



## Review Article

# Hydrogels in Skin Tissue Engineering: Future Developments and Applications

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The skin tissue engineering that can help to pass the challenge of conventional wound healing. The human skin, which is made up of the epidermis, the dermis and the hypodermis, is an important protective layer, and in extreme cases of burns and other chronic wounds, its healing capacity surpasses its natural ability. Hydrogels are cross-linked polymer networks that are highly utilized because of their high water concentrations, biocompatibility and the resemblance to the extracellular matrix. They sustain cell attachment, growth and differentiation and have the ability to deliver bioactive molecules in controlled way to facilitate regeneration. Having four stages, including hemostasis, inflammation, proliferation, and remodeling, wound healing is controlled by growth factors, including PDGF, FGF, VEGF, and EGF. These factors are sustained by hydrogels, which induce angiogenesis, collagen formation, and re-epithelialization. Scaffolds with the desired mechanical and biological characteristics are designed using both natural and synthetic polymers. Also, bioactive molecules and stem cells are important in enhancing skin regeneration. Although this has improved, there are still issues such as stability, biodegradability, immune response and clinical scalability. Generally, the use of hydrogel-based scaffolds has a very good potential to provide an effective platform to skin tissue regeneration.

**Keywords:** Scaffolds, Proliferation, Regeneration.

## INTRODUCTION

The skin is the biggest organ of the human body which is characterized by three parts that are connected (1). The layers are placed in layers, epidermis, dermis and hypodermis respectively one layer being laid over another most distinct layer to the nearest layer (2). The evolution of hydrogel-based skin tissue engineering has been fascinating since the 19th and early 20th centuries when hydrogel has been characterized as colloidal gel of inorganic salts, and subsequently as polymeric biomaterials such as poly(vinyl alcohol) (Ivalon) to serve as biomedical implants. The rapid growth of hydrogel research, especially since the 1970s, has led to the development of chemically crosslinked polymers designed to mimic the extracellular matrix (ECM) of natural skin and exhibiting excellent water affinity, biocompatibility, and elasticity (3). The process of skin regeneration

and repair is a complex biological process that deals with restoration and replacement of damaged or lost skin tissues after injury (4). Skin regeneration is the overall process of the restoration of damaged tissue and skin repair is the restoration of the tissue that is already there with much scarring whereas skin repair is the restoration of the structural functionality of the tissue, which is usually left as scar tissue because of the new collagen structure deposited by fibroblasts during the process of skin repair (5). It starts immediately after injury leading to an inflammatory response, which is characterized by vasoconstriction, platelet activation and the formation of a fibrin clot to contain blood and reduce the risk of infection, and then platelets move in with white blood cells and phagocytosis of cellular debris (6). During the proliferative stage, the fibroblasts move to the wound

contributing to collagen and extracellular matrix that strengthen the wound, promote angiogenesis to supply oxygen, and direct epithelial cells to re-establish the protective barrier of the skin (7,8). Each year a number of individuals across the world get injury or skin defects surgical interventions in the treatment and management. Although a number of strategies are available. It promote skin wound healing, all of those methods did not. imitate the surfaces of the extracellular matrix (9). The stratum corneum (SC) is the primary component of the physical barrier, although other significant components are the nucleated epidermis and its cell junction and the cytoskeleton proteins. The chemical/biochemical (antimicrobial, innate immunity) block is made up of lipids, acids, hydrolytic enzymes, antimicrobial peptides and macrophages (10). Humoral and cellular components of the immune system make up the (adaptive) immunological barrier the tissue engineering has recently made available the capability to repair the tissue defects, which the body cannot repair (11). Tissue engineering is a novelty in the medicine industry, the method which ensures the regeneration of injured tissue, in addition, other natural TE has also employed polymers like alginate, cellulose and chitosan (12). There is promising evidence with the use of the above natural polymers despite the challenges faced, there are also several disadvantages of these materials such as high cost, unfavourable mechanical properties.(12)A Synthetic and natural biomaterials play a pivotal role by supporting the extracellular matrix and regeneration studies are now concerned with creating the scaffolds out of polymeric substances that blend with the biomolecules or cells, which enhance tissue regeneration scaffolding solutions to tissue regeneration applications to batch variation, which make them hard to apply on clinical(1) . Applications Synthesized polymers on the other hand include polylactic acid (PLA) polyurethane (PU), poly(lactide-co-glycolide) (PLGA) and polycaprolactones (PCL) ,there disadvantages of these materials is high or low inflammation may cause skin damage or irritation Topical hydrogel scaffold can be developed via physical and chemical cross linking techniques physical cross linking and chemical cross were linking topical hydrogel are formed by weak van der Waal forces whereas chemical cross linking by covalent

bonds have been used extensively in TE because they have good mechanical properties and degradation rates .Nevertheless, most of the degradation products of these polymers are made of acidic compounds, which are damaging to the body and may lead to unwanted immune reaction. The most significant role of the good protective barrier between the interiors and the externals of the organism. These include the physical, the chemical/biochemical (antimicrobial, innate immunity) and the adaptive immunological barriers, all of which constitute the epidermis (14) .

## **2. Goal of achieving effective skin tissue regeneration and repair**

Effective healing and a full simulation of physiological skin with nearly native mechanical qualities and no host toxicity or immunological rejection are key objectives of skin Furthermore, repair of the skin's anatomy must include the restoration of skin pigmentation in addition to structural architecture rehabilitation. adnexa, vascular plexus, and nerve. The genotype of the trans, the biocompatibility of the materials utilized, and planted skin cells must all be taken into account while designing skin substitutes the intricacy of production and storage problems (15). In skin TE, maintaining an intact barrier and preventing infection are crucial, particularly when treating severe burns. In the case of chronic wounds, promoting wound healing is another crucial goal. Numerous efforts have been embraced to engineer a three-dimensional scaffold, which will bear and induce new tissue of varying cells. Restoration of skin structure must transcend recovery of structure. architectural pattern comprising of renewal of skin pigmentation, vascular plexus, nerve, and adnexa. The construction of skin substitutes also should be taken into consideration the genotype of the material to be used should be transplanted skin cells biocompatible and the complexity of fabrication and provision of storage problems. The restoration of an intact prevention and barrier of sepsis is very important in skin TE especially with the management of large burns. The skin substitute should retard effusion, infection, scarring and contraction. (16)

## **3. Hydrogel based scaffolds in skin regeneration.**

The 3D cross-linked polymeric networks are known as hydrogels. which is able to absorb and hold water

molecules. However, the hydrophilic was blocked by the cross-linked networks. polymeric chains do not convert to an aqueous phase. in the hydrogel scaffolds (17). The porosity of the hydrogel scaffold has a great role in diffusion of the nutrients and oxygen molecules among others are macromolecules and in case of absent functioning of blood vessels. Hydrogels showed with higher viscosity, pore size proved recent advances include the development of multifunctional hydrogels with improved mechanical strength, controlled drug release, and enhanced biological activity, using techniques like loading with nanoparticles or integrating bioactive molecules. Despite these promising developments, challenges remain in optimizing the mechanical properties, porosity, biodegradability, and functionality of hydrogels to closely match native skin tissue and to accelerate effective skin repair and wound management (18). Toft be productive with cellular growth (i.e., Fibroblasts and Keratinocytes) and extracellular matrix regeneration recent advances include the development of multifunctional hydrogels with improved mechanical strength, controlled drug release, and enhanced biological activity, using techniques like loading with nanoparticles or integrating bioactive molecules (19). Despite these promising developments, challenges remain in optimizing the mechanical properties, porosity, biodegradability, and functionality of hydrogels to closely match native skin tissue and to accelerate effective skin repair and wound management .Lastly, it seems that the integration of The proliferation of cells into the polymeric hydrogel scaffolds tends to be boosted(20) .Bioactive molecules can induce stem cells to differentiate into skin cell types like keratinocytes, endothelial cells, and hair follicle stem cells, which are crucial for skin repair and regeneration . These molecules regulate cellular processes such as dedifferentiation, proliferation, and migration, enhancing wound healing by activating the endogenous repair mechanisms in the skin (21). Polymeric scaffolds and in particular hydrogel are very popular because of their biocompatibility, biodegradability and biomimetic characteristics. Hydrogels offer a hydrated condition that is conducive to healing wounds and is porous in nature that facilitates the diffusion of nutrients and oxygen crucial in cell survival and tissue regeneration (22). Porosity of hydrogel scaffolds with high moisture

absorption capacity and superior moisture absorption had been vastly developed in the past. their application towards skin tissue engineering and regeneration (23). The major benefit of hydrogels over gels is that they are stable because of the cross-linked polymeric network that allows them to be easily handled during wound care. In comparison, gels have very loose structure that does not permit them to be fully removed out of the wound, which can cause wound infection. Compared to other systems, hydrogels have tremendous benefits including incorporation of bioactive agents and/or cells since processing conditions are mild. The bioactive molecules that are incorporated can then be administered in a more protracted form which is a huge plus as compared to their application topically (24). Although appropriate synthetic and natural polymers are available, a guarantee of controlled therapeutic release, be it by physical restriction or affinity between drug and material, is a daunting challenge. The development of polymer science has resulted in the development of biopolymers providing a biodegradable and biocompatible skeleton of hydrogels to enhance their use in targeted and efficient delivery of drugs. Nevertheless, reaching the necessary mechanical stability, biodegradability, and target selectivity and maintaining the safety and effectiveness of the physiological environment outline the current difficulty of hydrogel-based drug delivery systems design (25). Hybrid or semi-synthetic hydrogels are typically favored since they provide the benefits of a synthetic and natural polymer. Bioactivity and mechanical capacity. The hydrogel which is formed after a combination of natural proteins or polymers with synthetic polymeric materials offers bioactivity and mechanical properties. Development of the hydrogel on the basis of proteins and polyethylene glycol as the method of encapsulation of dorsal root ganglion cells. In addition, synthetic polymers can be tuned in terms of chemical and physical properties, and with greater reproducibility than natural hydrogels. (26)

#### **4. Polymer networks for advanced skin tissue regeneration**

Polymer-based skin tissue engineering involves using both natural and synthetic polymeric biomaterials to fabricate scaffolds that support skin tissue

regeneration by promoting cellular functions such as angiogenesis, re-epithelialization, and collagen synthesis (27). These polymer scaffolds often take the form of hydrogels due to their biocompatibility, moisture retention, and structural similarity to the native extracellular matrix (ECM). Natural polymers, such as collagen, chitosan, gelatin, biodegradability, and similarity to the native extracellular matrix (ECM). They promote cell adhesion, proliferation, and differentiation, which are crucial for skin regeneration similar to the skin extracellular

matrix, providing a conducive environment for tissue repair. Skin tissue engineering is a promising field aimed at regenerating damaged skin by creating biomimetic scaffolds using natural polymers. Natural polymers, such as collagen, chitosan, gelatin, biodegradability, and similarity to the native extracellular matrix (ECM). They promote cell adhesion, proliferation, and differentiation, which are crucial for skin (28)

**Table 1: Natural polymers and their applications**

| Polymer         | Source/ composition                      | Key role in skin regeneration                       | Examples of application                                |
|-----------------|--|---|--|
| chitosan        | Derived from chitin in crustacean shells | Antimicrobial enhances wound contraction hemostatic | Blended with alginate gelation in wound dressings (29) |
| Collagen        | Structural protein from animal tissues   | Promotes cell adhesion, growth and wound healing    | Collagen-based hydrogel skin graft scaffolds (30)      |
| Gelatin         | Denatured collagen                       | Biodegradable scaffold for fibroblast               | Hydrogel matrices for dermal regeneration. (31)        |
| Hyaluronic acid | Natural polysaccharide                   | Enhances hydration promotes angiogenesis            | Injectable hydrogel, wound fillers (32)                |

#### Synthetic polymer:

**Table no :2 Synthetic polymer and their applications**

| Polymer                           | Chemical type             | Key role in skin Regeneration                              | Examples of application                                  |
|-----------------------------------|---------------------------|--|--|
| Poly (lactic acid)                | Aliphatic polyester       | Biodegradable scaffold, supports tissue formation          | Electrospun PIA nanofibres for dermal matrices (33)      |
| Poly glycolic acid)               | Aliphatic polyester       | Fast-degrading scaffolds promoting tissue infiltration     | PGA meshes for dermal repair (34)                        |
| Poly (lactic -co - glycolic acid) | Copolymer                 | Controlled degradation and drug delivery                   | PLGA nanoparticles for growth factor delivery. (35)      |
| Polyethylene glycol               | Hydrophilic polymer       | Non-toxic forms hydrogel, supports for cells encapsulation | PEG-Based crosslinks hydrogel for skin regeneration (36) |
| Polycaprolactone(pcl)             | Semicrystalline polyester | Slow degradation, supports long term regeneration          | Nanofibres composites for skin scaffolds (37)            |

#### 5. Cellular bioactive molecules and the therapeutic delivery.

Keratinocytes represent the major protective layer of the skin and play a crucial role in the maintenance of skin barrier integrity. (38) In wound healing, this cell type is responsible for reepithelialization, an active process that consists of the coordinated proliferation, migration, and stratification of cells(39). When this mechanism fails, it gives rise to serious

complications, including dehydration, microbial invasion, and chronic non-healable wounds, sometimes ending with the death of the organism. Therefore, rapid and efficient reepithelialization is regarded as a key target in skin regenerative therapies (40). Clinically, keratinocytes are often needed as cell sheets or part of an engineered skin substitute to reconstruct lost epithelium. The availability of keratinocytes, however, is limited since patient-derived keratinocyte harvesting can be invasive, of

low yield, and unsuitable for large or deep wounds. Therefore, the search for alternative and expandable cell sources has become one of the important research goals in regenerative medicine and tissue engineering (41). One promising approach would be the use of bioactive small molecules to guide cells toward a keratinocyte identity. These molecules modulate cellular signaling pathways and transcriptional programs to promote keratinocyte lineage commitment in the absence of genetic manipulation (42). Most earlier efforts relied on viral vector-driven transgene expression, which carries risks of insertional mutagenesis and spatiotemporally unpredictable gene reactivation that limit therapeutic translation (43). By comparison, small-molecule-based reprogramming represents a non-integrative, reversible, and clinically safer method (44). Recent studies have identified that the combinatorial application of bioactive molecules effectively promotes the differentiation of ESCs and iPSCs into keratinocytes. These bioactive molecules are usually developmental stage-specific regulators. These molecules mimic developmental cues through modulation of pathways that regulate ectodermal specification. Selection of effective molecules depends on a detailed understanding of epidermal development and molecular signaling networks, along with lineage determinants (45). The epidermis develops during normal skin development from the primitive ectoderm, which expresses K8/K18. These markers are gradually substituted by K5/K14, representing the basal keratinocyte phenotype as the cells commit to the keratinocyte lineage. Subsequent stratification leads to terminal differentiation and formation of the mature epidermis, which expresses K1/K10(46). The decision of the primitive ectoderm to assume either an epidermal or a neural fate is

controlled by cross-talk between Wnt BMP, and FGF signaling events (47). In early ectoderm, active Wnt signaling maintains the epidermal option, increases sensitivity to BMP signals, and concurrently suppresses neural induction mediated by FGFs. In the absence of Wnt activity, the influence of FGF signaling becomes dominant, driving the ectoderm toward a neural lineage (48). A powerful downstream driver of epidermal development is p63, specifically the  $\Delta$ Np63 isoform, which has become absolutely essential for basal layer formation and maintenance of keratinocyte layers (49). BMP directs  $\Delta$ Np63 transcription through SMAD4/5, ensuring epidermal commitment while repressing neural differentiation.  $\Delta$ Np63 itself drives the expression of other keratin genes such as K14 and reinforces the cell identity of keratinocytes. These developmental pathways become targets for the bioactive molecules that can mimic this signaling environment required for keratinocyte specification. Such molecule-driven reprogramming is a highly appealing route for generating large numbers of transplantable keratinocytes for use in wound healing (49).

## 6. Role of growth factors in regenerative design

A lot of different types of cells release growth factors that send signals to start certain developmental programs that control Cell migration, differentiation, and proliferation Platelet-derived growth factor (PDGF), hepatocyte growth factor, and epidermal growth factor (EGF) are powerful mitogens that make cells grow. Nerve growth factor (NGF), on the other hand, makes cells migration and neurites extension All of these cellular events are important for tissues to grow (50).

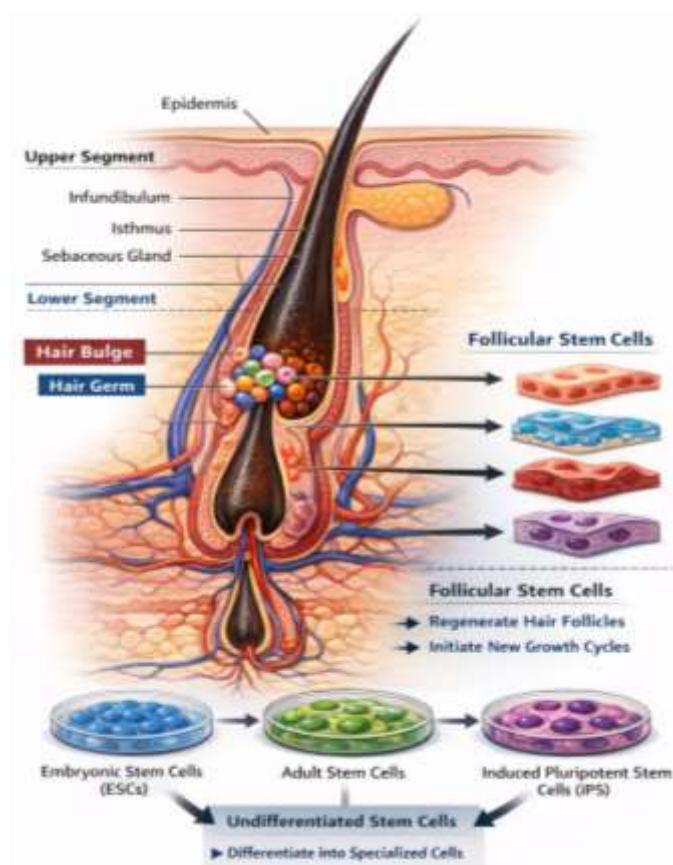
**Table no: 3 Growth factors parameters**

| <b>Growth factors</b>                     | <b>Major biological function</b>        | <b>Tissue engineering application</b>            | <b>Application in wound skin Regeneration</b>               |
|---|---|--|---|
| Platelet -Derived growth factor (PDGF)    | Regulates cell growth and ECM formation | Promotes fibroblast migration and proliferation  | Enhances granulation tissue formation (51)                  |
| Fibroblast growth factor (FGF)            | Ehnaces cell dermal repair              | Stimulates fibroblast proliferation angiogenesis | It promotes collagen synthesis and tissue regeneration (52) |
| Vascular endothelial growth factor (VEGF) | Promotes angiogenesis                   | Stimulates endothelial proliferation             | It improve blood vessel formation in damaged tissue (41,53) |
| Epidermal growth factor (EGF)             | Stimulates epidermal regeneration       | Promotes keratinocyte proliferation              | Accelerates wound closure and re-epithelialization (54)     |

## 7. Regenerating skin through stem cell technology

Hair bulge, a particular region of the hair follicle, and the hair germ, a collection of cells beneath it, contain a significant amount of these stem cells (55). Stem cells can move from this site to the basal layer of the interfollicular epidermis, the sebaceous gland, and the hair follicle matrix (56). There, they mature into precursor cells that eventually give rise to epidermal, glandular, or hair cells. The isthmus and infundibulum, which connect the hair canal to the

skin's surface, are part of the upper segment of the hair follicle, which stays constant (57). In contrast, the lower segment is temporary and cycles through growth (anagen), regression (catagen), and rest (telogen) phases. Follicular stem cells contribute to initiating new hair growth cycles and regenerating hair follicles. Because stem cells can differentiate into different tissue types through asymmetric replication, they could aid in the creation of skin components that are absent from tissue-engineered skin substitutes. (57,58)



**Figure no: 1 Stem cells in skin tissue engineering**

Two characteristics set stem cells apart: i) They are undifferentiated cells that divide to renew themselves throughout an organism's life, and ii) they have the amazing ability to differentiate into several cell types with distinct roles from a common precursor (59). Adult stem cells, embryonic stem cells (ESCs), and induced pluripotent stem cells (iPS) are some of the primary cell sources that could be utilized for skin regeneration and repair. (60)

## 8. Fibroblasts cells: The Major Regulators of Skin Tissues Repair.

It was already well known how to culture fibroblasts before Rheinwald and Green found a way to culture and expand keratinocytes in 1975. These cells need murine 3T3 fibroblast cells that have stopped growing to help them grow. Vascular endothelial growth factor (VEGF) and FGF are key players in the regulation of this process, which involves a number of factors (61). Stimulation of the bone marrow and endothelial progenitors at normal oxygen levels causes angiogenesis (62). In the last stage, fibroblasts stimulated by macrophages around a wound or in bone marrow transform into myofibroblasts.

Recognized as contractile cells, myofibroblasts play a remarkable role in wound closure (63). Both myoblasts and fibroblasts produce and deposit extracellular matrix (ECM) proteins, mostly collagen, which eventually form scars (64). Maintaining the equilibrium between ECM protein deposition and degradation is crucial because distortion of this process leads to abnormal scarring or explant culture, the latter being especially effective for procuring cells from smaller specimens. (64) Fetal calf serum is often added to the medium used to grow fibroblasts. The growth parameters and characteristics of fibroblasts in culture are affected by the passage number, donor age, fibroblast subtype (reticular or papillary dermis), and anatomical site (65). Older donor skin fibroblasts, in contrast to their younger counterparts, exhibit slower migration, attain cellular senescence sooner, and possess an extended cell population doubling time (64,65). Additionally, fibroblasts from older donors exhibit reduced responsiveness to growth factors, including platelet-derived growth factor, epidermal growth factor, dexamethasone, insulin, and transfer. When growth factors and cytokines like TGF- $\beta$ 1.15 are released, fibroblasts move into and multiply in injury sites (66). Fibroblasts deposit collagen and other pertinent substances to heal the wound. ECM elements nowadays, a lot of ES products rely on either cultured allogenic neonatal fibroblasts or autologous fibroblasts in order to produce them. Fibrocytes are found systemically in the bloodstream and bone marrow, but keratinocytes and fibroblasts can be extracted from local skin tissue. Since then, a number of studies have documented peripheral mononuclear cells differentiating into fibroblast-like cells (67). Additionally, fibroblasts from older donors exhibit reduced responsiveness to growth factors, including platelet-derived growth factor, epidermal growth

factor, dexamethasone, insulin, and transferrin in vitro. Older donor skin fibroblasts, in contrast to their younger counterparts, exhibit slower migration, attain cellular senescence sooner, and possess an extended cell population doubling time (68). Vascular endothelial growth factor (VEGF) and FGF are key players in the regulation of this process, which involves a number of factors. Furthermore, stimulation of the bone marrow and endothelial progenitors at normal oxygen levels causes angiogenesis. In the last stage, fibroblasts stimulated by macrophages around a wound or in bone marrow transform into myofibroblasts. Recognized as contractile cells, myofibroblasts play a remarkable role in wound closure (69). Both myoblasts and fibroblasts produce and deposit extracellular matrix (ECM) proteins, mostly collagen, which eventually form scars. Maintaining the equilibrium between ECM protein deposition and degradation is crucial because distortion of this process leads to abnormal scarring (70). Gene expression patterns (e.g., cell-cell signalling, matrix remodelling) show a variety of fibroblasts of various locations in the body, a phenomenon that supports the notion of fibroblast topographical heterogeneity. Thus, both age and anatomical location of human dermal fibroblasts have been reported to influence the differences in functionality e.g. to induce epidermal differentiation and to assist in wound healing (71). In fact, dermal fibroblasts of the identical topographic locations though separated into various individuals are more similar to each other as compared to the dermal fibroblasts of various regions, yet in the same subject. Passages in cell culture fail to alter this anatomical imprinting, or do so to a minimal extent. Environmental changes do not alter the anatomical imprinting either (72).

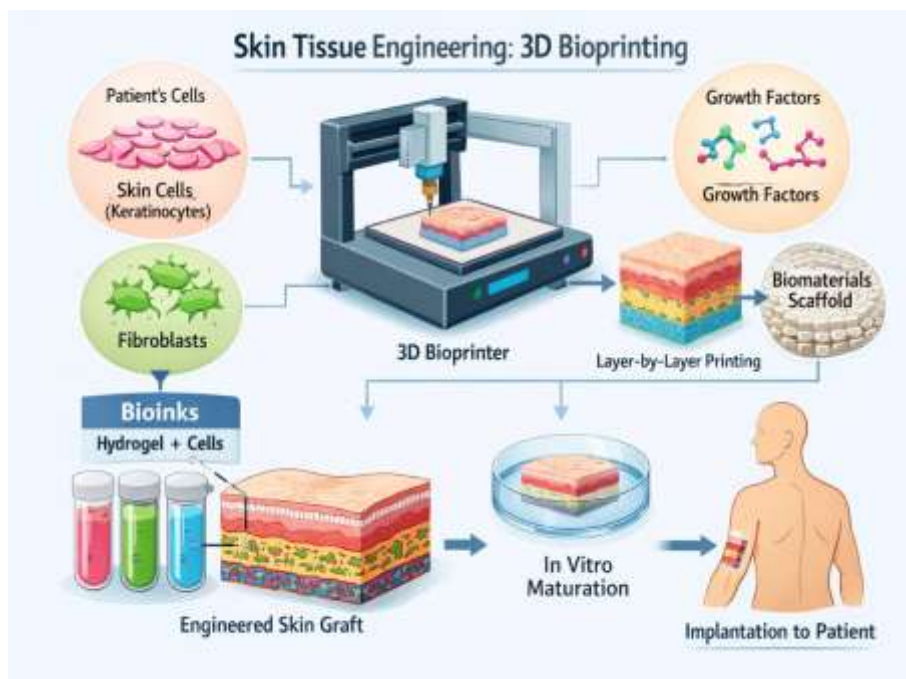


**Figure no: 2 Fibroblast cells in wound healing**

### 9. Advanced bioprinting strategies for skin repair and reconstruction

Additionally, fibroblasts from older donors exhibit reduced responsiveness to growth factors, including platelet-derived growth factor, epidermal growth factor, dexamethasone, insulin, and transferrin *in vitro*. Tissue engineering is very important for making skin equivalents that can be used to treat chronic wounds and especially burn wounds. In fact, there is no cellularized skin equivalent that can adequately replicate native skin (73). We used a laser-assisted

bioprinting (LaBP) method to make a skin substitute that is fully cellularized. LaBP's most unique feature different types of cells in a precise three-dimensional (3D) spatial pattern. To make the skin substitutes, we put fibroblasts and keratinocytes on top of a stabilizing matrix called Matrigel (74). Later, these skin constructs were tested in living animals using the dorsal skin fold chamber in nude mice. The transplants were put into full-thickness skin wounds, and when they were taken out after 11 days, they were fully connected to the tissue around them (74,75).



**Figure no: 3 Bioprinting in skin tissue engineering**

The printed keratinocytes created a multi-layered epidermis with the start of differentiation and a stratum corneum. The keratinocytes proliferated predominantly in the suprabasal layers. In vitro controls, cultivated at the air-liquid interface, also displayed proliferative cells, albeit distributed throughout the entire epidermis. E-cadherin serves as an indicator for adherens junctions and consequently tissue formation, observable in both in vivo and in vitro epidermis (76). In both scenarios, the printed fibroblasts partially remained atop the underlying Matrigel, synthesizing collagen, while a portion migrated into the Matrigel. Some blood vessels in the mice could be seen growing from the wound bed and the edges of the wound toward the printed cells. In conclusion, we demonstrated the successful 3D printing of a cellular construct using LaBP, followed by subsequent tissue formation in vivo (77). These findings constitute the essential foundation for the development of complex tissues, such as skin, composed of various cell types arranged in a sophisticated three-dimensional configuration (78).

### 10. Challenges involved in skin regeneration

Challenges recent years, the field of stem cell biology has developed considerably and presents huge potential for using human originated adult or embryonic stem cells as sources for in vitro generation

of tissues (79). Endothelial cells derived from human embryonic stem cells have been shown to generate functional vasculature. However, much more research is required to understand the cues and signals that regulate cell differentiation. In addition, research is required in scaling up these cells and using them for tissue engineering applications (80).

### FUTURE DIRECTIONS

Future treatments for wound healing and tissue regeneration may benefit from tissue-engineered skin substitutes. To extend their lifespan and improve their integration with host tissues, these substitutes' vascularization still needs to be improved (81). One approach of improving vascularization is by employing bioreactors to give mechanical stimulation essential to generate mature blood vessels. Standardizing the production process and cutting manufacturing costs will be crucial steps in creating dependable replacements. To increase their lifespans, standardization in storage and preservation is also crucial (82).

### CONCLUSION:

The field of skin tissue engineering is a fast-growing and one of the most promising approaches to recreating and repairing the injured skin. Combination

of hydrogel scaffolds, polymeric biomaterials, bioactive molecules, stem cells and subsequent bioprinting methods has greatly enhanced capability to mimic native extracellular matrix as well as the support of key biological processes cell adhesion, cell proliferation, angiogenesis and re-epithelialization. In particular, hydrogel offers a moist and biocompatible platform to aid tissue regeneration and controlled drug or growth factor delivery. Mechanical strength, biodegradability and biological performance can be optimised by the synergistic exploitation of natural and synthetic polymers. Moreover, bioactive molecules and stem cells are useful in improving cellular differentiation and increasing wound healing rates whereas 3D bioprinting technologies allow the accurate spatial organization of various cell types to recapitulate the intricate architecture of native skin with high accuracy. Nevertheless, reproduction of native skin is so difficult even with these developments, particularly in terms of vascularization, re-pigmentation, adnexal regeneration, immune compatibility and lasting functionality. The future studies should be aimed at enhancing the scaffold vascular integration, standardization of the manufacturing and storage processes, cost-effectiveness, and clinical safety and reproducibility. The combination of biomaterial science, cellular biology and tissue engineering technologies is, in general, a potential that is enormous in the development of clinically viable, fully functional skin substitutes in the treatments of burns, chronic wounds, and wide-ranging skin defects.

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