Applications of Bone Marrow Mesenchymal Stem Cell and Bioscaffolds in Skin Wound Healing

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Abstract: ***Introduction:*** Skin wound healing is a multi-step process. It involves coordinated interactions between growth factors, matrix, microenvironment around the wound, and various cells. Patients' quality of life in chronic wounds is affected because, in addition to sequential treatments, they incur significant medical costs. This review study aims to summarize the evidence and report current knowledge about tissue engineering, skin wound healing, and therapeutic strategies using bone marrow mesenchymal stem cells were performed. ***Methods:*** Thus, much effort has been focused on developing novel therapeutic approaches for wound treatment. Stem cell-based therapeutic strategies have been proposed to treat these wounds. They have shown significant potential for improving the speed and quality of wound healing and skin regeneration. A set of published data on the use of mesenchymal stem cells and a variety of biological scaffolds in wound healing is presented. Besides, we discussed different perspectives. ***Conclusion:*** We concluded that by activating bone marrow mesenchymal stem cells on a biological scaffold, the condition of the wound healing process can be improved.

Keywords: Humans, Mesenchymal Stem Cells, Quality of Life, Tissue Engineering, Wound Healing, Skin, Stem Cells.

INTRODUCTION

The healing process of skin wounds consists of three steps in harmony, with a large but distinct overlap. These steps include the inflammatory, proliferative, and regenerative steps. The wound healing process is regulated by the secretion of many different growth factors, cytokines and chemokines(1, 2). Disruption of the cellular and molecular signals of these steps can lead to the formation of chronic wounds(3). Common treatments for skin wounds include choosing the right dressing to maintain a good wound healing environment, in wounds with Causes such as ischemia and diabetes(4). However, the effectiveness of current treatments is limited, and the significant cost of treatment is important. The use of stem cells and biological scaffolds in regenerative medicine can be used as an alternative to provide higher quality treatment. It can also potentially heal wounds and maintain the natural structure of the skin(5). Stem cell-based therapy has become a promising new approach in restorative medicine. One of the important reasons for the focus on stem cells is the capacity of these cells to regenerate and differentiate into different cell types, which after injury, is very important for regenerating the physiological structure of tissue. Researchers suggest that applying mesenchymal stem cells to biological scaffolds can accelerate the healing process, close early, and prevent wound contraction(6). With the knowledge of regenerative medicine, skin tissue biological scaffolds are designed and manufactured. The advantage of artificial and engineered skins over natural skins is the lack of immune reactions and access to unlimited resources (7). Recently, the International Federation of Medical Sciences for Plastic and Reconstructive Surgical Treatments stated that Bone Marrow Mesenchymal Stem Cells (BMMSCs) could be one of the cellular sources for biological applications in restorative medicine. BMMSCs have the potential to differentiate in vitro into fat, bone cells, cartilage, myogenic cells, and endothelial cells(8). However, determining the optimal source of these cells, the method of administration from a clinical point of view, as well as the role of mesenchymal stem cells to heal wounds in the clinical condition and the reflection of these cells with a variety of biological scaffolds, still face many challenges(9). In this review, we will discuss the use of bone marrow-type mesenchymal stem cells on biological scaffolds to regenerate skin.

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ANATOMY OF SKIN (CUTIS, INTEGUMENT)

The skin (cutis, integument) and its derivatives constitute the integumentary system. The skin forms the external covering of the body and is its largest organ, constituting 15% to 20% of its total mass (Figure1)(10). The skin consists of three main layers(11): the epidermis is composed of a keratinized stratified squamous epithelium that grows continuously but main trains its normal thickness by the process of desquamation. Epidermis is derived ectoderm, the dermis is composed of e dense connective tissue that imparts mechanical support, strength, and thickness to the skin(12). Dermis is derived mesoderm. The hypodermis contains variable amounts of adipose tissue arranged into lobules separated by connective tissue septa. It lies deep to the dermis and its equivalent to subcutaneous fascia described in gross anatomy. In well- nourished individuals and in individuals living in cold climates, the adipose tissue can be quite thick(13). The hypodermis is the deepest layer of the skin consisting of loose connective tissue, and cells storing fat (half of the body fats stored in this place), blood vessels, and nerves. The tissue is especially rich in proteoglycan and glycosaminoglycan's absorbing fluid into the tissue (holds the water inside) and giving it mucous-like properties(14) .The epidermal derivatives

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of the skin (epithelial skin appendages) include the following structures and integumentary products: Hair follicle and hair, sweat (sudoriferous) glands, sebaceous glands, nails, mammary glands. There are four different types of cells in the epidermis: Keratinocytes are highly specialized epithelial cells designed to perform a very specific function: separation the organism from its external environment. They account for 85% of the cells in epidermis. Melanocytes are the pigment- producing cells of the epidermis. They account for approximately 5% of the cells in epidermis. Langerhans cells are the antigen-presenting cells involved in signaling in the immune system. They account for approximately 2% to 5% of the cells in epidermis. Merkel's cells are the sensitive mechanoreceptor cells associated with sensory nerve endings. They account for approximately 6%to 10% of the cells in the epidermis(15).

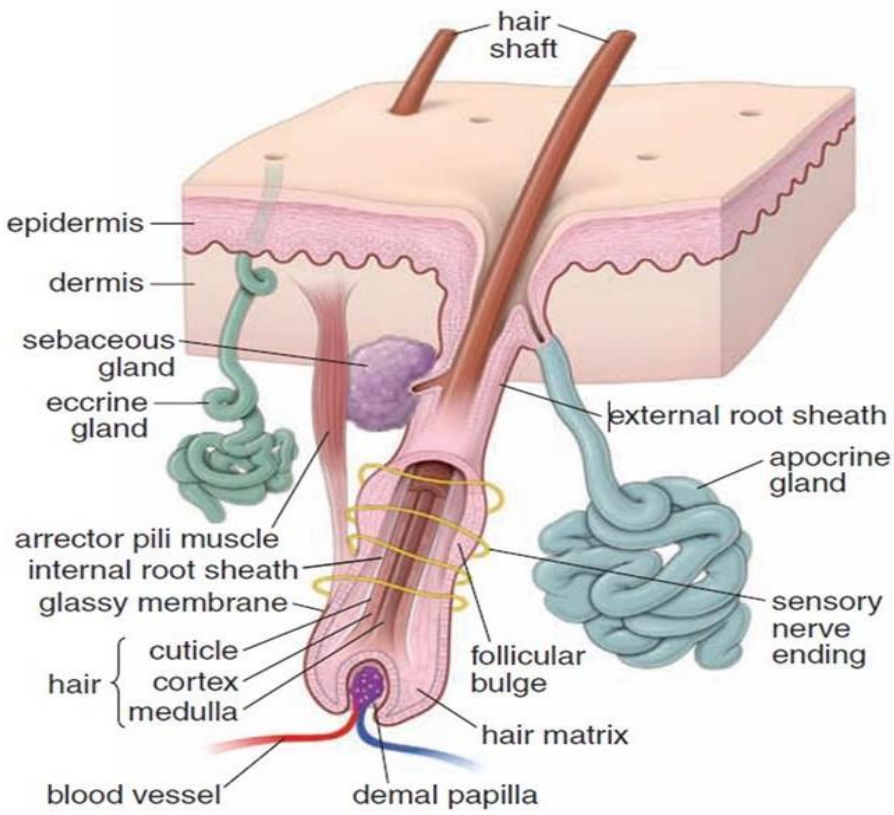

Figure 1: Diagram showing a hair follicle and other skin appendages. The sebaceous gland consists of the secretory portion and a short duct that empties into the infundibulum, the upper part of the hair follicle. The arrector pili muscle accompanies the sebaceous gland. Pili muscle forms the follicular bulge that contains epidermal stem cells. Nerve endings (yellow) surround the follicular bulge with nearby insertion of arrector pili muscle. The apocrine sweat gland also empties into the infundibulum. Note that eccrine sweat glands are independent structures and are not associated directly with the hair follicle. Adapted from Ross histology.

WOUNDS IN THE CLINICAL CONDITION

Over the past few decades, significant advances have been made in the production of wound care products. Understanding the different types of wounds and the pathophysiology of the wound environment is important in order to maximize the healing potential by choosing management options(figure2)(16). Surgical wounds, foot ulcers of diabetic vasculopathic origin, as well as pressure ulcers and trauma are the most common chronic wounds being treated(17). It is clear that some of the patient's characteristics predispose them to delayed wound healing. Local factors include oxygenation, infection, foreign bodies, or venous disease. Important systemic factors include age, stress, ischemic factors, obesity, immunosuppression, Smoking, and nutrition(18). There are several methods for managing wounds in the clinical setting, and careful consideration of each of these is beyond the scope of this article. As this article is most concerned with current tissue engineering strategies for wound healing, the use of skin alternatives will be discussed. Skin substitutes can be used alone or as a skin graft supplement to cover wounds. There are three types of skin alternatives are classified based on their respective biological function (Table2)(19). The relevance of this table can be seen in how different skin products are targeted in the market for different types of wound healing(Figure 2 and Table3). This distinction is especially useful for researchers in this field to be able to tailor tissue engineering products to the required patient groups. Thus, the challenge of producing tissue repair is the ability to regenerate native tissue in a way that allows the function to be restored to lost tissue in both acute and chronic conditions. Tissue engineering can be done using three factors: strategies, scaffolding, and cell

growth factors to create three-dimensional (3D) structural units that aim to restore function to skin tissue(20). These strategies mainly include covering wounds with a matrix scaffold dressing and/or polymer scaffold, injecting the cell directly into the wound site, or encapsulating the cell inside the material to be implanted. In the following sections, we discuss the main applications of tissue engineering in skin wound healing, including scaffolding, cell therapy, and growth factors, to create biological skin alternatives. Our focus is on current challenges as well as future scientific technologies that are always evolving.

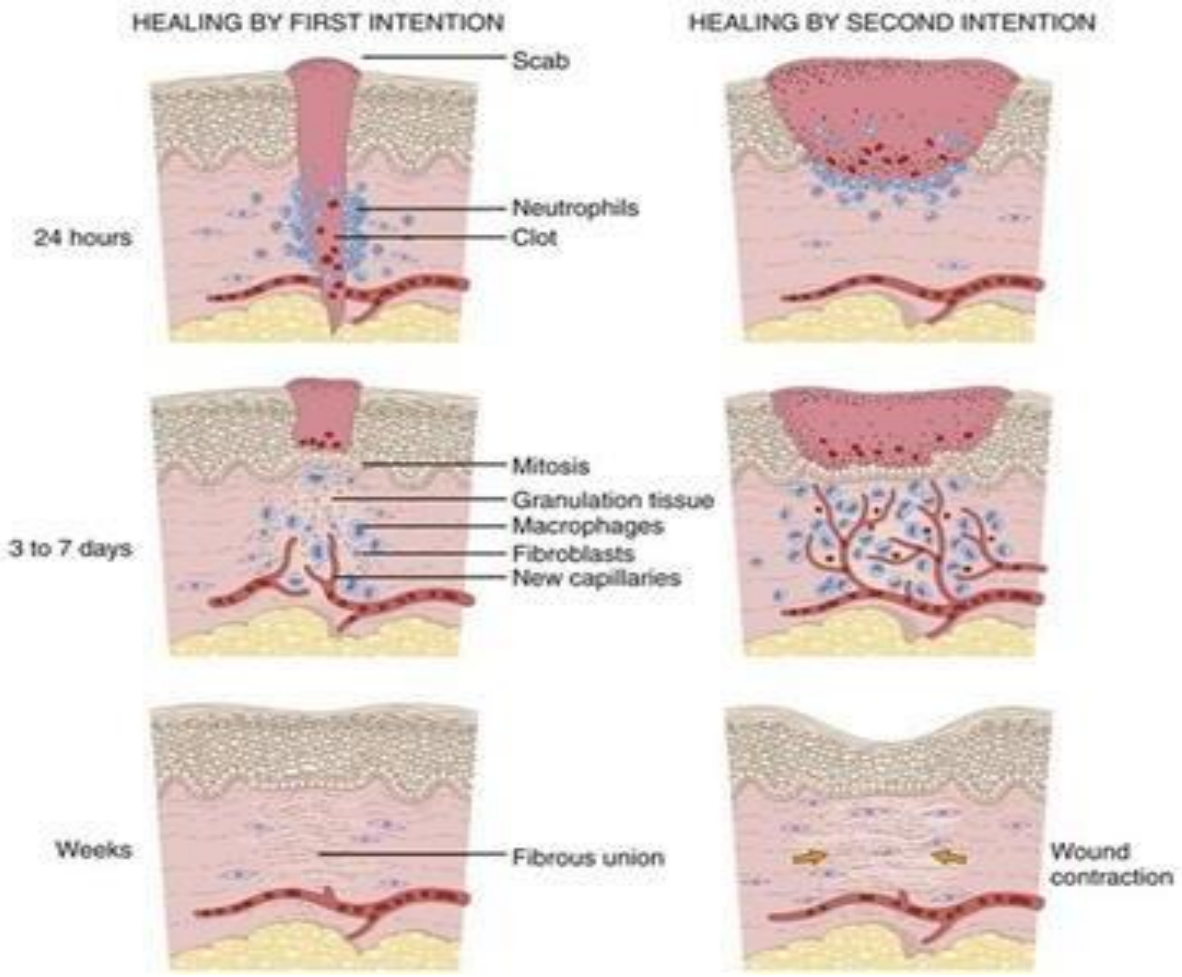

Figure 2: Wound healing with scar formation(16). A, Healing of wound that caused little loss of tissue: note the small granulation tissue and formation of a thin scar with minimal contraction. B, Healing a large wound: note large amounts of granulation tissue and scar tissue, and wound contraction.

STRATEGIES IN TISSUE ENGINEERING

There are two main goals in achieving the production of engineered tissues: The first goal is to scaffold that have the ability to support and maintain the cells on which they are placed and to encourage the cell to produce its own matrix and thus produce have a tissue for transplantation. The second goal is to use scaffolds that have the ability to deliver or transmit growth factors and drugs. For this purpose, the scaffolds are combined with growth factors, and with the help of the cells that are on it, it creates an opportunity to produce a new matrix and finally the desired tissue. These two goals are exclusively separate and are used in combination. The location where the cell and the scaffold are combined must be compatible with the intended purpose. In the sense that the choice of cell type, composition (construction) topography, and architecture of scaffolds should be selected in such a way that it has the ability to affect cell interaction and cell binding(40). Scaffold architecture is one of the important factors that changes in cellular responses, followed by the formation of new tissue. Such as mineralization in a specific area of the scaffold. Tissue engineering using biomaterials, polymer, and cellular precursors has achieved this to some extent. It is based on creating an environment similar to the extracellular matrix (ECM) in vitro(41). Synthetic polymers have the largest classification of biological materials. A wide range of these polymers are made of nano fiber(42). However, there are a variety of surface modification techniques to overcome limitations such as cell transfer and cell proliferation on the hydrophobic surface, which is a major issue in polymer scaffolds(43). In the following sections, we review the applications of tissue engineering in skin wound healing, including scaffolding, cell therapies to create biological skin equivalents in regenerative medicine.

Table 1: Key contributing cells and factors involved in the phases of wound healing.

Hemostasis	Inflammation	Proliferation	Remodeling
Classical timing	4–5 days	14 days	12–18 months
Main donating cells; Keratinocytes	Neutrophils	Macrophages	T-lymphocytes
Endothelial	Monocytes	Fibroblasts	Fibroblasts
Platelets	Macrophages	Myofibroblasts	Myofibroblasts
Main donating cytokines			
IL-1	EGF	EGF	TGF-b
TGF-a/TGF-b	TGF-b	TGF-b	IGF

FGF, fibroblast growth factor; IGF, insulin-like growth factor; IL-1, interleukin 1; PDGF, platelet-derived growth factor; TGF, transforming growth factor; TNF.

Table 2: The grading of skin substitutes according to biological actions.

Skin Grafts and Biologic Skin Substitutes	Explanation
Temporary wound coverings	Thin materials that are placed on fresh wounds until they heal.
Semi-permanent wound coverings	Autologous skin grafting materials are added in a two-step surgical procedure
Permanent wound coverings	An epidermal compound, skin analog or together as a permanent skin replacement solution

Table 3: Current available commercial tissue-engineered therapies for wound healing.

Commercialized products	Method of presenting	the type of wound	Duration of effect	Laboratory model	Therapeutic effects	resources
Grafix® (Osiris Therapeutics, Inc.)	Cryopreserved amnion-derived tissue	chronic diabetic foot ulcers	12weeks	Human	Re-epithelialisation, reduced diabetic foot complications	(21)
Tisseel® (Baxter International, Inc.)	Fibrin	Surgery repair	-1week	Human	mesh fixation	(22)
Hyalomatrix® (Anika)	Silicon membrane bound to hyaluronic acid	Close large cutaneous wounds (e.g., burn wounds.)	5weeks	Human	vascularized dermal bed with minimal bacterial colonization	(23)
EVICEL® (Ethicon)	Fibrin	Knee joint	-12month	Human	improves clinical outcome and wound healing	(24)
MySkin (Celltran Ltd.)	culture and expansion of the patient's own skin cells	chronic non-healing wounds	3days	Human	re-epithelialization	(25)
Dermagraft® (Organogenesis, Inc.)	Neonatal foreskin-derived fibroblast seeded in polyglycolic acid or polyglactin-910 mesh	diabetic foot ulcers,	4weeks	Human	Overcoming the factors that contribute to delayed healing	(26)

Table 4: Current available stem cells and biological growth factors therapies for wound healing.

Stem cells types	Delivery mode	Wound Types	Correction efficiency	Model source use	Treatment effect notes	Reference
BMMSCs with Acellular amniotic membrane(AAM)	Subjection	Flap surgery	7 days	rats	Skin mast cell promotion	(27)
BMMSCs Through Biological Growth Factor Biological Growth Factor	Subjection	Skin flap	7 days	rats	improvement of small vessels and decrease in mast cell type 3 lead to the reduction of scarring and fibrosis	(8)
BMMSCs	Subjection	ischemic diabetic random skin flap	7 days	rats	presence of vascular endothelial growth factor (VEGF)+ cells	(28)
BMMSCs with chicken embryo extract (CEE)	Injected locally	Ischemia-Reperfusion Injury	7 days	rats	Increase flap viability	(29)
autologous MSC	Fibrin spray	Skin wound	12weeks	Murine and human	closure of full-thickness wounds in diabetic mice and wound healing repair	(30)
BM-SCs	Scratch wound assay	Skin wound	3 days	Human	fibroblasts, migration of keratinocyte and synthesis ECM proteins	(31)
BM-SCs	Aspiration	Non healing wound	5days	Human	Increase synthesis of collagen	(32)
bone marrow stromal cell (BSCs)	BSCs with Cryopreserved fibroblast implants	chronic wounds	1, 3, and 5 days	Human	accelerating growth factor secretion	(33)
MSCs	MSCs Injection	Cutaneous wound	2weeks	wound	Promote angiogenesis	(34)
hiPSC-MSCs-Exos	Injected locally	Injured tissues	Facilitated cutaneous wound healing	Humanrat	Accelerated re-epithelialization, reduced scar widths, the promotion of collagen maturity, promoted the generation of newly formed vessels, accelerated their maturation in wound sites	(35)
Allogeneic BM-SCs	Intradermal	Excisional wound	14 days	Murine	Accelerate wound closure, increase re-epithelialization and angiogenesis	(36)
Combination hMSC with bFGF		Cutaneous wound	42 days	Rat	Increase re-epithelialization	(37)
MSCs	Mechanical loading	Incision wound		Mouse	Enhancement of angiogenesis	(38)
BMMSCs	subcutaneously administered in eight areas surrounding wound margin	diabetic wound	day 7	Rat	Increases of biomarkers in tissue regeneration	(39)

BONE MARROW MESENCHYMAL STEM CELLS

Bone marrow mesenchymal stem cells (BMMSCs) has the capacity to regenerate and differentiate into a variety of cells and tissues. Allogeneic and autologous MSC grafting deep in burn wounds reduces inflammation and increases angiogenesis and granulation tissue These cells produce bioactive substances that appear to accelerate the regeneration process after wounding (44) . BMMSC is involved in the repair of surgical wounds such as arteries, diabetes and chronic wounds. BMMSC and other cellular sources such as ADSCs (Adipose Tissue-Derived Stem Cells) were compared, both cells activation of cancer lymphocytes similarly and showing similar healing capacity. Recently, several studies have reported that human BMMSCs show a higher capacity to reduce ischemic area in rat wound models than ADSCs(28, 45).

REGENERATIVE MEDICINE

Medical treatment situations are not solely dependent on the pharmacokinetic activity, pharmacodynamics activity of drugs, and other therapeutic agents. While the use and availability of biological agents and bioavailability in human systems is increasing(46). The scaffolds used in orthopedics were injectable and are special biodegradable polymers that are injected into the desired location in the bone or tumor site in the bone. Osteconductive Bio-polymer is used to make bone, which is also obtained with suitable pores. Which is currently widely used in orthopedic surgeries. Scaffolding plays an important role in bone tissue engineering. By placing the scaffold at the site of injury, it preserves the bone and reveals its special effect by creating a suitable space for infiltration, angiogenesis and transfer of therapeutic factors (47). In one study, the full thickness of the dermis from the corpse skin was considered as a tissue-regenerating matrix and transplanted into the recipient along with adipose-derived stem cells. In such studies, the importance of creating an autologous organ in soft tissue scaffolds has been demonstrated (48). The human amniotic membrane is a biological material that can be easily prepared, processed and transferred. The amniotic membrane is composed of epithelial cells, basement membrane, vein-free collagen, and stroma. Amniotic membrane with wound healing properties, anti-fibroblastic activity and anti-antigenic properties is a good choice for reconstructive surgery. Amniotic membrane matrix components, such as collagen, elastin, laminin and fibronectin, are excellent candidates for scaffolding in tissue engineering programs its epithelial and stromal region is considered to facilitate autologous / allogeneic cell transfer (49).In recent years, studies on cardiovascular implants and the use of PURS (polyurethane with a bio stable structure) in their construction have made great progress and attempts have been made to compare and evaluate the construction of these scaffolds with the structure of natural vessels(44).

In cardiovascular tissue engineering, in addition to the biodegradability of scaffolding, special attention has been paid to biocompatible scaffolds with elongation and tensile strength. It has been noted that the required properties are exhibited by PU elastomers made from lysine ethyl ester, 1, 4-diisocyanatobutane (BDI), or PCL-b-PEG-b-PCL or PCL macrodiols, and from putrescine chain extenders (50).

Nano scaffolds are very important in the field of tissue engineering with their many features. Nanotechnology has made great strides in medicine. For example, we can refer to the technology of using nanowires. Which encapsulates the drug and controls the release rate of the drug. Easy administration of these polymers is by injection (intravenously) and if drug molecules such as proteins, peptides, genes, vaccines, antigens, human growth factors in combination with PLGA poly (D, L-lactide-co -glycolide) is based on micro nano(51) .Nano silvers are also new products that have been produced with the help of nanotechnology and have medical applications that have a well-known silver antibacterial property and in recent years have many applications that have been very effective in the treatment of burns(52) .Silver nano crystals, which are widely used to cover all types of burn wounds, are typically composed of nano crystals with a thickness of 900 nm and a crystal size of 10-15 nm placed on polyethylene and produced in two layers(53). it can be concluded; What is clinically important is selection management, design of biological scaffolds, and the use of tissue engineering strategies for various wounds. The future of tissue engineering is in wound regeneration using scaffolds that mimic the biological structure of the skin.

SUMMARY

The field of tissue engineering has made progress over the past decade. There are still concerns and limitations in the transfer of cellular therapies for wound healing, including safety, cost, and effectiveness of treatment. Presenting stem cells to wounds through 3D scaffolding seems to be the most promising method. With the advancement of understanding stem cell biology along with technical advances in biological scaffolding, it is hoped that in the near future tissue engineering methods will be standard and routine for wound healing, especially skin wounds.

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REFERENCES

[1] Auger FA, Lacroix D, Germain L. Skin substitutes and wound healing. Skin pharmacology and physiology. 2009;22(2):94-102. https://doi.org/10.1159/000178868

[2] Guo Sa, DiPietro LA. Factors affecting wound healing. Journal of dental research. 2010;89(3):219-29. https://doi.org/10.1177/0022034509359125

[3] Bayat M, Chien S, Chehelcheraghi F. Co-localization of Flt1 and tryptase of mast cells in Skin wound of rats with type I diabetes: Initial studies.Acta Histochemica. 2021;123(2):151680. https://doi.org/10.1016/j.acthis.2021.151680

[4] Dickinson LE, Gerecht S. Engineered biopolymeric scaffolds for chronic wound healing. Frontiers in physiology. 2016;7:341. https://doi.org/10.3389/fphys.2016.00341

[5] Ruggeri M, Bianchi E, Rossi S, Vigani B, Bonferoni MC, Caramella C, et al. Nanotechnology-Based Medical Devices for the Treatment of Chronic Skin Lesions: From Research to the Clinic. Pharmaceutics. 2020;12(9):815. https://doi.org/10.3390/pharmaceutics12090815

[6] Chaushu L, Rahmanov Gavrielov M, Chaushu G, Vered M. Palatal Wound Healing with Primary Intention in a Rat Model—Histology and Immunohistomorphometry. Medicina. 2020;56(4):200. https://doi.org/10.3390/medicina56040200

[7] Laurent A, Hirt-Burri N, Scaletta C, Michetti M, de Buys Roessingh AS, Raffoul W, et al. Holistic Approach of Swiss Fetal Progenitor Cell Banking: Optimizing Safe and Sustainable Substrates for Regenerative Medicine and Biotechnology. Frontiers in bioengineering and biotechnology. 2020;8. https://doi.org/10.3389/fbioe.2020.557758

[8] Chehelcheraghi F, Anbari K. Histological Evaluation of Different Types of Mastocytes in the Skin Flap Using Bone Marrow Mesenchymal Stem Cells Through Biological Growth Factor. Journal of Babol University of Medical Sciences. 2018;20(3):21-8.

[9] Dai J, Jiang C, Chen H, Chai Y. Treatment of Diabetic Foot with Autologous Stem Cells: A Meta-Analysis of Randomized Studies. Stem Cells International. 2020;2020. https://doi.org/10.1155/2020/6748530

[10] Kolarsick PA, Kolarsick MA, Goodwin C. Anatomy and physiology of the skin. Journal of the Dermatology Nurses' Association. 2011;3(4):203-13. https://doi.org/10.1097/jdn.0b013e3182274a98

[11] Cormack GC, Lamberty BG. The arterial anatomy of skin flaps: Churchill Livingstone; 1994. https://doi.org/10.1002/bjs.1800820959

[12] Candi E, Schmidt R, Melino G. The cornified envelope: a model of cell death in the skin. Nature reviews Molecular cell biology. 2005;6(4):328-40. https://doi.org/10.1038/nrm1619

[13] Gaboriau HP, Murakami CS. Skin anatomy and flap physiology. Otolaryngologic Clinics of North America. 2001;34(3):555-69. https://doi.org/10.1016/s0030-6665(05)70005- 0

[14] Kabashima K, Honda T, Ginhoux F, Egawa G. The immunological anatomy of the skin. Nature Reviews Immunology. 2019;19(1):19-30. https://doi.org/10.1038/s41577-018-0084-5

[15] Di Meglio P, Perera GK, Nestle FO. The multitasking organ: recent insights into skin immune function. Immunity. 2011;35(6):857-69. https://doi.org/10.1016/j.immuni.2011.12.003

[16] Sussman C, Bates-Jensen BM. Wound care: a collaborative practice manual: Lippincott Williams & Wilkins; 2007.

[17] Guest J, Vowden K, Vowden P. The health economic burden that acute and chronic wounds impose on an average clinical commissioning group/health board in the UK. Journal of wound care. 2017;26(6):292-303. https://doi.org/10.12968/jowc.2017.26.6.292

[18] Velnar T, Bailey T, Smrkolj V. The wound healing process: an overview of the cellular and molecular mechanisms. Journal of International Medical Research. 2009;37(5):1528-42. https://doi.org/10.1177/147323000903700531

[19] Horch R. Skin Substitutes-an Overview of Cultured Epithelia to Treat Wounds. Surgery in Wounds. 2004:435-46. https://doi.org/10.1007/978-3-642-59307-9_43

[20] Claxton MJ, Armstrong DG, Boulton AJ. Healing the diabetic wound and keeping it healed: modalities for the early 21st century. Current diabetes reports. 2002;2(6):510-8. https://doi.org/10.1007/s11892-002-0121-3

[21] Lavery LA, Fulmer J, Shebetka KA, Regulski M, Vayser D, Fried D, et al. The efficacy and safety of Grafix® for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. International wound journal. 2014;11(5):554-60. https://doi.org/10.1111/iwj.12329

[22] Campanelli G, Pascual M, Hoeferlin A, Rosenberg J, Champault G, Kingsnorth A, et al. Post-operative benefits of Tisseel®/Tissucol® for mesh fixation in patients undergoing Lichtenstein inguinal hernia repair: secondary results from the TIMELI trial. Hernia. 2014;18(5):751-60. https://doi.org/10.1007/s10029-014-1263-3

[23] Myers SR, Partha VN, Soranzo C, Price RD, Navsaria HA. Hyalomatrix: a temporary epidermal barrier, hyaluronan delivery, and neodermis induction system for keratinocyte stem cell therapy. Tissue engineering. 2007;13(11):2733-41. https://doi.org/10.1089/ten.2007.0109

[24] Budde S, Noll Y, Zieglschmid V, Schroeder C, Koch A, Windhagen H. Determination of the efficacy of EVICEL™ on blood loss in orthopaedic surgery after total knee replacement: study protocol for a randomised controlled trial. Trials. 2015;16(1):299. https://doi.org/10.1186/s13063-015-0822-y

[25] Moustafa M, Bullock AJ, Creagh FM, Heller S, Jeffcoate W, Game F, et al. Randomized, controlled, single-blind study on use of autologous keratinocytes on a transfer dressing to treat nonhealing diabetic ulcers. 2007. https://doi.org/10.2217/17460751.2.6.887

[26] Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. Advances in wound care. 2015;4(9):560-82. https://doi.org/10.1089/wound.2015.0635

[27] Chehelcheraghi F, Abbaszadeh A, Tavafi M. Skin mast cell promotion in random skin flaps in rats using bone marrow mesenchymal stem cells and amniotic membrane. Iranian biomedical journal. 2018;22(5):322. https://doi.org/10.29252/ibj.22.5.322

[28] Chehelcheraghi F, Chien S, Bayat M. Mesenchymal stem cells improve survival in ischemic diabetic random skin flap via increased angiogenesis and VEGF expression. Journal of cellular biochemistry. 2019;120(10):17491-9. https://doi.org/10.1002/jcb.29013

[29] Chehelcheraghi F, Bayat M, Chien S. Effect of mesenchymal stem cells and chicken embryo extract on flap viability and mast cells in rat skin flaps. Journal of Investigative Surgery. 2020;33(2):123-33. https://doi.org/10.1080/08941939.2018.1479006

[30] Falanga V, Iwamoto S, Chartier M, Yufit T, Butmarc J, Kouttab N, et al. Autologous bone marrow–derived cultured mesenchymal stem cells delivered in a fibrin spray accelerate healing in murine and human cutaneous wounds. Tissue engineering. 2007;13(6):1299-312. https://doi.org/10.1089/ten.2006.0278

[31] Walter MN, Wright KT, Fuller HR, MacNeil S, Johnson WEB. Mesenchymal stem cell-conditioned medium accelerates skin wound healing: an in vitro study of fibroblast and keratinocyte scratch assays. Experimental cell research. 2010;316(7):1271-81. https://doi.org/10.1016/j.yexcr.2010.02.026

[32] Han S-K, Yoon T-H, Lee D-G, Lee M-A, Kim W-K. Potential of human bone marrow stromal cells to accelerate wound healing in vitro. Annals of plastic surgery. 2005;55(4):414-9. https://doi.org/10.1097/01.sap.0000178809.01289.10

[33] Kim S-H, Han S-K, Yoon T-H, Kim W-K. Comparison of Bone Marrow Stromal Cells with Fibroblasts in Wound Healing Accelerating Growth Factor Secretion. Archives of Plastic Surgery. 2006;33(1):1-4.

[34] An Y, Liu W, Xue P, Ma Y, Zhang L, Zhu B, et al. Autophagy promotes MSC-mediated vascularization in cutaneous wound healing via regulation of VEGF secretion. Cell death & disease. 2018;9(2):1-14. https://doi.org/10.1038/s41419-017-0082-8

[35] Zhang J, Guan J, Niu X, Hu G, Guo S, Li Q, et al. Exosomes released from human induced pluripotent stem cells-derived MSCs facilitate cutaneous wound healing by promoting collagen synthesis and angiogenesis. Journal of translational medicine. 2015;13(1):49. https://doi.org/10.1186/s12967-015-0417-0

[36] Wu Y, Chen L, Scott PG, Tredget EE. Mesenchymal stem cells enhance wound healing through differentiation and angiogenesis. Stem cells. 2007;25(10):2648-59. https://doi.org/10.1634/stemcells.2007-0226

[37] Nakagawa H, Akita S, Fukui M, Fujii T, Akino K. Human mesenchymal stem cells successfully improve skin-substitute wound healing. British Journal of Dermatology. 2005;153(1):29-36. https://doi.org/10.1111/j.1365-2133.2005.06554.x

[38] Kasper G, Dankert N, Tuischer J, Hoeft M, Gaber T, Glaeser JD, et al. Mesenchymal stem cells regulate angiogenesis according to their mechanical environment. Stem cells. 2007;25(4):903-10. https://doi.org/10.1634/stemcells.2006-0432

[39] Kuo Y-R, Wang C-T, Cheng J-T, Wang F-S, Chiang Y-C, Wang C-J. Bone marrow–derived mesenchymal stem cells enhanced diabetic wound healing through recruitment of tissue regeneration in a rat model of streptozotocin-induced diabetes. Plastic and reconstructive surgery. 2011;128(4):872-80. https://doi.org/10.1097/prs.0b013e3182174329

[40] Ikada Y. Challenges in tissue engineering. Journal of the Royal Society Interface. 2006;3(10):589-601. https://doi.org/10.1098/rsif.2006.0124

[41] Chan B, Leong K. Scaffolding in tissue engineering: general approaches and tissue-specific considerations. European spine journal. 2008;17(4):467-79. https://doi.org/10.1007/s00586-008-0745-3

[42] Maitz MF. Applications of synthetic polymers in clinical medicine. Biosurface and Biotribology. 2015;1(3):161-76. https://doi.org/10.1016/j.bsbt.2015.08.002

[43] Paital SR, Dahotre NB. Wettability and kinetics of hydroxyapatite precipitation on a laser-textured Ca–P bioceramic coating. Acta biomaterialia. 2009;5(7):2763-72. https://doi.org/10.1016/j.actbio.2009.03.004

[44] Kloeters O, Schierle C, Tandara A, Mustoe TA. The use of a semiocclusive dressing reduces epidermal inflammatory cytokine expression and mitigates dermal proliferation and inflammation in a rat incisional model. Wound repair and regeneration. 2008;16(4):568-75. https://doi.org/10.1111/j.1524-475x.2008.00404.x

[45] Kim D-W, Staples M, Shinozuka K, Pantcheva P, Kang S-D, Borlongan CV. Wharton's jelly-derived mesenchymal stem cells: phenotypic characterization and optimizing their therapeutic potential for clinical applications. International journal of molecular sciences. 2013;14(6):11692-712. https://doi.org/10.3390/ijms140611692

[46] Lin JH, Lu AY. Role of pharmacokinetics and metabolism in drug discovery and development. Pharmacological reviews. 1997;49(4):403-49.

[47] Dorozhkin SV. Calcium orthophosphate (CaPO4) scaffolds for bone tissue engineering applications. Journal of Biotechnology and Biomedical Science. 2018;1(3):25. https://doi.org/10.14302/issn.2576-6694.jbbs-18-2143

[48] Rodgers K, Jadhav SS. The application of mesenchymal stem cells to treat thermal and radiation burns. Advanced drug delivery reviews. 2018;123:75-81. https://doi.org/10.1016/j.addr.2017.10.003

[49] Chehelcheraghi F, Eimani H, Homayoonsadraie S, Torkaman G, Amini A, Majd HA, et al. Effects of acellular amniotic membrane matrix and bone marrow-derived mesenchymal stem cells in improving random skin flap survival in rats. Iranian Red Crescent Medical Journal. 2016;18(6). https://doi.org/10.5812/ircmj.25588

[50] Amani H, Mostafavi E, Arzaghi H, Davaran S, Akbarzadeh A, Akhavan O, et al. Three-dimensional graphene foams: synthesis, properties, biocompatibility, biodegradability, and applications in tissue engineering. ACS biomaterials science & engineering. 2018;5(1):193-214.

[51] Zhao C, Tan A, Pastorin G, Ho HK. Nanomaterial scaffolds for stem cell proliferation and differentiation in tissue engineering. Biotechnology advances. 2013;31(5):654-68. https://doi.org/10.1016/j.biotechadv.2012.08.00 1

[52] Rahimi M, Noruzi EB, Sheykhsaran E, Ebadi B, Kariminezhad Z, Molaparast M, et al. Carbohydrate polymer-based silver nanocomposites: Recent progress in the antimicrobial wound dressings. Carbohydrate polymers. 2020;231:115696. https://doi.org/10.1016/j.carbpol.2019.115696

[53] Khan SU, Saleh TA, Wahab A, Khan MHU, Khan D, Khan WU, et al. Nanosilver: new ageless and versatile biomedical therapeutic scaffold. International journal of nanomedicine. 2018;13:733. https://doi.org/10.2147/ijn.s153167