growth factors found in bioinks of 3D-printed skin grafts can be used to provide skin-like replacement. Hydrogels, including alginate and gelatin, provide a hydrated scaffold, whereas cell adhesion is enhanced using components of the extracellular matrix (ECM), such as collagen (Lee et al., 2014). The process of angiogenesis and tissue healing occurs due to the intensification of growth factors, such as VEGF and FGF. Noteworthy cell types, such as epidermal keratinocytes, dermal fibroblasts, melanocytes involved in pigmentation, and endothelial cells that can participate in vascularisation were added to create functional constructs of skin (Ng et al., 2016). These features are specially structured to act similarly to the multidimensional organization of skin and help in a wound healing process.

Bioink properties are the determinants of effectiveness. Cell viability can be ensured by biocompatibility, whereas structural integrity can be achieved through printing and implantation, thanks to mechanical strength. Regulated rates of degradation are associated with the activity of remodeling in tissues, as this process eliminates premature destruction of scaffolds (Gungor-Ozkerim et al., 2018). Modification of bio-ink biomaterials, including the use of self-healing hydrogels, enables the dynamic recovery of loading, thereby enhancing construct stability during printing. The hydrogel, which contains transformed bioactive peptides that promote improved cell signaling and differentiation,

enhances graft functionality (Vijayavenkataraman et al., 2016). Such breakthroughs are leading to advancements in bioinks, which can be used to create scalable and patient-specific skin grafts.

2.3. Structural Design of Bioengineered Skin

The 3D-printed bioengineered skin prototype attempts to mimic the laminated structure of native skin, comprising the outermost layer, the epidermis, the dermis layer underneath, and the hypodermis layer below. The outer skin, also known as the epidermis, protects against elements and is primarily composed of keratinocytes. The inner skin is structurally strong and consists of fibroblasts and collagen. The hypodermis, owing to adipocyte incorporation, increases both cushioning and insulation (Lee et al., 2014). Modern bioprinting technologies can layer these components and achieve both functional mimicry and full integration into host tissue, promoting wound healing (Ng et al., 2016).

The process of inserting vascular and neural networks is essential to the survival and functioning of grafts. The endothelial cells constitute the vascular networks, allowing for the provision of nutrients and the drainage of waste products, thus overcoming the shortcomings of avascular grafts (Bajaj et al., 2014). Sensory restoration can be supported by neural integration, which, nonetheless, remains a challenging endeavor. Computational modelling is critical in the design of the scaffold data, where imaging information is rendered optimally for areas of cell placement and scaffold porosity. It is utilized in enhancing the biomechanical stability and vascularization of the construct, where finite element analysis and computational fluid dynamics are employed to improve the performance of grafts (Vijayavenkataraman et al., 2016). Those developments allow custom skin grafting in the clinical setting.

2.4. Bioprinting Process Parameters

Parameters implemented at the next stage of the bioprinting process effectively determine the quality of 3D-printed skin grafts. The accuracy of cell and bio-ink deposition is dependent on a printing resolution of 10-100 μm, which is essential for recreating the stratified structure of the skin (Murphy and Atala, 2014). Greater resolution improves anatomical fidelity, which can decrease printing speed and affect scalability. The optimal speed is one at which the throughput is maximised and where the necessity to kill cells through shear stress is not excessive (Ng et al., 2016). Innovative printers optimise resolution and printing speed to achieve strong, multilayered structures.

Maintaining the stability of the bio-ink and keeping the cells alive throughout the printing process is critical, relying on the use of environmental controls, such as temperature (2037 °C), humidity (>80%), and sterile conditions (Mandrycky et al., 2016). Bioinks would not dry and would not be contaminated by special conditions provided in controlled environments; therefore, the graft would remain intact. Bioreactor systems enable tissues to self-develop by providing dynamic conditions (mechanical stimulus, nutrient perfusion, etc.), thereby sustaining cell differentiation and extracellular matrix (ECM) deposition during post-printing maturation (Vijayavenkataraman et al., 2016). Bioreactors simulate physiological conditions, enhancing vascularization and maturation of skin grafts to prepare them for clinical use.

3. Experimental Validation of 3D-Printed Skin Grafts

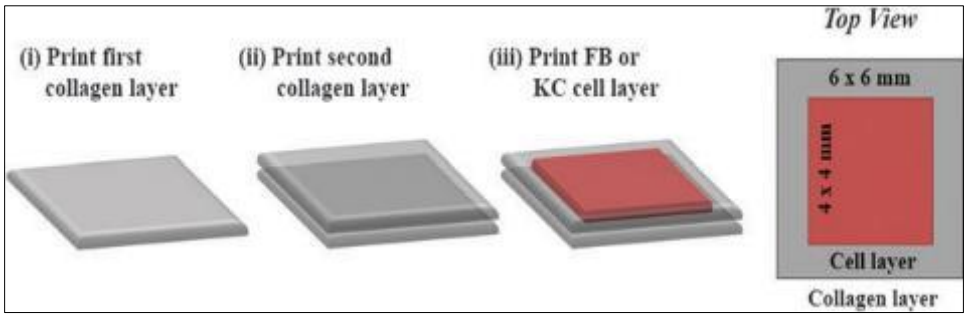
This section examines the experimental validation of 3D-printed skin grafts, focusing on in vitro and in vivo studies. It explores cell viability, functional outcomes, and integration, highlighting preclinical advancements and limitations in translating bioengineered skin to clinical applications.

3.1. In Vitro Studies

In vitro, the functionality of cells on the 3D-printed construct is a decisive factor in establishing the usability of the fabricated skin, specifically the viability of the cells and their proliferation within the suspended structures. The viability of the hydrogel-based bio-inks (>90%) is high with keratinocytes and fibroblasts, and their proliferation rate is tissue-forming (Lee et al., 2014). The gene expression profile indicates that skin-specific marker genes (e.g., keratin, collagen I) are more likely to be expressed in highly differentiated and functionally mature cells (Ng et al., 2016). The fact that bio-printed structures can reproduce the cell composition of native skin verifies that further developments can be made.

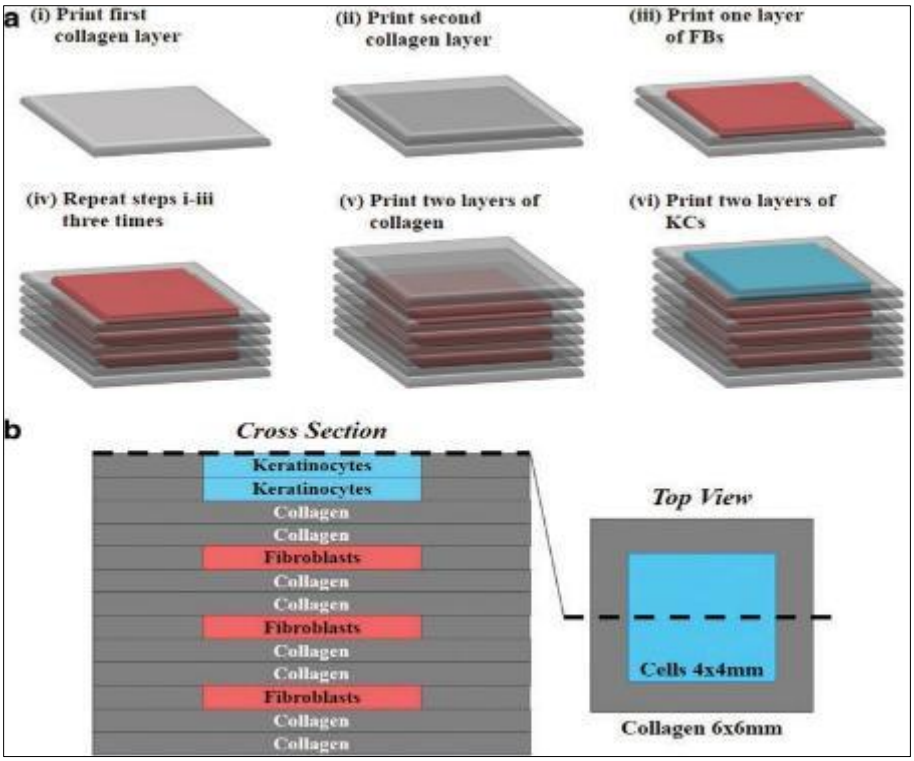
The bioengineered skin is also tested to establish its barrier strength, as well as its mechanical properties, which are determining factors in determining the integrity and application of the bioengineered skin. Multiple printed structures exhibit similar tensile resistance values to the native dermis and have the potential to provide a beneficial defensive effect, as evidenced by their low transepidermal water loss (Vijayavenkataraman et al., 2016). The integration of appendages, such as hair follicles or sweat glands, is also possible yet challenging due to their specific requirements. A

unique bioink formulation is being introduced to consider these requirements, including follicular stem cells and glandular precursors (Abaci et al., 2018). Such improvements enhance the physiologic relevance of 3D-printed grafts; however, scalability, coupled with appendage functionality, remains to be refined to achieve improvements in clinical use.



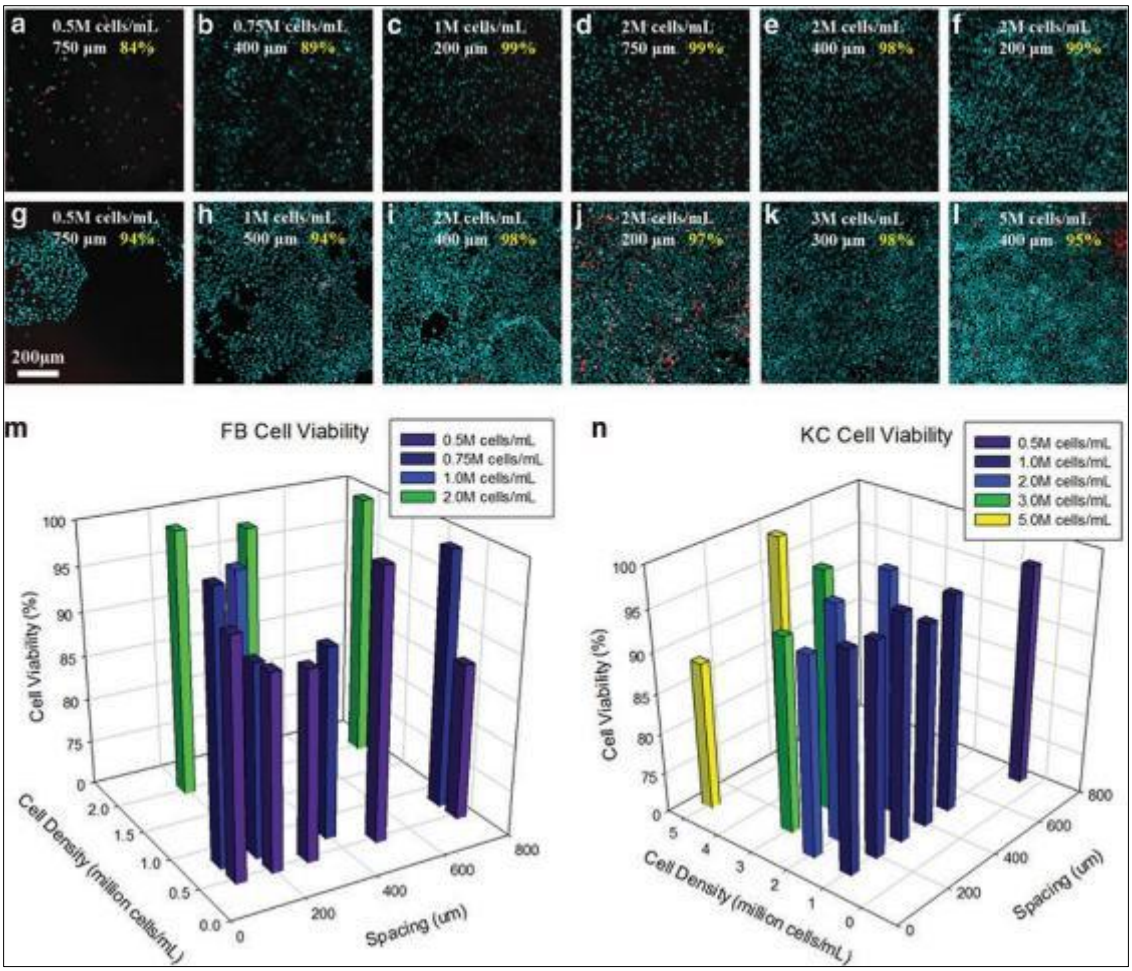
Adapted from Lee et al., 2014.

Figure 2 Schematic of the layered 3D bioprinting process for in vitro skin constructs. (i) Initial collagen base layer is printed, (ii) followed by a second collagen layer, and (iii) topped with a 4 × 4 mm fibroblast (FB) or keratinocyte (KC) cell layer on a 6 × 6 mm base



Adapted from Lee et al., 2014.

Figure 3 Multilayer bioprinting process of skin construct. (a) Schematic showing stepwise deposition: (i–iii) sequential printing of collagen and fibroblast layers, (iv) repetition for triple FB layering, (v) addition of two collagen layers, and (vi) final deposition of keratinocyte layers; (b) Cross-sectional and top-view illustration of the construct: three fibroblast layers embedded in collagen with two keratinocyte layers atop, mimicking dermal-epidermal structure (cell region: 4 × 4 mm; collagen base: 6 × 6 mm)



Adapted from Lee et al., 2014.

Figure 4 Microscopic images (a–l) and quantitative analysis (m–n) of fibroblast (FB) and keratinocyte (KC) cell viability at varying seeding densities and inter-pattern spacing. Cell viability was assessed using live/dead assays, with blue indicating live cells and red indicating dead cells. High cell viability (>90%) is observed across conditions, with optimal performance at higher densities and moderate spacing. 3D plots show quantitative trends in viability based on spacing and cell concentration

3.2. *In Vivo* Animal Models

The animal models (mice, pigs, and rabbits) used to study 3D-printed skin grafts in vivo are selected because their physiological similarities to humans, particularly in terms of skin and wound healing, remain similar. Porcine skin exhibits the closest similarities to human skin structure, followed by mouse skin, which is amenable to genetic manipulation, and rabbit skin, which is more cost-effective and suitable for large-scale studies (Sullivan et al., 2001). They are tested in these models since they assess the effectiveness of grafts in realistic physiological conditions. The outcome of wound healing positively influences the activities of re-epithelialisation, which is achieved through the horizontal growth of keratinocyte cells and robust angiogenesis via endothelial cells (Gaetani et al., 2018). Such optimized bio-inks generate reduced scarring and have more desirable cosmetic as well as functional results.

Essential standards are immunological reaction and graft integration. There is a low rejection of autologous or hypoimmunogenic bioinks in immunocompetent models, which approves the abstinence of immunosuppression in xenogeneic grafts (Ng et al., 2016). The long-term functionality and remodeling demonstrate the long-term viability of grafts, as its content of collagen relocates and vascular networks mature through months (Lee et al., 2014). Nevertheless, these studies have been combined with previous ones to identify some barriers to complete appendage regeneration and integration stability across models, which require certain refinements before clinical translation.

3.3. Advances in Preclinical Testing

Preclinical tests of innovative 3D-printed skin grafts have been conducted, demonstrating their translational potential. They are humanized, in which human skin is grafted onto immunodeficient mice, giving a more humane representation of the human body and allowing the testing of graft integration and compatibility with the immune system (Ng et al., 2016). High-throughput screening is used to optimize bioink compositions, as potential bioink formulations are subjected to a rapid assessment of cell viability, mechanical properties, and biocompatibility of multicomponent formulations (Ozbolat and Hospodiuk, 2016). Such platforms facilitate the identification of the best bioinks for specific types of wounds. Real-time monitoring of graft performance is possible using non-invasive imaging methods, such as optical coherence tomography (OCT) and multiphoton microscopy. OCT measures structural integrity and vascularization, whereas multiphoton microscopy measures cellular dynamics (and ECM remodeling) (Mandrycky et al., 2016). The tools provide an elaborate picture of how grafts work without compromising the quality of data by using euthanized animal models. When combined, such developments further enhance the reliability and reproducibility of preclinical results, addressing significant unmet gaps in vascularization and sustained functionality that can be translated to clinical applications (Lee et al., 2014).

3.4. Key Findings and Limitations

Advanced 3D-printed skin grafts represent the possibility of recreating native skin structure and functions. Bio-printed structures produce a stratified epidermal-dermal surface with barrier functionality, keratinocyte differentiation, and collagen production, closely resembling human skin. Wound closure and tissue combining appear promising in vivo experiments, especially in pig models and hold therapeutic possibilities. Such successes point to the prospect of bioprinting to create biologically reasonable grafts during burn and therapeutic management.

However, severe flaws remain regarding vascularization and compatibility of the immune system. Denser grafts also exhibit low angiogenesis, which inhibits the nutritional supply to the graft and thus affects its survival. Allograft immune rejection still has a tendency, and to avoid it, one must resort to the use of patient-specific cells or immunomodulatory medications. The issue of normalizing the results of experiments to be able to use them with others is very serious, as bio-inks, cell sources, and 3D printing protocols are all variable. It is challenging to write or discuss such setbacks without highlighting the precise requirements of better vascular networks, standardized protocols, and valid preclinical models to attain reproducibility, thereby simplifying clinical translation.

4. Clinical Translation of 3D-Printed Skin Grafts

The regulatory pathway for 3D-printed skin grafts would depend on their content and potential future applications, which could be governed by either medical device or advanced therapy medicinal product (ATMP) regulations. Grafts containing non-viable components can be handled as devices, and those containing cells, such as keratinocytes or fibroblasts, for example, are likely to be ATMPs, and their application is governed more strictly (Iglesias-Lopez et al., 2019). These regulatory routes will be different in different countries: the Center for Biologics Evaluation and Research of the Food and Drug Administration regulates ATMPs in the U.S., where applications of Investigational New Drugs are needed, and the Committee for Advanced Therapies of the European Medicines Agency controls their counterparts in Europe (Hourd et al., 2014). The inability to obtain international approvals for medical technologies is partly due to a lack of global harmonization.

Regulations for clinical trials are centered on effectiveness and safety. They place great emphasis on preclinical demands in such areas as biocompatibility, immunogenicity, and functionality in animal studies. Phase I trials screen for safety and examine potential side effects. Phase II and Phase III trials try to observe the effectiveness of the treatment and the healing of wounds following the stabbing (Ng et al., 2016). GMP processes in bioprinting laboratories ensure the consistency and sterility of products. Under GMP guidelines, cleanrooms, appropriate equipment, and traceable bio-inks are necessitated. To prevent contamination and increase the size of clinical-grade grafts, it is essential to adhere to Good Manufacturing Practice (GMP) guidelines. The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (Ozbolat and Hospodiuk, 2016) establish these guidelines.

4.1. Clinical Trial Design

The legal characterization of 3D-printed skin grafts depends on their composition and intended purpose, whether as medical devices or advanced therapy medicinal products (ATMPs). Grafts consisting of non-viable material are considered devices. In contrast, those that include living cells, such as keratinocytes or fibroblasts, are typically Advanced Therapy Medicinal Products (ATMPs), which are highly regulated (Iglesias-López et al., 2019). Regulatory pathways differ around the world. The U.S. FDA's Centre for Biologics Evaluation and Research regulates ATMPs

through Investigational New Drug submissions, while the EMA's Committee for Advanced Therapies oversees corresponding procedures in Europe (Hourd et al., 2014). International harmonization is yet to be achieved, so cross-country approvals are becoming increasingly complex.

Preclinical data are highly demanding in terms of safety and efficacy, as they are conducted in animal models, encompassing biocompatibility, immunogenicity, and functionality, all of which are assessed. During Phase I trials, recording adverse effects measure safety, while efficacy is evaluated by the rate of wound closure (Ng et al., 2016). Bioprinting Good Manufacturing Practices (GMP) ensure product consistency and sterility due to the controlled environment, validated equipment, and traceable bioinks. To ensure a low risk of contamination, GMP requirements established by the FDA and EMA should be adhered to make it possible to scale up clinical-grade grafts (Ozbolat and Hospodiuk, 2016).

4.2. Manufacturing and Scalability

Further development of an automated bioprinting system would be crucial for the large-scale manufacturing of 3D-printed skin grafts, and high-throughput manufacturing is indeed feasible. These systems combine robotic arms and multi-nozzle printers to dispense bio-inks, creating standardized grafts suitable for clinical practice (Ozbolat and Hospodiuk, 2016). Quality control ensures batch-to-batch consistency by rigorously testing cell viability, mechanical properties, and sterility, whereas shelf life can be optimized by adopting cryopreservation approaches (Ng et al., 2016). The need to avoid contamination requires maintaining sterility throughout the entire printing and storage process to ensure regulatory compliance.

Supply chain logistics encompasses the delivery of high-quality biologics, such as hydrogels and growth factors, as well as cell banks of patient-specific cells or allogeneic cells. Effective cell banking systems guarantee scalable (traceable) cell supplies (Hourd et al., 2014). Price competitiveness remains an issue, but automation allows for saving labor expenses, and modular bioprinting platforms decrease production expenditures. Future reimbursement plans rely on evidence of clinical effectiveness and cost-benefit analysis compared to traditional grafts, with health economic models helping support payer negotiations (Iglesias-López et al., 2019). Such developments stimulate the development of scalable, low-cost solutions that can become clinical.

4.3. Integration into Clinical Practice

To be integrated into clinical practice, improvement of surgical skills is necessary to apply 3D-printed skin grafts accurately. The grafting process is executed using the least invasive techniques to ensure compatibility with the wound bed, thereby inducing adhesion and vascularization (Ng et al., 2016). Within the course of postoperative care, close monitoring of graft take is done, and this is evaluated through imaging. Since bio-inks are sensitive to infection, infection control measures are implemented using sterile dressings and antibiotics, and rehabilitation involves physical therapy to regain functionality (Sen, 2019). For the successful use of grafts, healthcare professionals require specialized training. There are specialized courses that educate surgeons and nurses on the concept of bioprinting, its application techniques, and the treatment of complications (Hourd et al., 2014). Patient education will ensure informed consent, making them aware of the benefits, such as minimised scarring and risks associated with graft loss. Expectation management involves aesthetic outcome counselling and recovery plan promotion to foster trust and compliance (Iglesias-Lopez et al., 2019). These plans will address the glitches that may occur during integration with the clinical practices.

5. Challenges and Future Directions

5.1. Technical Challenges

One of the remaining challenges is to achieve complete vascularization and innervation of skin grafts created using 3D printing. The resultant limited resolution and stability of bio-inks used in bioprinting restrict the networked vascular circulation necessary to allow the delivery of nutrients and the survival of graft tissue, thereby limiting the formation of thick tissue structures (Talò et al., 2018). Innervation, a critical component of a sensory process, is a complicated process because the integration of neural cells and their interconnected ability to communicate is a challenging task (Ng et al., 2016). Complex bioinks and microfluidic devices are essential for enhancing vascular and neural integration. Replicating skin appendages, such as hair and sweat glands, as well as generating natural pigmentation, is challenging to reproduce. The process of incorporating follicular stem cells and melanocytes requires specific spatial control. Multiple studies in this field indicate that using current technology; it is challenging to repeatedly control the spatial aspects of this process (Abaci et al., 2018). It is necessary to enhance the mechanical strength of grafts, as they often lack the tensile strength of native skin, which can lead to tearing upon application. Such limits to clinical success can be

surmounted by the development of novel biomaterials and cross-linking procedures that promote structure stability and overall durability (Ozbolat and Hospodiuk, 2016).

5.2. Biological Challenges

To avoid the rejection of 3D-printed skin grafts, especially allogenic ones, the topic of immune modulation is considered very important. The solutions that can address the problems with immunogenicity comprise immunosuppressive bio-likes that can be combined with patient-derived bio-likes. However, some issues arise from the need for long-term immune tolerance without compromising the host's immune defense (Ng et al., 2016). Failure in EC maturation, as well as the reorganization of collagen molecules, leads to poor long-term graft stability and remodeling, ultimately causing graft attrition (Lee et al., 2014). Bioink formulation, as well as the conditions of the bioreactor, need to be optimized to enhance durability.

Patient-specific responses to the healing process complicate clinical outcomes. The individual implications of age, comorbidity, and underlying genetic differences affect the levels of graft integration and wound healing and thus necessitate individualized methods (Sen, 2019). The ability to predict individual responses is limited in current models; hence, standardization is also limited. The current trends of genomic profiling and machine learning have the potential to produce individual designs of grafts to accommodate inter-patient variability and enhance the efficacy of therapy (Ozbolat and Hospodiuk, 2016). These biological hurdles underscore the importance of developing new solutions that ensure consistent clinical success.

5.3. Clinical and Commercial Challenges

The bioprinting patent is also costly, which poses a significant challenge to its use in clinics. The equipment required to produce bioprinted structures using advanced bioprinters that contain growth factors and are GMP-compliant, along with the necessary plants and facilities, is a significant investment, which can make it inaccessible to healthcare systems (Hourd et al., 2014). It is also challenging to scale up production while maintaining quality. Automation has the potential to enhance production, outlining that maintaining batch-to-batch cell survivability and graft functionality requires high standards of quality control and consistency in standardized applications (Ozbolat and Hospodiuk, 2016). Competition from established therapies, such as autografts and commercial skin substitutes, poses a threat to market adoption. These therapies are more familiar to clinicians and are often less expensive. Achieving better clinical results, including quicker healing and a decrease in scarring, is also essential for market success (Ng et al., 2016). Regulatory obstacles and uncertainty in reimbursement rates also complicate commercialization, and it requires a strong health economic evidence base to support adoption (Iglesias-Lozano et al., 2019). To address these issues, strategic collaborations and innovations are necessary to reduce operational costs.

5.4. Emerging Innovations

Future innovations involving 3D-printed skin grafts may combine them with CRISPR-based gene editing, potentially enhancing their functionality and effectiveness. Changing cells through CRISPR makes grafting more functional (i.e., improved wound healing and scar reduction or immune compatibility generation) to make customized grafts (Li et al., 2019). Bioprint can be optimized using Artificial Intelligence (AI) 1) with predictive modeling of tissue behavior and 2) automation of processes to increase the precision and scalability of the process (Ng et al., 2016). This enables the printing of bioinks directly onto wounds, facilitating close incorporation and thereby enhancing wound healing (Albanna et al., 2019). The combination therapies enhance the effects of the graft by using bioactive dressings that have antimicrobial action or growth factors and by utilizing stem cells, such as mesenchymal stem cells, to promote vascularisation and regeneration (Ozbolat and Hospodiuk, 2016). These new developments eliminate existing deficiencies, opening up new possibilities for individualized, feasible, and clinically effective skin graft releases.

6. Case Studies and Real-World Applications

6.1. Early Clinical Trials and Pilot Studies

Early clinical trials of 3D-printed skin grafts in burn care have shown promising results. A 2025 pilot study in Australia applied autologous 3D-printed skin directly to burn wounds, achieving faster healing, reduced pain, and minimal scarring compared to traditional autografts (Albanna et al., 2019;). In chronic wound management, such as diabetic foot ulcers, a trial using bioprinted grafts with autologous fibroblasts and keratinocytes demonstrated 78% wound closure by eight weeks, significantly outperforming standard care (Uccioli, 2003;). These grafts provided structural support and growth factors, enhancing reepithelialization In cosmetic and reconstructive surgery, 3D-printed grafts have been explored for aesthetic restoration post-Mohs surgery and vitiligo treatment. Pilot studies reported improved

pigmentation and reduced donor site morbidity using epidermal grafts, with patients noting enhanced cosmetic outcomes (Trufant et al., 2016;). While these trials highlight the potential for personalized grafts, challenges like scalability and long-term stability persist, necessitating further research for widespread adoption (Ng et al., 2016).

6.2. Industry Developments

Leading companies and research institutions are advancing 3D-printed skin grafts. Companies like Organovo and CTIBIOTECH pioneer bioprinting technologies, with CTIBIOTECH developing CTISkin, a skin model for wound healing. Institutions like Columbia University, Rensselaer Polytechnic Institute, and Wake Forest Institute for Regenerative Medicine lead research, creating vascularized grafts and in situ bioprinting solutions (Albanna et al., 2019). Collaborations between academia, industry, and healthcare drive progress. Organovo's partnership with Autodesk integrates design software with bioprinting, while academic-industry alliances develop advanced grafts validated in clinical settings (Hourd et al., 2014). The intellectual property landscape is dynamic, with patents focusing on bioprinting methods and bioinks. Columbia's Hasan Erbil Abaci holds a pending patent for edgeless skin constructs, and Penn State secured a 2024 patent for multilayered grafts with hair follicle potential (Ozbolat et al., 2024). Balancing IP protection with open-source collaboration remains a challenge, as startups navigate ethical access and commercialization (Hourd et al., 2014).

6.3. Patient Perspectives

3D-printed skin grafts significantly enhance quality of life post-treatment. Patients report reduced pain, faster healing, and improved mobility, particularly in burn and chronic wound cases, enabling quicker return to daily activities (Albanna et al., 2019). Aesthetically superior outcomes, with minimal scarring, boost self-esteem and social reintegration (Trufant et al., 2016). Psychological benefits include reduced anxiety and depression, as advanced grafts restore appearance and function, fostering confidence. Socially, patients experience improved interpersonal interactions due to enhanced cosmetic results, positively impacting relationships and professional life (Ng et al., 2016). Access disparities pose challenges, with high costs and limited availability restricting 3D-printed grafts to well-funded healthcare systems, exacerbating global health inequities. Low-income regions face barriers due to inadequate infrastructure and trained personnel, hindering adoption (Hourd et al., 2014). Addressing these disparities through cost-reduction strategies and international collaborations is critical to ensure equitable access, maximizing the global health impact of this transformative technology.

7. Discussion

The discussion synthesizes experimental and clinical insights for 3D-printed skin grafts, emphasizing the need to bridge laboratory advancements with clinical realities. Preclinical studies demonstrate robust tissue mimicry, yet translating these to scalable, reproducible clinical outcomes requires overcoming regulatory and manufacturing hurdles. Balancing innovation such as vascularized constructs with practical implementation involves optimizing cost-effective production and surgical integration. Interdisciplinary collaboration among bioengineers, clinicians, and regulators is crucial to align cutting-edge technologies with patient needs, ensuring practical solutions for burn care and chronic wounds.

Broader implications for regenerative medicine highlight lessons from skin grafts applicable to 3D-printed cartilage and organs, particularly in vascularization and scaffold design. Ethical considerations underscore equity in access, as high costs may limit availability to affluent regions, exacerbating global health disparities. The dual potential for therapeutic and cosmetic applications raises questions about prioritization, while long-term societal impacts include shifts in healthcare delivery and patient expectations. Current research is limited by insufficient long-term clinical data and inconsistent protocols, necessitating standardized reporting to enhance comparability and reliability. These insights guide future efforts toward equitable, impactful clinical translation.

8. Conclusion

Advances in 3D-printed skin graft technology have revolutionized regenerative medicine, achieving functional skin constructs with layered architectures and promising preclinical outcomes. Progress toward clinical implementation is evident in early trials demonstrating enhanced wound healing and aesthetic results, yet challenges like vascularization, immune compatibility, and scalability persist. Opportunities lie in innovations such as in situ bioprinting and CRISPR-enhanced grafts, driving personalized, on-demand solutions. The vision for the future envisions seamless integration into standard medical care, transforming wound care for burns and chronic wounds by offering tailored grafts that restore function and appearance. To realize this potential, increased funding for translational research is critical to bridge laboratory and clinical gaps. Collaboration among bioengineers, clinicians, industry, and regulators is essential

to standardize protocols and accelerate adoption. A commitment to equitable access will ensure these transformative therapies reach diverse populations, addressing global health disparities and maximizing impact in regenerative medicine.

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