REVIEW

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Role of secretomes in chronic wound treatment: a review

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ABSTRACT

Living with a chronic wound may prove to be devastating to patients both physically and psychologically. Wound increases economic and society burden due to low healing rate, prolonged hospital treatment, and increased epidemiology worldwide. Therefore, application wound treatment modalities are necessary for patient recovery. However, each modality has their own advantage and limitation. As a newly-founded modality, secretome, which originated from Mesenchymal stem cells (MSCs) plays an important role in chronic wound healing due to its ability in promoting tissue regeneration and self-renewal that supports cell proliferation and migration. However, different therapeutic potentials can arise according to each source of stem cells. This review highlights the importance of secretome as a modality in treating chronic wounds. Secretome types, stem cell origin, and results when applied in vitro and in vivo will also be comprehensively reviewed.

Keywords: closed wounds, open wounds, secretome, wound healing, wound treatment modalitites.
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INTRODUCTION

Wound is a loss of tissue due to body barrier disruption by external causes.[1] Based on its contamination level, wound is differentiated into two types such as closed and open wounds. Closed wounds are caused by a direct blow. Degree of injury differs according to force and direction of this external blow. Tissue repair is not exposed to external factors, thus had little to no contamination.[2] On the other hand, open wounds are caused by sharp objects. Higher risk of contamination and infection are present due to external and/or internal injuries inflicted on body tissue, thus increasing tissue exposure to harmful bacteria.[3]

Incurable wounds can have devastating effects for patients both physically and psychologically.[4,5] Physically, wound causes more pain, infection, prolonged treatment, and difficulty in performing daily activities mainly in moving and working.[5] Psychologically, wound is closely related to stress, body image problems, social isolation, sleep problems, mobility impairment, anxiety, depression and an overall decrease of quality of life, especially when the wound oozes and smells bad.[5] Wound and stress can also form a vicious cycle, where the presence of stress can cause wound exacerbation and vice-versa.[4] In addition, financial costs of chronic wound treatment is an additional burden to patients due to rising medication prices, longer wound healing time, and increased hospitalization in some cases where infection is present.[5] According to these effects, wound care is necessary to ensure recovery, prevent infection, accelerate healing process, minimize scarring, and avoid diseases such as metabolic deficiencies, infection, diabetes, and arterial and venous disease.[6] Secretome refers to all factors secreted by cell, especially protein secreted to extracellular spaces, such as growth factors, cytokines, chemokines, proteases, and adhesion molecules that has an important role in cell communication, signaling, and migration.[7] Secretomes can also be described as a mixture of proteic soluble fraction (growth factor and cytokine) and vesicular fraction (exosomes and microvesicles) where its vesicular fraction is able to deliver drugs and protein to damaged area in order to create therapeutic effects. Secretomes can also support cell-proliferation, growth, and differentiation.[8] Due to its ability to increase cell proliferation and migration, secretome is considered effective in wound healing. In addition, secretome can serve as an antimicrobial factor in dealing with drug-resistant conditions.[9] A review of the role of secretome in skin regeneration is beneficial due to improvement chronic wound treatment.

SECRETOME IN DERMATOLOGY

Closed and Open Wounds

Common types of closed wounds include bruising/contusion/hematoma and whiplash. While common types of open wounds are classified into abrasion, puncture, laceration, incision, and avulsion. In **Table 1** each type of wound will be further explained.

Epidemiology

Skin wounds produce an impact to the global healthcare setup by creating considerable burden to economy and society. Low healing rates amplified this issue, as it was reported that almost one billion people worldwide experience acute and chronic wounds which contributes to 3% of the financial expenditure for their management. Cutaneous wound can be divided into acute and chronic wounds based on the pathogenesis and

Table 1. Definition of each type of closed and open wound

Type of wound	Definition
1. **Closed wound**	
- Bruising/contusion/hematoma[2]	Swelling caused by slight blow as a result of blood infiltration into tissues. Damage to underlying tissues (nerves, bone, blood vessels, and joints) can be present due to higher impact.
- Whiplash[2]	Displacement to body parts due to sudden bending, twisting, or deceleration when one body part is fixed while another is mobile.
2. **Open wound**	
- Abrasion[3]	Small wound with little to no bleeding due to skin rubbing against a rough surface.
- Puncture[3]	Hole-shaped wound that may need further treatment if deep enough and/or contaminated.
- Laceration[3]	Irregular and deep cut that can result in more skin tearing and bleeding.
- Incision[3]	Regular-shaped scar usually made during surgery. However, can cause heavy bleeding when suffered in other circumstances.
- Avulsion[3]	Partial or complete skin tearing, usually as a result of accidents. It can lead to limb dislocation in some cases.

progression. Chronic wounds cannot resolve. It will sustain continuous inflammation, persistent infections, even necrosis. Meanwhile, acute wounds will resolve by regaining structural integrity.[10] Acute wounds can be divided to traumatic wound and surgical wound. Traumatic wound is found in the form of incision, abrasion, skin avulsion, puncture, or trauma-related closed wound such as hematomes and whiplash injury. On the other hand, surgical wound can be identified as an incision or surgical site needle-puncture injury.[11] In 2018, a study by Furtado et al showed from 770 patients assessed at care units, 17.5% (135 patients) suffered from wounds. According to total wounds discovered, 82% were chronic wounds and 18% were acute wounds. From this 18%, traumatic (76%) and surgical wounds (22%) were the most common.[12]

Hematomes are commonly caused by skin injury and often called as bruises. This type of wound is commonly found in the pediatrics population on the lower extremities, mostly on the shins and knees and caused by temperate climate or sport-related injuries.[13,14] Bruising is also caused by ligament injury such as anterior cruciate ligament injury (ACL). A study review shown that out of eleven cases of ACL patients, five reported bone-bruise locations on both the femur and tibia.[15]
Whiplash traumas are commonly caused by traffic accidents and other types of trauma causing acceleration-deceleration mechanism in the cervical spine.[16] It is found that traffic crashes cause 69% of soft tissue injury to the neck and 50% of neck sprains.[13] A study by Oka et al in 2017 analyzed 4,616 collision cases. 1,571 patients (37.7%) had experienced Whiplash-associated disorders (WAD) and the prevalence in the general population was 1.3% in male and 1.0% in female. Meanwhile, another kinematic study stated that higher acceleration happens in females compared to males in similar crashes and other head neck motion responses.[17] Even though WAD has good prognosis, studies have discovered that approximately 50% of the affected individuals were still dealing with the symptoms one year post injury. This injury can be followed by depression, fear, and hyperbolic negative perception of anticipated pain that can prolong WAD treatment.[16]

In terms of wounds healing, abrasions are the simplest type of injury as it results in minimal bleeding at most. Studies shown that abrasions are the most prevalent type of injury in children contributing to 70% of all cases of injury. The most common sites are the head and torso, accounting for 50% of all abrasions cases with 15.4% cases found in upper limbs and 34.6% cases found in the lower limbs. Intentional injuries are found more common in middle age groups. Meanwhile, unintentional abrasions are prevalently linked with falls in older patients and sport-related traumas in children. However, abrasions are mainly accidental and can happen at any phase of life with no particular likelihood for age or sex.[18]

Puncture wounds are common injuries to the plantar surface of foot and other areas of the distal extremities. In a survey consisting of 200 patients in the emergency department, 44% reported at least one previous plantar puncture injury. The main complication from this type of injury is infection, ranging from mild soft tissue inclusion to osteomyelitis. From 156 wounds identified in the previous study, 50% caught medical attention in which the self-reported infection prevalence was 11%.[19]

Another type of skin wound is hand and finger lacerations which account for 587,451 emergency department visits annually. Identified patients are commonly white (70.5%), male (63.4%), and aged from 18 until 44 years old (46.3%). Common etiologies of this wound are injuries caused by knives (30.5%), metal containers (4.2%), and drink ware (3.8%). Most of patients (97.4%) are successfully managed and treated without hospital admission. Meanwhile, 0.2% are sent for further management to other hospitals.[20]

Skin tear or avulsion are found approximately from 3.3% to 22% in hospital settings, and 5.5% to 19.5% of them are treated at home. This type of wound is primarily linked to old age and

Table 2. Previous modalities of wound healing

	Modality	Mechanism	Function	Limitation
1.	Skin substitutes[27]	Fibroblasts generate growth factors, cytokines, and glycosaminoglycans	Replace large tissue surface areas in burns and/or surgical defects	- Costly - Rejection - Hypersensitivity (in some cases)
2.	Split-thickness autograft (Gold standard)[28]	Graft a full-thickness fascia from a donor site over a compromised region	Not identified	- Scarring and/or contracture of wound site - Limitation of quality skin donor - Risk of complications - Pain - Infection - Inappropriate for burns with large surface areas
4.	Donor keratinocytes[28]	Proliferation of newborn keratinocytes due to secreted factors from neighboring cells	Increase cell density with varying concentration of keratinocytes	- Decrease of effectiveness in elderly population
5.	Cultured epithelial autographs (CEA)[28]	1. Harvest cells with punch biopsy 2. Expand cells in vitro by supporting them with 3T3 fibroblast cells in a growth-stimulatory medium consisting of EGF and cholera toxin 3. Harvest sheets of epithelia with dispase enzyme, and graft sheets of the cultured epithelia onto wound bed	- Provide skin replacement without risk of rejection - Enhance wound repair	- Longer sheet preparation time for grafting - Risk of sepsis
4.	Negative pressure wound therapy[27]	1. Optimize blood flow 2. Remove exudates 3. Apply pressure 4. Maintain moist environment.	Reduce wound volume and infection rates	Not identified
5.	Growth factors[27]	- Increase Epidermal growth factor (EGF) and Fibroblast growth factor (FGF) - Maintain Growth factor-β (TGF-β), PDGF, and Vascular endothelial growth factor (VEGF)	Broadly regulate deficient and deregulated factors	- Limited research due to interpretation difficulty and inability to control results. - Possible risk of cancer when used excessively
6.	Hyperbaric oxygen[27]	Not identified	- Promote fibroblast proliferation - Enhance immune function - Stimulate angiogenesis.	- Effectiveness unclear (not widely practiced) - Possible side effects including myopia, oxygen toxicity, seizures, and pneumothorax
7.	Wound dressings[28]	Dressings serve as carrier in cell transfer to wound bed	- Increase wound stability - Hydrate wound. - Optimize wound regeneration - Protect wound from infection	- Co-morbidities in high risk patients (hyaluronic acid) - Increase infection rates (biobrane)
8.	Stem cells[28]	Stimulate angiogenesis by releasing angiogenic factors	- Enhance wound healing by promoting angiogenesis - Reduce formation of scar	- Painful when harvested from living tissue - Donor site morbidit

Table 3. Secretory profile of secretome based on mesenchymal stem cell (MSC)

MCS stem cell type	MCS stem cell origin	Target cell and/or wound type	Secretome component	Outcome
Adipose tissue-derived stem cells	Human Adipose tissue[32]	Human umbilical vein endothelial cell (HUVEC); full-thickness skin-wound in rat	Not identified	In vitro: Enhance cell migration and proliferation, fibrin formation, and capillary-like structure formationIn vivo: Enhance endothelial blood vessel formation and pericyte coverage
	Rat Adipose Tissue[33]	Rat dermal fibroblast cell line and macrophages; full-thickness skin excision model on SD rats	Vascular epithelial growth factor (VEGF) and proliferating cell nuclear antigen (PCNA)	In vitro: Enhance viability, proliferation, and migration of dermal fibroblasts; reduce the level of lipopolysaccharides-induced NO and proinflammatory cytokines (IL-6, TNF-α)In vivo: Accelerate wound healing rate; increase VEGF expression and cell proliferation; reduce therelease of proinflammatory cytokines (IL-6 and TNF-α)
	Human Adipose Tissue[34]	Full-thickness skin-wound in rat	Transforming growth factor β1 (TGF-β1) and vascular epithelial growth factor (VEGF)	In vivo: Accelerate wound healing rate and internal tissue (adipose and muscle) regeneation; increase collagen synthesis, formation of skin appendages, and promote angiogenic response
	Human Adipose Tissue[35]	Cultured skin cells; full-thickness excisional skin wounds	Epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and hepatocyte growth factor (HGF)	In vitro: Accelerate proliferation and migration of keratinocytesIn vivo: Accelerate wound healing rate; increase epidermal and dermal thicness; enhance angiogenesis and vascularization;icrease immune cell (monocytes and macrophages recruitment; decrease scar formation
Umbilical Cord/ Wharton's Jelly Mesenchymal Stem Cells	Human umbilical cord[36]	Rat fibroblast cell; skin-punctured ulcer in diabetic-induced rat	Vascular epithelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and pro-collagen 1.	In vivo: Accelerate wound closure; increase re-epithelialization; enhance collagen formation
	Human umbilical cord[37]	Human dermal fibroblasts; full-thickness excisional skin wounds	Not identified	In vitro: Promote dermal fibroblast proliferation and migration In vivo: Accelerate wound healing; increase re-epithelialization and vascularization; promote scarless wound healing by decreasing collagen accumulation at wound site
	Human umbilical cord[38]	Human keratinocytes (HaCAT), human umbilical vein endothelial cell (HUVEC), and human splenic fibroblasts (HSF) cells; ex vivo skin culture.	Not identified	In vitro: Promote cell proliferation; protect cells from apoptosis; inhibit ROS production; reduce level of proinflammatory cytokines (IL-1α, TNF-α); increase regulation of col-I and decrease regulation of mmp-1 expression that result in improved ECM composition and strong skin defense
	Human umbilical cord[39]	Full-thickness excisional skin wounds	Human fibroblast growth factor (hFGF), humahepatocyte growth factor (hHGF), human granulocyte colony stimulating factor (hGC-SF), human interleukin 1 receptor agonist (hIL-1Ra), and human vascular endothelial growth factor (hVEGF)	In vivo: Reduce level of proinflammatory cytokines (IL-10, IFN-γ, TNF-α); decrease inflammatory cells (polymorphonuclear leukocytes (PMNL)); enhance epithelialization and angiogenesis; improve wound healing rate
	Human umbilical cord[40]	Human umbilical vein endothelial cell (HUVEC); β-ray radiation-induced skin injury rat	Not Identified	In vitro: Increase cell proliferation; increase genes expression involved with angiogenesis (VEGF, EGF, bFGF, and KDR); decrease genes expression involved with inflammation (IFN, TNF, IL-1, and IL-6) In vivo: Improve wound healing rate; increase cutaneous appendages growth; increase dermal thickness; increase the number of vessels

MCS stem cell type	MCS stem cell origin	Target cell and/or wound type	Secretome component	Outcome
Placenta-derived mesenchymal stem cell	Human placenta[41]	Staphylococcus aureus-infected burn skin wounds in rats	Basic fibroblast growth factor (Bfgf), vascular epithelial growth factor (VEGF), monocyte chemo attractant protein-1 (MCP-1), IL-6 (interleukin 6), and IL-8 (interleukin 8).	In vivo: Increase clearing of microorganisms in the wound; decrease inflammation; enhance re-epithelialization; and promote formation of well-vascularized granulation tissue
	Human placenta[42]	Human keratinocytes (HaCAT) and dermal fibroblasts (DFL); burn skin wounds in rats	Plasminogen activator inhibitor-1 (PAI-1), thrombospondin-1 (TSP-1), insulin-like growth factor binding protein 3 (IGFBP-3), vascular epithelial growth factor (VEGF), tumor necrosis factor receptor 1 (TNFR1), dickkopf-related protein 3 (Dkk-3), angiopoietin Like 4 (ANGPTL4), granulocyte colony stimulating factor (G-CSF), periostin	In vitro: Promote angiogenesis (tube formation); decrease apoptotic rate; promote cell prolifertion; increase cell migration In vivo: Improve wound healing rate; enhance re-epithelialization, inhibit cell apoptosis; promote neovascularization
Bone Marrow-derived mesenchymal stem cell	Rat bone marrow[43]	A full-thickness skin wound in rats	Not identified	In vivo: Accelerate wound healing rate; enhance immune cells recruitment during early phase of wound healing; enhance angiogenesis and vascularization; enhance collagen fibers deposition
	Rat bone marrow[44]	Murine excisional skin wounds in non-obese diabetic-induced rats	Insulin-like growth factor (IGF-1), keratinocyte growth factor (KGF), hepatocyte growth factor (HGF), vascular epithelial growth factor (VEGF), angiotensin 2 (Ang-2), CoL-1, matrix metalloproteinase 1 (MMP-1), and prostaglandin E2 (PGE2).	In vivo: Accelerate wound closure; enhance re-epithelialization; stimulate the formation of new skin appendage structure; absence of severe leukocyte infiltration in wounds; enhance granulation tissue formation; promote vascular proliferation; increase deposition of collagen fibers
Fetal skin-derived mesenchymal stem cell	Human fetal skin[45]	Human umbilical vein endothelial cell (HUVEC); Sr-90 radiation-induced skin injury model of rats	Collagen type III α 1 (Col3A1), transforming growth factor β3 (TGF-β3), angiotensin 1 (Ang-1), angiotensin 2 (Ang-2), vascular endothelial growth factor (VEGF), and placental growth factor (PLGF)	In vitro: Increase proliferation and tube formation In vivo: Accelerate wound healing rate; promote cutaneous appendages growth, including hair follicles, sweat gland, and sebaceous glands; enhance angiogenesis and vascularization

dependent on each individual's daily life activities.[21] During January 2010 until December 2013, 54 patients were admitted to the trauma center with large area avulsion injury in the lower limbs. Patients consisted of 34 males and 20 females, aged 16 to 65 years. Mechanism of injury was mainly by traffic accidents condoning 44 cases, hit by heavy objects in eight cases, height falls in two cases, hemorrhagic shock in sixteen cases, femoral fractures in five cases, and tibio-fibular fractures in seven cases.[22]

Steps of Wound Healing

Wound healing is a crucial process to preserve skin integrity after an injury. It is a complex process consisting of both molecular and cellular events that often overlap.[23] There are three stages of wound healing which involve hemostasis/inflammatory stage, proliferative stage, and remodeling stage. The initial stage known as inflammatory stage begins at the onset of injury in order to terminate further damage, whereas the site of injury will be closed by hemostasis.[24] Hemostasis consists of coagulation process and vasoconstriction to stop bleeding, start inflammatory cells migration by activating chemotaxis response, and transfer leukocytes to injury area which results in the activation of immune response and pro-inflammatory cytokines.[23] This stage may last for 24 hours until two weeks in normal condition.[25]

The second stage of wound healing is the proliferative stage which is initiated

during the first 48 hours following the onset of injury. There are three main processes in this stage which includes reepithelization, angiogenesis, and fibroplasia.[24] All three processes have the same objective to close the wound and lower the risk of further injuries. Reepithelization focuses on forming epithelium tissue and the components around it.[25] This process will rebuild the outer part of the injury, taking the role as a protective layer to stop the body from another injury.[24,25] Meanwhile, angiogenesis involves making new vascularization to facilitate oxygen and nutrients supply to the tissue. This course of action is supported by vascular endothelial growth factor (VEGF) that is released by macrophage prior to this proliferative stage.[25]

The terminal stage is the remodeling stage, which is the most essential step in scar formation.[26] Scarring happens due to collagen build-up around wound area, lasting from weeks to years depending on the patient's condition and genetics.[23,24] The objective of this phase is to form more asserted tissue by altering composition and arrangement of the cellular matrix.[24] This process involves production of type I collagen and degradation of several other structures. For instance, degradation of fibronectin and hyaluronic acid by plasma metalloproteinase enzyme.[26]

Existing Wound Treatment Modalities

Wound care is necessary for patient recovery. Therefore, many treatments have been used to support wound care. However, each modality has their own advantage and limitation. In **Table 2**, current wound treatment modalities will be explained.

Stem Cell Secretome and Its Tissue Source

The study about secretome and its role in wound healing and regeneration has been significantly gaining interest. Secretome contains soluble factors (growth factors, cytokines, chemokines, and enzymes) and extracellular vehicles (exosomes and microvesicles) that is secreted by stem cells. Components of secretome can vary, in particular, according to tissue source of stem cells. Therefore, tissue source is an important factor to be considered before doing secretome isolation.[29]

Mesenchymal stem cells (MSCs) are multipotent adult stem cells orginiated form mesodermal germ layer. MSCs have an important role in wound healing and tissue regeneration due to its multilineage potential and self-renewal ability. MSCs have also been demonstrated to have an influence in cell-to-cell interaction and regulation of multiple biological processes through paracrine signaling by producing secretome. MSCs isolated from various tissue origins also produce different secretory profile, which consequently can lead to different therapeutic potentials.[30,31] MSC secretome derived from various origins has been used to assess its effect on skin cell functionality as well as its effects on wound healing using in vitro and in vivo models (summarized in **Table 3**).

CONCLUSION

Role of MSC Secretomes in cell-to-cell interaction and multiple biological process regulation leads to an increase in skin functionality and wound healing. However, further details about this topic are necessary in determining MSC Secretomes therapeutic potentials.

CONFLICT OF INTEREST

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Author CFL is the main author in conducting the research method. Authors MHI and DCA participated in constructing the research manuscript.

REFERENCES

1. Suryadi IA, Asmarajaya AAGN, Maliawan S. Wound healing process and wound care. E-Jurnal Medika Udayana. 2013;2(2):254-72.
2. Deng X, Gloud M, Ali MA. A review of current advancements for wound healing:
3. Biomaterial applications and medical devices. J Biomed Mater Res. 2022;110:2542–2573. DOI: 10.1002/jbm.b.35086
4. Bilgin Y, Birisik F. Retrospective analysis of puncture wounds with retained foreign bodies in the extremities requiring surgical intervention. Medicine Science. 2021;10(2):416-21. DOI: 10.5455/medscience.2021.01.028
5. Upton D, South F. The psychological consequences of wounds – a vicious circle that should not be overlooked. Wounds UK. 2011;7(4):136-8.
6. Bowers S, Franco E. Chronic wounds: Evaluation and management. American Family Physician. 2020;101(3):159-166.
7. Annesley SH. Current thinking on caring for patients with a wound: a practical approach. Br J Nurs. 2019:28(5):290-4. DOI: 10.12968/bjon.2019.28.5.290
8. Park SR, Kim JW, Jun HS, Roh JY, Lee HY, Hong IS. Stem Cell Secretome and Its Effect on Cellular Mechanisms Relevant to Wound Healing. Mol Ther. 2017 Oct 5;26(2):606–617. DOI: 10.1016/j.ymthe.2017.09.023
9. Teixeira FG, Salgado AJ. Mesenchymal stem cells secretome current trends and future challenges. Neural regeneration research. 2020;15(1):75-7. DOI: 10.4103/1673-5374.264455
10. Damayanti RH, Rusdiana T, Wathoni N. Mesenchymal stem cell secretome for dermatology application: a review. Clin Cosmet Investig Dermatol. 2021;14:1401-12. DOI: 10.2147/CCID.S331044
11. Raziyeva K, Kim Y, Zharkinbekov Z, Kassymbek K, Jimi S, Saparov A. Immunology of acute and chronic wound healing. Biomolecules. 2021;11(5):1-25. doi: 10.3390/biom11050700
12. Nicks B, Ayello E, Woo K, et al. Acute wound management: Revisiting the approach to assessment, irrigation, and closure considerations. International Journal of Emergency Medicine. 2020;3(4):399-407. DOI: 10.1007/s12245-010-0217-5
13. Furtado KAX, Infante P, Sobral A, Gaspar P, Eliseu G, Lopes M. Prevalence of acute and chronic wounds - with emphasis on pressure ulcers - in integrated continuing care units in Alentejo, Portugal. Int Wound J. 2020;17(4):1002-10. DOI: 10.1111/iwj.13364
14. Shi H. Ding Li, Jiang Y, Zhang H, Ren S, Hu X, Liu Z, Huang H, Ao Y. Bone Bruise Distribution Patterns After Acute Anterior Cruciate Ligament Ruptures. Orthopaedic Journal of Sports Medicine. 2020;8(4):1-8. DOI: 10.1177/2325967120911162
15. Prabhakar D. Child abuse and neglect: Diagnosis, treatment and evidence. JAMA. 2011;306(5):554-555. DOI: https://doi.org/10.1001/jama.2011.1077
16. Patel SA, Hageman J, Quatman CE, Wordeman SC, Hewett TE. Prevalence and location of bone bruises associated with anterior cruciate ligament injury and implications for mechanism of injury: a systematic review. Sports Medicine. 2013;44(2):281–93. DOI: 10.1007/s40279-013-0116-z
17. Styrke J, Stålnacke BM, Bylund PO, Sojka P, Björnstig U. A 10-year incidence of acute whiplash injuries after road traffic crashes in a defined population in northern sweden. PM&R. 2012;4(10):739-47. DOI: 10.1016/j.pmrj.2012.05.010
18. Oka H, Matsudaira K, Fujii T, Tanaka S, Kitagawa T. Epidemiology and psychological factors of whiplash associated disorders in Japanese population. J Phys Ther Sci. 2017;29(9):1510-13. DOI: 10.1589/jpts.29.1510

19. Shrestha R, Krishan K, Ishaq H, Kanchan T. Abrasion. 2023. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan (February 13th 2024). Available on: https://pubmed.ncbi.nlm.nih.gov/32119352/
20. Ruben FL, Norden CW, Rockwell K, Hruska E. Epidemiology of accidental needle-puncture wounds in hospital workers. The American Journal of Medical Sciences. 1983;286(1):26-30. DOI: 10.1097/00000441-198307000-00004
21. Sandler AB, Scanaliato JP, Raiciulescu S, Nesti LJ, Dunn JC. The epidemiology of hand and finger lacerations in united states emergency departments. J Emerg Med. 2022;62(6):707-15. DOI: 10.1016/j.jemermed.2021.12.022
22. Strazzieri-Pulido KC, Peres GRP, Campanili TCGF, Santos VLC de G. Skin tear prevalence and associated factors: a systematic review. SciELO Brazil. 2015;49(4): 674-80. DOI: 10.1590/S0080-623420150000400019
23. Chen Y, Liu L. Clinical analysis of 54 cases of large area soft tissue avulsion in the lower limb. Chin J Traumatol. 2016;19(6):337-41. DOI: 10.1016/j.cjtee.2016.09.003
24. Wang PH, Huang BS, Horng HC, Yeh CC, Chen YJ. Wound healing. Journal of the Chinese Medical Association. 2018;81(2):94–101. DOI: 10.1016/j.jcma.2017.11.002
25. Gonzalez AC de O, Costa TF, Andrade Z de A, Medrado ARAP. Wound healing - a literature review. Anais Brasileiros de Dermatologia. 2016;91(5):614–20. DOI: 10.1590/abd1806-4841.20164741
26. Tottoli EM, Dorati R, Genta I, Chiesa E, Pisani S, Conti B. Skin wound healing process and new emerging technologies for skin wound care and regeneration. Pharmaceutics. 2020;12(8):735. DOI: 10.3390/pharmaceutics12080735
27. Sorg H, Tilkorn DJ, Hager S, Hauser J, Mirastschijski U. Skin wound healing: an update on the current knowledge and concepts. European Surgical Research. 2016;58(1-2):81–94. DOI: 10.1159/000454919
28. Han G, Ceilley R. Chronic wound healing: a review of current management and treatments. Adv Ther. 2017;34(3):599-610. DOI: 10.1007/s12325-017-0478-y
29. Dreifke MB, Jayasuriya AA, Jayasuriya AC. Current wound healing procedures and potential care. Mater Sci Eng C Mater Biol Appl. 2015;48:651-62. DOI: 10.1016/j.msec.2014.12.068
30. Daneshmandi L, Shah S, Jafari T, Bhattacharjee M, Momah D, Saveh-Shemshaki N, et al. Emergence of the Stem Cell Secretome in Regenerative Engineering. Trends in Biotechnology. 2020;38(12):1373-84. DOI: 10.1016/j.tibtech.2020.04.013
31. Zhang T, Lee YW, Rui YF, Cheng TY, Jiang XH, Li G. Bone marrow-derived mesenchymal stem cells promote growth and angiogenesis of breast and prostate tumors. Stem Cell Res Ther. 2013;4(70):668-74. DOI: 10.1186/scrt221
32. Ahangar P, Mills SJ, Cowin AJ. Mesenchymal stem cell secretome as an emerging cell-free alternative for improving wound repair. International Journal of Molecular Sciences. 2020;21(19):7038. DOI: 10.3390/ijms21197038
33. Silveira BM, Ribeiro TO, Freitas RS, Carreira ACO, Gonçalves MS, Sogayar M, et al. Secretome from human adipose-derived mesenchymal stem cells promotes blood vessel formation and pericyte coverage in experimental skin repair. PLoS One. 2022:17:1–21. DOI: 10.1371/journal.pone.0277863
34. Ma H, Lam PK, Siu WS, Tong CSW, Lo KKY, Koon CM, et al. Adipose tissue-derived mesenchymal stem cells (Admscs) and admsc-derived secretome expedited wound healing in a rodent model – a preliminary study. Clin Cosmet Investig Dermatol. 2021:14:753-64. DOI: 10.2147/CCID.S298105
35. An YH, Kim DH, Lee EJ, Lee D, Park MJ, Ko J, et al. High-efficient production of adipose-derived stem cell (ADSC) secretome through maturation process and its non-scarring wound healing applications. Front Bioeng Biotechnol. 2021;9:1-12. DOI: 10.3389/fbioe.2021.681501
36. Park SR, Kim JW, Jun HS, Roh JY, Lee HY, Hong IS. Stem cell secretome and its effect on cellular mechanisms relevant to wound healing. Mol Ther. 2018;26(2):606-17. DOI: 10.1016/j.ymthe.2017.09.023
37. Hendrawan S, Kusnadi Y, Lagonda CA, Fauza D, Lheman J, Budi E, et al. Wound healing potential of human umbilical cord mesenchymal stem cell conditioned medium: an in vitro and in vivo study in diabetes-induced rats. Vet World. 2021;14(8):2109-17. DOI: 10.14202/vetworld.2021.2109-2117
38. Li M, Luan F, Zhao Y, Hao H, Liu J, Dong L, et al. Mesenchymal stem cell-conditioned medium accelerates wound healing with fewer scars. Int Wound J. 2017;14(1):64-73. DOI: 10.1111/iwj.12551
39. Wang X, Wang Q, Yin P, Liang C, Zhao X, Wen D, et al. Secretome of human umbilical cord mesenchymal stem cell maintains skin homeostasis by regulating multiple skin physiological function. Cell Tissue Res. 2023;391(1):111–25. DOI: 10.1007/s00441-022-03697-8
40. Mathen C, Ghag SM, Gupta R, Dsouza W, Krishna SG. Evaluation of potential application of wharton's jelly-derived human mesenchymal stromal cells and its conditioned media for dermal regeneration using rat wound healing model. Cells Tissues Organs. 2021;210(1):31-44. DOI: 10.1159/000513895
41. Sun JY, Zhang YF, Song XJ, Zhu J, Zhu QS. The healing effects of conditioned medium derived from mesenchymal stem cells on radiation-induced skin wounds in rats. Cell Transplant. 2019;28(1):105-15. DOI: 10.1177/0963689718807410
42. Kudinov VA, Artyushev RI, Zurina IM, Lapshin RD, Snopova LB, Mukhina I V., et al. Antimicrobial and regenerative effects of placental multipotent mesenchymal stromal cell secretome-based chitosan gel on infected burns in rats. Pharmaceuticals. 2021;14(12):1263. DOI: 10.3390/ph14121263
43. Li JY, Ren KK, Zhang WJ, Xiao L, Wu HY, Liu QY, et al. Human amniotic mesenchymal stem cells and their paracrine factors promote wound healing by inhibiting heat stress-induced skin cell apoptosis and enhancing their proliferation through activating PI3K/AKT signaling pathway. Stem Cell Res Ther. 2019;10(1):247. DOI: 10.1186/s13287-019-1366-y
44. Abolgheit S, Abdelkader S, Aboushelib M, Omar E, Mehanna R. Bone marrow-derived mesenchymal stem cells and extracellular vesicles enriched collagen chitosan scaffold in skin wound healing (a rat model). J Biomater Appl. 2021;36(1):128-39. DOI: 10.1177/0885328220963920
45. De Mayo T, Conget P, Becerra-Bayona S, Sossa CL, Galvis V, Arango-Rodríguez ML. The role of bone marrow mesenchymal stromal cell derivatives in skin wound healing in diabetic mice. PLoS One. 2017;12(6):e0177533. DOI: 10.1371/journal.pone.0177533
46. Rong X, Li J, Yang Y, Shi L, Jiang T. Human fetal skin-derived stem cell secretome enhances radiation-induced skin injury therapeutic effects by promoting angiogenesis. Stem Cell Res Ther. 2019;10(1):383. DOI: 10.1186/s13287-019-1456-x