

# Role of Tissue Scaffolds in Skin Wound Healing: A Systematic Review

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Received: 31 May 2015/ Accepted: 18 June 2015

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## Abstract

Researchers have evaluated the biological and synthetic scaffolds to create a similar replacement tissue that is suitable for repairing of human skin wounds. In this review we examine the wound healing role of these tissue scaffolds in recent articles. In this study we search multiple medical databases (Pub Med, Science Direct, and ProQuest) with Cochrane guideline and limit the search to “systematic review” for identifying the role of various tissue scaffolds in the wound healing process. We apply these major sources of data without any limitation in terms of study designs. A total of 3254 different articles that are published over the last five years were located through the search, of which 33 met inclusion criteria. Twenty three of these were identified through Science Direct, five from Pub Med and five from Pro Quest. We find various research designs in this study such as case-control, comparative, in vitro scaffold testing and review articles. Research finding that show new scaffolds with various wound healing properties concomitant with application of different growth factors or stem cell seeding. In this article, searching the databases is the most effective means of ensuring that all relevant papers are included in the systematic review. Next step in this research includes further human research about healing effects of proper and biologically tested tissue scaffolds in real patients.

**Key Words:** Tissue Scaffolds; Traumatic Wound Healing; Skin; Nursing; bio-engineering; Systematic Review

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## Introduction

The wound is an anatomical and functional disturbance in the skin that can be caused by pathological processes, which occurs inside or outside the affected limb. It is usually associated with hemorrhage, capillary contraction, coagulation, tissue complement, and activation of inflammatory reactions. Deep incisional injuries demand more time to repair due to the extent of destruction and fewer

skin remnants. In this type of traumatic wounds, creation of scar tissue and fibroplasia in depth of injury are probable. Healing of these wounds is a dynamic and slow process with various stages that is directed by intracellular connections via cytokines and growth factors (1).

Wound healing process may endure four to six weeks and is measured by various parameters, such as epithelialization processes, the formation of

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extracellular scaffolding, remodeling of collagen, increase in cell density, the presence of fibroblast, and neo-vascularization. In this regard, we can explore biological analysis and allergic reaction. The pattern of incisional wound has a significant role in the selection of appropriate biological scaffolds. The use of keratinocytes and fibroblast cell implantation ameliorates the repairing ability of these biological coverings. Keratinocytes constitute 95% to 97% of epidermal cells in undamaged skin, autografted skin, and repaired skin grafts (2). These stem cells implanting in extracellular matrixes can cause cellular proliferation and tissue regeneration. Fibroblast migrate to damaged area in response to a traumatic injury and release cytokine and tumor growth factor beta-1.

Effective healing of traumatic wounds depends on many factors in patients, including pervious diabetic history, socio-environmental status and physico-chemical characteristics of the tissue scaffold that apply for these wounds (3). Scar tissue formation is inevitable because of acellular nature of skin; therefore, during the wound healing process, extracellular matrixes for dermal and epidermal regeneration will be created. This dynamic and complex process involves many cells, including cells within extracellular matrixes, cytokines, and blood cells (4). Tissue scaffolding acts as a physical barrier to protect the wound against microorganisms, but it is permeable to oxygen and moisture (5). Also, these tissues produce skin healing and proper environment for epithelial regeneration. The process of skin repairing performs under proper wound oxygenation, humidity, and low bacterial condition.

On the other hand, free radicals postpone the wound healing processes that would result in fat oxidation,

enzymatic degradation, breakage of DNA strands, and wound susceptibility to microbial attacks (6). Despite the public who believe that the wounds healing process takes 2 to 3 weeks, incisional wound healing occurs during a one-year period after a traumatic injury.

All of these mechanisms as a part of the healing process occur in four phases: hemostasis, inflammatory, proliferative, and maturation (7). The impairment in one or all the phases of the healing process may cause chronic wounds(8). Different materials, such as medicinal plants, fats, and honey are being used in wound healing. These substances can be applied in debridement, anti-bacterial property, obstruction, and cell adhesion (9, 10). To stimulate wound healing and maintenance of its moisture, nurses utilize different bio-engineered dressing, including hydrocolloids, hydrogels, solid hydrogel foams, alginates, collagen, cellulose, and polyurethane compounds for traumatic wounds (11-14).

Allogenic substitutes is another issue for replacement of injured skin tissue and a method for wound healing, which consists of three types, namely, autograft, allograft and xenograft (15). Even though highly used in the traumatic wound, autograft is associated with a few restrictions on suitability of donor site. On the other side, allograft is a frequently used type in skin replacement, but it has some disadvantages in tissue rejection and transmission of diseases. To reach better healing, scientists apply a new degradable framework and primary support for skin cell to attach this extracellular matrix, proliferate and differentiate in proper manner. This extra cellular structure should provide new vascularization tissue and skin regeneration in site of traumatic wound and

nominated as scaffold tissue from 1974(16). In skin bioengineering, we need specific tissue scaffolds that are capable of restructuring the pervious uninjured skin (17). In this field, the clinical healing role of these tissue scaffold are very important for nursing personnel who caring for patients with various wounds. In this article we explore the healing role of these biological and synthetic scaffolds in major biomedical databases.

A systematic review is performed according to the Cochrane guideline; this study includes formulating research questions, selection of databases, data gathering, analysis and process of interpretation. The process of systematically reviewing article pertinent to study according to ( p.i.c.o) guide questions was apply in this research as following:

**Problem:** exploring the wound healing role of various tissue scaffolds in recent and major biomedical databases.

**Intervention:** completely different tissue scaffolds are studied consistent with the skin healing outcome.

**Comparison:** we compare the articles by examining the effect of each scaffold in skin healing.

**Outcome:** in this section, we study the role of each scaffold in skin wound healing.

**Target population:** we select articles applying human research or animal models and sample size in animal model is limited to 5 or 6 rat or other laboratory animal in any comparative group. On the other hand, in human research, Sample limited to one or two person that participated in surgical application of skin tissue scaffold and healing outcome of this operation evaluated. For this reason, mentioned sample sizes are not inserted in table2.

**Selection bias:** article with any methodological design is extracted for this review for prevention of any biases. These articles are selected in recent period of time for better viewing of more upto dated scientists view in wound healing dimension of novel scaffolds.

**Source of data:**we explore articles which are published over the last five years in major health databases (Pub Med, Science direct and ProQuest). Table one presents characteristics of these articles meeting the inclusion criteria.

**Search terms:**Tissue Scaffold, Skin and Wound Healing MeSH keywords are searched in recent literature for better knowing of scientists' new view in advanced wound healing research.

**Role of first author:** first author retrieve articles with above pico questions and accepted abstract form and so compare and analyze article intervention and result section with respect of healing outcome. In second part of research, first author gathering result, interpret whole extracted articles with Cochrane guideline and write the manuscript.

**Role of second & third authors:**second and third author supervise whole research from data gathering to the end of study with the Cochrane search strategy and mentioned abstract form. In the second part whole article revise and vigorously inspected for any biases.

**Inclusion criteria of study:** we include the role of skin tissue scaffolds in the wound healing process. All papers we used in this review are in English language and most recent full text articles or abstract are retrieved consistent with major keywords for narrowing the results and better matching the wound healing properties of searched articles.

*Exclusion criteria:* any article or abstract that doesn't matched with wound healing outcome and abstract form or published before the last five years was excluded from this study.

Table 1. Characteristics of selected articles

Databases	Number of articles related to tissue scaffold	Number of articles related to wound healing	Number of articles related to tissue scaffold and wound healing	Final number of articles meeting inclusion criteria
ProQuest	7523	23144	222	5
Science Direct	760	105	2924	23
Pub Med	1719	5521	108	5

## Results

In this study, articles selected according to the tissue scaffold which are being used for skin wound healing. The mentioned keywords were examined in three major medical databases and formulated through the search strategy. According to this strategy, a total 3254 articles are retrieved, of which 33 met the inclusion criteria.

Researchers vigorously inspected healing role of these tissue scaffolds in wound repairing process in animal models and human research. We found thirteen case-control studies, seventeen with comparative research design, two reviews and one laboratory tissue scaffold testing. Totally, 3% and 75% of these studies have been done on human samples and animal models respectively. 22% of these articles related to in vitro scaffold testing and review articles. 54% of the these articles have been used vascular endothelial growth factor, Platelet Derived Growth Factor-BB (PDGF-BB), human epidermal keratinocytes, melanocytes, Epidermal

Growth Factor (EGF), Basic Fibroblast Growth Factor (BFGF), NIH3T3 fibroblast cell, insulin, hydrocortisone, mesenchymal stem cell, Adipose Stem Cells (ADSCs), pancreas-derived stem cells, CD31, alpha Smooth Muscle Actin( $\alpha$ -SMA), and retinoic acid as cellular growth factors.

Skin repairing scaffolds fall into several categories: natural-derived, collagen-based, gelatin based, synthetic, fibrin-based and hybrid scaffolds (18). By exploring the articles, we reached several new skin scaffolds (listed in Table 2), including gelatin/zeolite, Pullulan-collagen composite hydrogel, novel bi-layer 3D activated carbon fibers, ginsenoside-Rg3(Rg3), ultrashort peptide hydrogel, Alkanin/shikonin biopolymers, anticoagulant coated nanofibers,

Table 2. Details of included studies

Reference article	Name of scaffold	Type of scaffold	Type of Research (human or non-human)	Control group	Method of study	Wound healing effect(outcome)	Application of growth agent
(19)	Gelatin/Zeolite	Gelatin-based	Animal model	Yes	Case-Control	Antibacterial with copper ion release & wound healing	None
(20)	Highly porous collagen scaffold	Collagen-based	Animal model	None	Comparative	Skin regeneration & reduces scar tissue	None
(21)	Chitosan & poly ethylene oxide	Synthetic	Animal model	Yes	Case -control	Increases angiogenesis, re-epithelialization and control granulation tissue	VEGF & PDGF-BB
(22)	Collagen & elastin made from salmon and a prion free scaffold	Compound Collagen	Animal model	Yes	Case-control	Skin healing as same as bovine derived collagen sponge	None
(23)	Xe-Derma or acellular porcine dermis	Natural-driven	Human research	Yes	Case-control	Proliferation, migration and differentiation of patient's keratinocytes	Keratinocyte
(24)	Porcine acellular dermal matrix(ADM)	Natural-driven	Animal model	Yes	Case-control	Full thickness wound repair	Human & mouse keratinocytes
(25)	Modified Gelatin and Poly Caprolactone	Gelatin-based	Animal model	Yes	Case-control	Faster epidermal wound closure	Human keratinocyte cells
(26)	Novel bi-layer 3D activated carbon fibers	Synthetic	Animal model	Yes	Case-control	Enhances fibronectin and type I collagen expression with antibacterial properties	Fibroblasts
(17)	Engineered Pulluan-collagen composite hydrogel	Collagen compound	Animal model	Yes	Case-control	Improve wound closure and a cell delivery matrix	Human fibroblasts, murine mesenchymal stem cells and endothelial cells
(27)	Electrospun gelatin and polycaprolactone nanofibers	Gelatin-based	Animal model	Yes	Case-control	Accelerating wound healing and therapeutic agent delivery	Human dermal fibroblasts and human dermal keratinocytes

(28)	New cationic biopolymer guar gum alkylamine(GGA A) with silver nanoparticle	Natural	Animal model	Yes	Comparative	Skin re-epithelialization & antibacterial	None
(29)	Self-assembling peptide(SAP)nano fiber scaffold	peptid derived	Animal model	Yes	Comparative	Cutaneous wound repair	Epidermal growth factor(EGF) and human dermal fibroblasts and keratinocytes
(30)	Micronized acellular dermal matrix(MADM)	Natural-derived	Animal model	Yes	Case-control	Micro carrier for the skin regeneration	Fibroblasts
(31)	Poly(ether)urethane-polydimethylsiloxane/fibrin-based scaffold	Fibrin-based	Animal model	Yes	Case-control	Increases wound healing rate	(VEGF) and basic fibroblast growth factor(bFGF)
(32)	Gelatin/carboxymethyl chitosan hybrid hydrogel	Hybrid	None	No	Comparative	Proper flexibility, antimicrobial, water absorption and wound healing capacity	In vitro NIH3T3 fibroblast cell proliferation on hydrogel films
(33)	3-D dual-layer nano/ microfibrinous chitosan/poly(D,L-Lactide) scaffold	Synthetic	Animal model	Yes	Comparative	Better cell proliferation and fasten wound healing	Human skin fibroblast cells
(34)	Biopolymer gel of atelocollagen and chitosan	Collagen-based	animal model	Yes	Comparative	Enhances cellular activity and wound healing	None
(35)	Chitin and chitosan application in various scaffold	Natural	Retrieved articles	No	Review	Healing effects in various tissue	Application of different growth factor
(36)	Chitosan application in various scaffold	Natural	Retrieved articles	No	Review	Healing effects in various tissue	Application of different growth factor
(37)	Core-shell nanofiber of polymeric gelatin-PLLCL solution	Gelatin-derived	None	No	Comparative	Skin regeneration	Epidermal growth factor, insulin, hydrocortisone and retinoic acid

(38)	Poly D-L lactic acid scaffold	Synthetic	Animal model	Yes	Comparative	Better microscopical cicatrization	Mesenchymal stem cell
(39)	Electrospun four biocompatible polymer containing Alkanin/shikonin	Synthetic with natural substances	Biopolymer testing	No	Comparative	skin repair	None
(40)	Poly(L-Lactic acid) nanofibrous scaffold with dlivery of silver ions at polymeric binder surfaces	Synthetic	None	Yes	Comparative	The first study to show that silver ions can be delivered without any nanoparticle	None
(41)	Poly(ethylene glycol_ poly (DL-Lactide)or (PELA)	Synthetic	Animal model	Yes	Comparative	Higher wound recovery and re-epithelialization	Basic fibroblast growth factor(b FGF)
(42)	Sericin-polyacrylamide 3-D scaffold	Natural- derived		No	Material testing	Act as a reconstructive dermal gelable sealant	None
(43)	Heparin coated nanofiber	Syntethic	Animal model	Yes	Comparative	increase epidermal cell migration in wound	None
(44)	Gene Activation of collagen-chitosan scaffold	Collagen-based	Animal model	Yes	Comparative	Enhances angiogenesis and better skin grafting	VEGF
(45)	Matriderm scaffold	Collagen-based	Animal model	Yes	Case-control	Significantly increase epidermalization, vascularization and healing in full-thickness wounds	Pancreas-derived stem cells
(46)	Knitted mesh-reinforced collagen-chitosan	Hybrid	Animal model	Yes	Comparative	Promoting angiogenesis and skin regeneration	None
(47)	Four different plant extracts incorporating in PCL scaffolds	Synthetic with natural substances	Animal model	Yes	Comparative	Early and intermediate epidermal differentiation and wound healing	Adipose stem cells(ADSCs)
(48)	Ultrashort peptide hydrogel	Peptid based	Animal model	Yes	Comparative	Accelerating autolytic debridement and epithelial cell proliferation	None

(49)	Gensenoside – Rg3(Rg3)	Synthetic	Animal model	Yes	Comparative	Repair of skin and inhibit scar formation	None
(50)	Novel porous scaffold with collagen, hyaluronic acid and gelatin	Collagen compound	Animal model	Yes	Case-control	Higher water absorption ability 20g water/g scaffold, less neutrophil infiltration and closure would be more rapid and a degradable scaffold	Human epidermal keratinocytes, melanocytes and dermal fibroblasts were seeded on this scaffold

Cationic biopolymer Guar Gum Alkylamine(GGAA), Core-shell nanofiber of polymeric gelatin-PLLCL solution, Micronized acellular dermal matrix(MADM), hybrid plant extract scaffold tissues and factor activated collagen-based nanofibers. These new bio-engineered scaffolds are assigned to the categories mentioned above.

**Discussion**

In traumatic wounds, contractile cells (myofibroblasts) cause a prominent decrease in wound size. A porous collagen increases skin wound healing and produces new dermal tissue with pausing wound contraction mechanism (20, 51). However any disturbances in contractile cell mechanism are not considered as the only process of wound healing. The novel porous collagen scaffold can be used in traumatic skin wound for better regeneration of dermis.

Pullulan-collagen composite hydrogel is another porous scaffold that is capable of skin regeneration in cotaneous wounds. Pullulan-based hydrogel is extremely integrated in dermal wounds.

Collagen with other natural scaffolds may be made from various origins (traditional & salmon-derived). Scientists apply this scaffolding material for seeding of fibroblast cells and better healing of skin incisional injuries in animal models. Marine based collagen-elastin scaffold is a better substitute for bovine collagen-elastin scaffold as it prevents the transmission of prion disease.

Using of natural scaffold for the treatment of wound infection is another wound healing issue. Gelatin/Copper Faujasites (CAF) composite scaffold is able to enhance wound oxygen supply and accelerate cellular proliferation (19). Gelatin is a proper natural scaffold for its biodegradability, low immunogenicity and bio compatibility (52) and can be applied for better viability of NIH3T3 fibroblast cells. In vivo study of Gelatin/Copper composite shows skin regeneration in 20 days after incisional wound creation (19). Silver ion releasing poly (L-Lactic acid) scaffold display wound repair with maintaining excellent viability of fibroblast and keratinocyte cells. In this scaffold, silver ions release from a polymeric binder (53). Another antibacterial scaffold that enhances fibronectin and type I collagen expression is the novel bilayer 3D activated carbon

fiber with proper release of incorporated gentamycin from its poly ( $\gamma$ -glutamic acid)/gelatin membrane. The outstanding features of this bilayer novel scaffold are wound healing and antibacterial properties (26).

Modified Gelatin/Poly-caprolactane scaffold is an alternative biocompatible membrane for human keratinocyte seeding, cellular proliferation and re-vascularization. This scaffold enhances skin wound repair owing to its best built epidermis regeneration in nude mouse. (25).

Nanofibrous scaffold can be impregnated with dual growth factors in mesh type structure. Applications of growth agents with nanofibrous scaffolds are very distinguished in recent literatures. Coating dermal injuries with this mesh type scaffolding tissue is associated with quick releasing of VEGF and slow releasing of PDGF-BB. These growth factors accelerate full thickness wound healing (21).

Smart ultrashort aliphatic peptide hydrogel with properties of non-cytotoxic and non-immunogen is another scaffold that has a major tendency to the helical fiber formation. This scaffold promotes epithelial and dermal regeneration with high closure rate of skin wound and burn repair. Scientists use this scaffold without seeding of growth agents (48).

Acellular porcine or Xe-Derma scaffold may be a different scaffold that has an important healing effect on the human skin wound and burn tissue. Keratinocytes confluences occurring in 7-10 days and in vitro differentiation of cultured epidermal cells to normal epidermal cells are best achieved with Xe-Derma scaffold coating (23). Moreover, porcine Acellular Dermal Matrix (ADM) scaffold has been used with various proportions of the human and rat

keratinocytes for full thickness skin wound healing in animal models (24). These scaffold tissues have numerous healing and regenerative function. Table 2 presents the most healing outcome of skin tissue scaffolds and growth agents being applied in the retrieved articles.

## **Conclusion**

In present study, essential information about traumatic wounds and their healing scaffolds were discussed. The scaffold types that used in these traumatic wounds were classified according accepted guideline of biological medicine.

Nowadays, various tissue scaffolds have been engineered in the field of wound healing. These nanostructures are vigorously examined in vitro & in vivo studies. Scientists apply these nanostructures to traumatic wounds in animal research. Some of these scaffold tissues are natural and others are serving as therapeutic agent carriers. These nano-fibers scaffolds carry antibacterial agents and growth factors to the target injured tissues.

Application of these new scaffolds such as Pulluan collagen composite hydrogel as a cell delivery matrix that forms a reliable framework for stem cell seeding, use of sericin poly-acrylamide scaffold with natural origin which apply as a gelable sealant for reconstruction of injured dermal tissue, use of micro carrier elements for skin regeneration in micronized acellular dermal matrix(MADM), use of plant extracts with novel collagen compound, application of copper ion releasing gelatin/zeolite scaffold with antibacterial capability, use of ultrashort peptide scaffold with skin repairing activity and better knowledge about recent scaffold healing role especially gene activation collagen compound scaffold that presented in table2. Use of these new

scaffold tissues in animal models are very prominent than in real patients. In this regard, safe applications of nontoxic and non-mutagenic scaffolds need to be changed for better compliance with wound healing in patients.

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