

Chronic Wound Treatment Using Mesenchymal Stem Cells: A Systematic Review

Dominique Taugher, Department of Health Sciences
Carroll College, Helena, Montana

Introduction

Chronic wounds affect almost 7 million adults,¹ annually in the United States, costing about \$25 billion.² Chronic wounds affect all ages, genders, and races, significantly lowering quality of life and increasing risk of infection. Pre-existing conditions such as diabetes,³ malnutrition, and peripheral artery disease are all contributing factors of chronic wounds.⁴

Traditionally, chronic wounds are treated through regular cleaning and wound dressings.⁶ If the wounds are not healing; skin grafts, vacuum assisted closure, hyperbaric oxygen therapy are also used.⁶

Mesenchymal stem cells (which have the ability to self-renew and differentiate) are an alternative treatment for chronic wounds.² Currently, there is limited research focusing on patients with chronic wounds being treated with mesenchymal stem cells. Therefore, the focus of this study is to review relevant literature to determine if patients who undergo mesenchymal stem cell treatment for chronic wounds have improved skin outcomes. The findings of this study should help inform clinicians treating chronic wound patients and raise awareness about the impacts of chronic wounds.

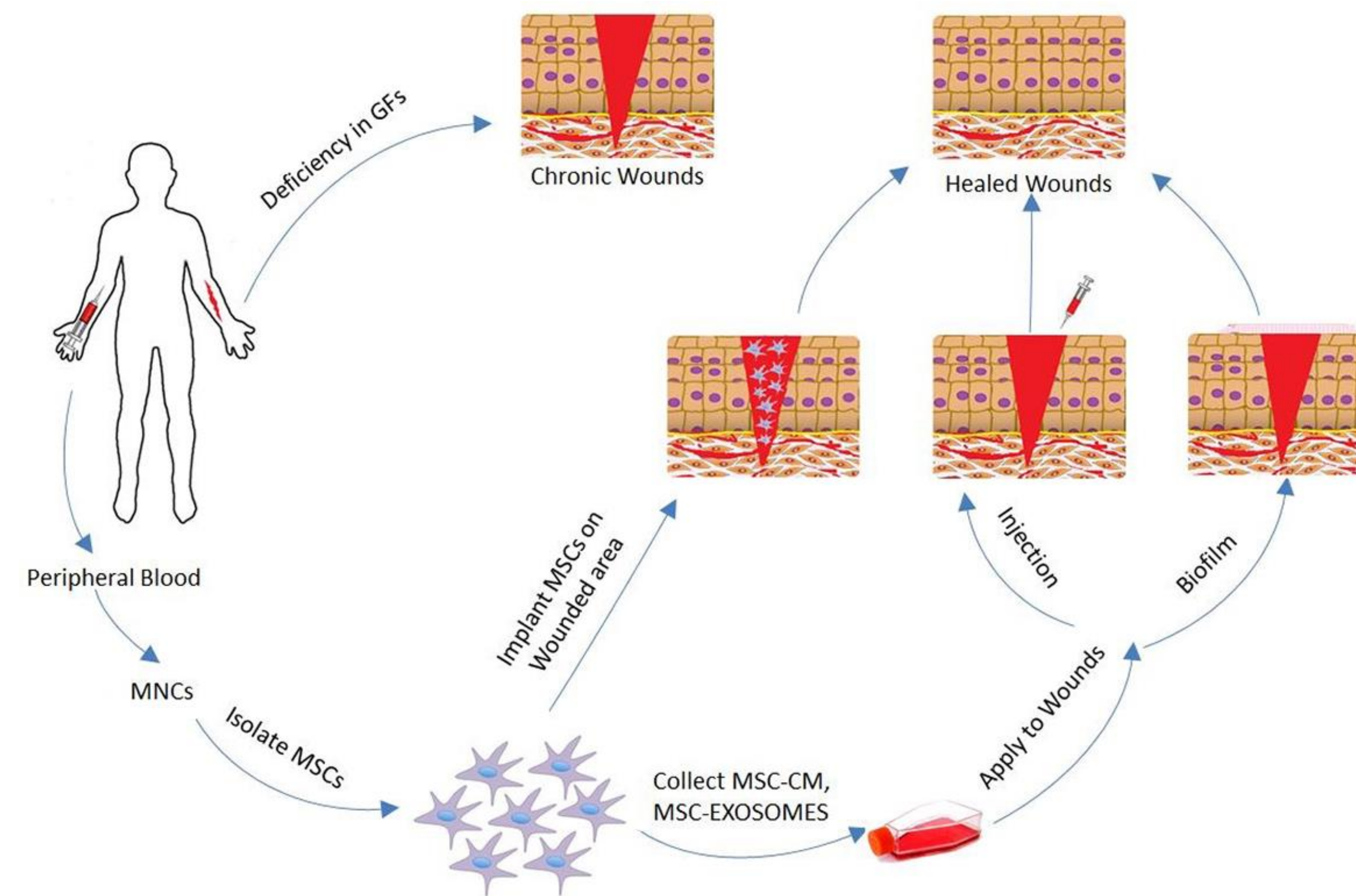


Figure 2: Potential applications for MSCs in wound healing.¹

Results

The review yielded eight relevant studies, including five randomized clinical control trials,⁷⁻¹¹ two nonrandomized clinical control trials^{12,13} and one case report.¹⁴ Five of the articles examined skin reactions to injections of mesenchymal stem cells.^{7,9,10,13,14} These test subjects had either psoriasis,⁷ atopic dermatitis,^{8,10,12} diabetes mellitus,¹⁴ acute skin wounds,⁹ or recessive dystrophic epidermolysis bullosa.¹³ Two of the articles examined the success of applying an atopic cream containing mesenchymal stem cells on patients with atopic dermatitis.^{8,12} The last study examined in this review investigated the success rate of applying an atopic cream containing mesenchymal stem cells on burns on Yorkshire pigs.¹¹

- All five studies that examined skin reactions to injections of mesenchymal stem cells found skin improvement.^{7,9,10,13,14}
- Many of the studies used a corneometer to measure the hydration of stratum corneum or something of equivalence.^{8-10,12,13}
- In the two studies completed on patients with atopic dermatitis and treated with topical mesenchymal stem cells, their stratum corneum indicated improvement.^{8,12} This indicates that the patients' chronic wounds were showing significant improvement.

Acknowledgments

Thank you to Dr. Gerald Schafer for his guidance in putting together this project.

Discussion

Studies analyzed in this review provide evidence that mesenchymal stem cells promote improvement of chronic wounds. These studies demonstrate that both mesenchymal stem cell injections as well as atopic USC-CM cream application on chronic wounds are effective ways of treatment. Neither the mesenchymal injections nor the cream results indicate one treatment is more effective than the other. Results from this study also did not identify a preferred dosage of mesenchymal stem cells, however several studies explored this idea.^{7,8,11-13}

One strength of this review is that these studies compare multiple different chronic skin wounds being treated in the same manner. A weakness of this study is that the sample sizes are relatively small. A challenge of this therapy is ethical concerns surrounding stem cells derived from aborted fetal tissue. For the purpose of this review, only mesenchymal stem cells were studied, a much less controversial branch of human derived cells, primarily derived from adult bone marrow and stromal cells.²

The findings of this systematic review can guide clinical practice to improving chronic wound treatment with mesenchymal stem cells. However further research should be done regarding finding the ideal dosing of mesenchymal stem. For this treatment to be adopted in practice, further clinical trials should be done focusing on the dosages and long-term effects of the intervention. Overall, this review found that mesenchymal stem cells can be a viable treatment option for chronic wounds.

References

1. Otero-Viñas M, Falanga V. Mesenchymal Stem Cells in Chronic Wounds: The Spectrum from Basic to Advanced Therapy. *Adv Wound Care*. 2016;5(4):149-163. doi:10.1089/wound.2015.0627
2. Isakson M, de Blacam C, Whelan D, McArdle A, Clover AJP. Mesenchymal Stem Cells and Cutaneous Wound Healing: Current Evidence and Future Potential. *Stem Cells Int*. 2015;2015:1-12. doi:10.1155/2015/831095
3. Chen Y, Ma Y, Li N, et al. Efficacy and long-term longitudinal follow-up of bone marrow mesenchymal cell transplantation therapy in a diabetic patient with recurrent lower limb bullosis diabeticorum. *Stem Cell Res Ther*. 2018;9(1):99. doi:10.1186/s13287-018-0854-9
4. Lee SE, Lee SJ, Kim SE, et al. Intravenous allogeneic umbilical cord blood-derived mesenchymal stem cell therapy in recessive dystrophic epidermolysis bullosa patients. *JCI Insight*. 2021;6(2):143606. doi:10.1172/jci.insight.143606
5. Yao Z, Niu J, Cheng B. Prevalence of Chronic Skin Wounds and Their Risk Factors in an Inpatient Hospital Setting in Northern China. *Adv Skin Wound Care*. 2020;33(9):1-10. doi:10.1097/01.ASW.0000694164.34068.82
6. *What Are the Treatment Options for Chronic Wounds?* Institute for Quality and Efficiency in Health Care (IQWiG); 2018. Accessed October 19, 2022. <https://www.ncbi.nlm.nih.gov/books/NBK326436/>
7. Cheng L, Wang S, Peng C, et al. Human umbilical cord mesenchymal stem cells for psoriasis: a phase 1/2a, single-arm study. *Signal Transduct Target Ther*. 2022;7(1):263. doi:10.1038/s41392-022-01059-y
8. Kim YJ, Ahn HJ, Lee SH, Lee MH, Kang KS. Effects of conditioned media from human umbilical cord blood-derived mesenchymal stem cells in the skin immune response. *Biomed Pharmacother Biomedicine Pharmacother*. 2020;131:110789. doi:10.1016/j.biopha.2020.110789
9. Zhou L, Wang H, Yao S, Li L, Kuang X. Efficacy of Human Adipose Derived Mesenchymal Stem Cells in Promoting Skin Wound Healing. *J Healthc Eng*. 2022;2022:6590025. doi:10.1155/2022/6590025
10. A C, M O, A M, et al. Mesenchymal Stem Cells Profile in Adult Atopic Dermatitis and Effect of IL4-IL13 Inflammatory Pathway Inhibition In Vivo: Prospective Case-Control Study. *J Clin Med*. 2022;11(16). doi:10.3390/jcm11164759
11. Eylert G, Dolp R, Parousis A, et al. Skin regeneration is accelerated by a lower dose of multipotent mesenchymal stromal/stem cells—a paradigm change. *Stem Cell Res Ther*. 2021;12(1):1-11. doi:10.1186/s13287-020-02131-6
12. Kim HS, Lee JH, Roh KH, Jun HJ, Kang KS, Kim TY. Clinical Trial of Human Umbilical Cord Blood-Derived Stem Cells for the Treatment of Moderate-to-Severe Atopic Dermatitis: Phase I/IIa Studies. *Stem Cells Dayt Ohio*. 2017;35(1):248-255. doi:10.1002/stem.2401
13. Lee SE, Lee SJ, Kim SE, et al. Intravenous allogeneic umbilical cord blood-derived mesenchymal stem cell therapy in recessive dystrophic epidermolysis bullosa patients. *JCI Insight*. 2021;6(2):143606. doi:10.1172/jci.insight.143606
14. Chen Y, Ma Y, Li N, et al. Efficacy and long-term longitudinal follow-up of bone marrow mesenchymal cell transplantation therapy in a diabetic patient with recurrent lower limb bullosis diabeticorum. *Stem Cell Res Ther*. 2018;9(1):99. doi:10.1186/s13287-018-0854-9

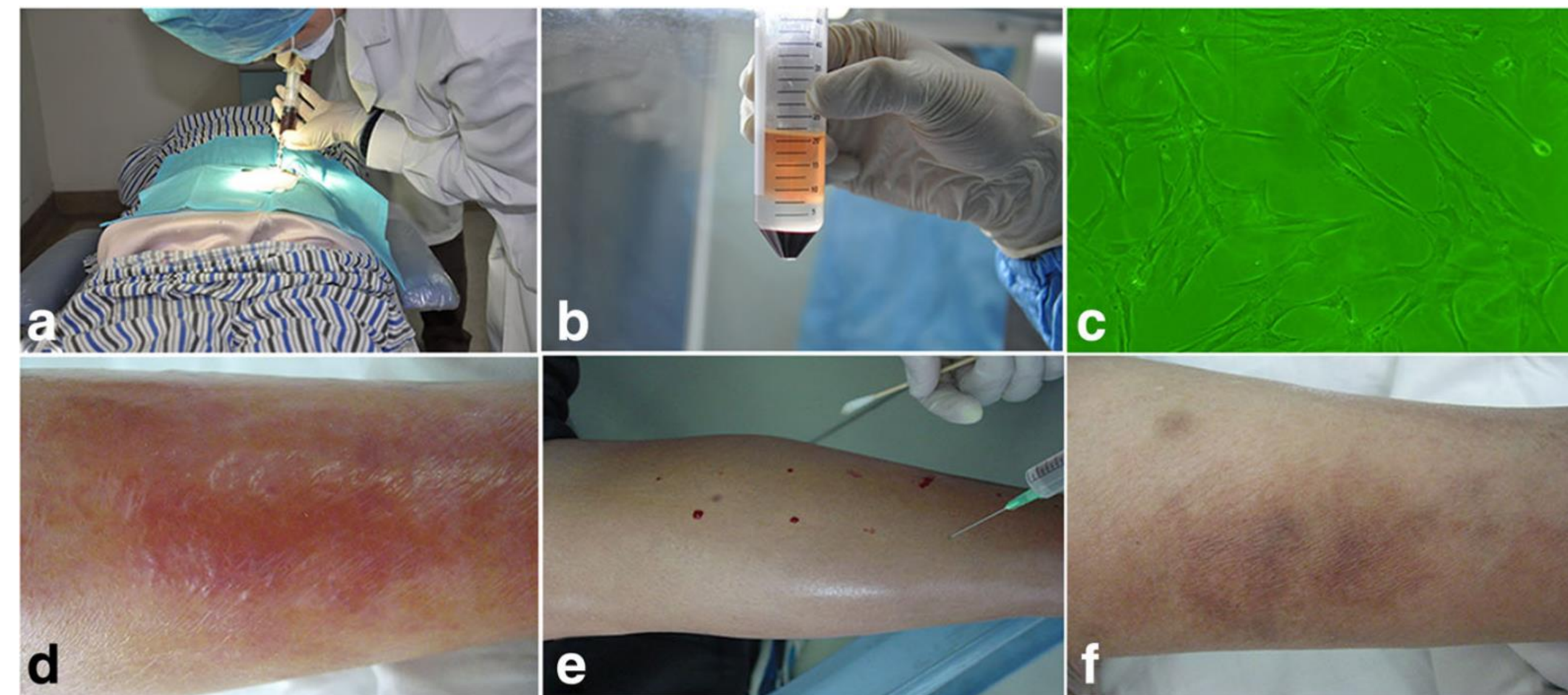


Figure 1: MSC transplant procedure. a: extraction of MSCs b: stem cell layer was harvested c: MSCs morphology after 21 days d: subcutaneous cellulitis with bullosis diabeticorum e: administer MSCs f: the left lower limb after 10 years.³

Methods

- Search methods: Primary sources were retrieved in September and October of 2022 using primarily PubMed and CINAHL. Key words: dermal wounds OR dermal treatment OR skin wounds OR skin treatment OR mesenchymal stem cells.
- Data Extraction: The initial search identified 124 articles which were narrowed down to 8 articles. The selection of articles was done through the removal of duplicates articles resulting in 67 studies, then the removing irrelevant articles resulting in 25 relevant studies, then the removal of inaccessible studies resulting in 19 studies, resulting in 8 studies that investigated mesenchymal stem cell therapy and overall skin regeneration.