

MESENCHYMAL STEM CELLS (MSCS) AS A THERAPY FOR CHRONIC WOUND HEALING IN DIABETIC FOOT ULCERS: A REVIEW ARTICLE

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ABSTRAK

Ulkus kaki diabetik merupakan komplikasi kronik dan paling sering terjadi pada pasien diabetes. Ulkus kaki terjadi pada 15-25% penderita DM dan mayoritas pasien ulkus berakhir dengan amputasi. Terapi yang sudah ada saat ini belum cukup efektif untuk menurunkan angka kejadian amputasi. Dengan demikian, dibutuhkan metode lain yang efektif untuk membantu proses penyembuhan ulkus kaki diabetik. Saat ini, sel punca diyakini dapat menjadi terapi penunjang yang menjanjikan. Salah satu jenis sel punca yang banyak digunakan sebagai terapi pada penyembuhan luka kronik adalah Mesenchymal Stem Cells (MSCs). Melalui berbagai mekanisme kerja, MSCs dapat mempersingkat waktu penyembuhan luka, mempercepat regenerasi jaringan dan mengurangi risiko terjadinya komplikasi seperti amputasi. Artikel ini berfokus pada merangkum dan meninjau secara kritis literatur tentang penggunaan MSCs dalam menyembuhkan luka kronik pada ulkus diabetik.

ABSTRACT

Mesenchymal Stem Cells (MSCs) as a Therapy for Chronic Wound Healing In Diabetic Foot Ulcers: A Review Article. Diabetic foot ulcer is a chronic and frequent complication in diabetic patients. Foot ulcers occur in 15-25% of people with diabetes, and most of them require amputation. Conventional treatments for DFU have not been effective enough to reduce the amputation rates. Thus, an effective method to accelerate the healing of diabetic foot ulcers is required. Recently, stem cells have emerged as a promising adjuvant therapy. One of the numerous types of stem cells used in chronic wound healing therapy is Mesenchymal Stem Cells (MSCs). MSCs may be associated with shorter wound healing time, rapid tissue regeneration, and reduced risk of lower limb amputation through all mechanisms. This article summarizes and critically reviews the published literature on the use of MSCs to enhance chronic wound healing in DFUs.

INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia that occurs due to abnormalities in insulin secretion, insulin action, or both. The pathogenesis of central damage in type 2 DM is attributed to insulin resistance in muscle and liver cells and pancreatic beta-cell loss. Various epidemiological studies show a trend of increasing incidence and prevalence of type 2 DM in various parts of the world. WHO predicts an increase in type 2 DM patients in Indonesia from 8.4 million in 2000 to around 21.3 million in 2030.¹

The hyperglycemia condition that occurs in DM sufferers increases the risk of microvascular and macrovascular complications, such as retinopathy, cardiovascular disease, nephropathy, and peripheral neuropathy, which can result in diabetic ulcers.²

Diabetic foot ulcers are chronic wounds in the area below the ankle caused by peripheral neuropathy, peripheral arterial disease, or both. 1 Diabetic foot ulcers occur in 15-25% of DM sufferers. Around 56% of diabetic foot ulcer sufferers experience infection, and 1 in 5 sufferers end up with amputation. Amputation occurs if this disease does not receive proper treatment. Meanwhile, the death rate for diabetic foot ulcers is 48% in the last five years. This figure exceeds the death rate for cancers such as breast cancer and lymphoma.^{2, 3} The disease also has a major impact on social and economic conditions, including costs associated with treatment and prolonged hospitalization and psychosocial problems such as loss of employment and reduced productivity.⁴

Wound care is one of the treatments used for diabetic foot ulcers. Several research studies have investigated stem cell treatment's efficacy in treating diabetic foot ulcers. Stem cells can renew themselves and differentiate into any cells. Bone-marrow-derived mesenchymal stem cells (BM-MSCs) are a commonly utilized form of stem cell for treating chronic wounds. Mesenchymal stem cells (MSCs) can be located in different locations, including bone marrow, adipose tissue, and amniotic fluid. MSCs (mesenchymal stem cells) are thought to possess significant potential in tissue regeneration and restoration following injury. MSCs are involved in bone, cartilage, fat, and muscle formation.⁵ This article aims to provide an informative review of the role of Mesenchymal Stem Cells (MSCs) as a therapy for chronic wound healing in diabetic foot ulcers.

METHOD

The researchers collected data for this article by searching recent publications in the PubMed, NCBI, Elsevier, and Google Scholar databases using the keywords "mesenchymal stem cells, diabetic foot ulcers, chronic therapy." They sorted the articles until no similar titles were found and then sorted based on predetermined inclusion and exclusion criteria. Inclusion criteria, namely 1. published in Indonesian and English; 2. published within the last 12 years; and 3. discuss the relationship between Mesenchymal Stem Cells (MSCs) and diabetic foot ulcers. Exclusion criteria were opinion articles, reports, and comments. The final results then obtain the articles that will be analyzed.

RESULT AND DISCUSSION

History and Development of Stem Cells

The Russian histologist Alexander Maksimov (1874-1928) first introduced stem cells at *the Congress of the Hematologic Society* in Berlin, Germany, in 1908. ¹ According to the words that

compose it (*stem* = stem, *cell* = cell), it is the beginning of the formation of various cells that comprise the entire human body.⁵ In Indonesian, the term *stem cell* is translated as stem cell, which means (stem = beginning); this word, together with stem cell, was proposed by the National Bioethics Commission and has been approved by the Language Center for Indonesian zing *Stem Cells*.⁶

Initially, stem cells had no clinical applications for treating human organs. Even more than 87 years after Maksimov's publication, stem cells were only developed in laboratories (*by research*) and only tested on animal organs. Until November 5, 1998, researchers at the University of Wisconsin and *John Hopkins University* reported stem cells isolated from human embryos. James A. Thompson at *the University of Wisconsin* isolated cells from the inner cell mass of ancient human embryos, developing the first embryonic stem cell line. Meanwhile, John D. Gearhart, at Johns Hopkins University, isolated stem cells from cells in fetal gonad tissue. The development of stem cell research is progressing very quickly. Robert Lanza initially declared the generation of human embryonic stem cells without causing harm to the embryo in January 2008 at Advanced Cell Technology and UCSF. The synthesis of human embryonic stem cells without harming the embryo was disclosed by Robert Lanza at *Advanced Cell Technology and UCSF* in January 2008. Kim et al. introduced "*induced pluripotent stem cells*" (iPS) in 2009 to alter patient skin cells. The first human embryonic stem cell experiment was done in 2010.^{6,7}

Stem Cell Characteristics

Stem cells are unspecialized cells that can differentiate into any cell and renew themselves.⁸ Based on their ability to differentiate into other cells (potency), *stem cells* are divided into 1. totipotent cells, which have the potential to develop into any form of cell, including these cells, known as zygote blastomeres; 2. Pluripotent cells are cells that can differentiate into all cells except cells from the embryonic membrane, including embryonic cells; 3. Multipotent stem cells can differentiate into many types of cells, for example, hematopoietic cells; 4. Oligopotent cells can differentiate into several types of cells, for example, myeloid or lymphoid tissue; 5. Unipotent stem cells are stem cells that only produce one type of cell.^{7,8}

Based on their source of origin, stem cells fall into two categories: embryonic *and* adult *stem cells*. Embryonic stem cells originate from embryos at the blastocyst stage, which occurs 5-7 days following fertilization. The cells were extracted from the inner cell mass and cultivated in a controlled environment outside the organism. Embryonic stem cells can differentiate into several cell types in adult organisms, including blood cells, muscle cells, liver cells, and other cell types. Meanwhile, adult stem cells are found in the body through developmental phases. Adult stem cells have the characteristics of being able to proliferate to renew themselves over a long period. They can differentiate to produce.

specialized cells with unique morphological characteristics and functions. The function of these cells is to enable the process of healing, growth, and replacement of cells that are lost daily. The cells in adult stem cells include 1. *Mesenchymal Stem Cells* (MSCs) are found in the spinal cord stroma, periosteum, fat, and skin. MSCs can differentiate into bone, muscle, ligament, tendon, and fat cells; 2. *Hematopoietic stem cells* are blood-forming stem cells capable of forming red blood cells, white blood cells, and platelets. The sources of these cells are bone marrow, peripheral blood, and umbilical cord blood; 3. *Neural cells* build nerve cells such as *oligodendrocytes* and *astrocytes*; 4. *Skin stem cells*, such as keratinocytes.^{7,8}

Diabetic Foot Ulcers

Diabetic foot ulcers are chronic wounds in the area below the ankle caused by peripheral neuropathy, peripheral arterial disease, or both.¹ Diabetic polyneuropathy is described as dysfunction of peripheral sensory and motor nerves such as the hands, arms, legs, and feet. The innervation farthest from the bone marrow, such as the leg nerves, is the part that experiences the most neuropathy. Symptoms of polyneuropathy include paresthesia such as burning or prickling; loss of feeling and pain in the hands, legs, and feet; muscle weakness in the hands and feet; tingling; changes in the level of sensitivity to pain and temperature; loss of body balance and difficulty in walking. Polyneuropathy increases the risk of injury due to loss of foot sensation. Over time, the wound will become infected, leading to the formation of ulcers on the feet.⁹ Classification of diabetic foot ulcers can be done using the Wagner criteria in Table 1.

Table 1. Classification of Diabetic Foot Ulcers (Wagner)¹

Degrees	Characteristics
0	Intact foot skin may be accompanied by deformity or cellulitis
1	Superficial ulcers of the skin and subcutaneous tissue
2	Ulcers extend to ligaments, tendons, joint capsules, or deep fascia without abscess or osteomyelitis
3	Deep ulcers with osteomyelitis or abscess
4	Gangrene in part of the forefoot or heel
5	Extensive gangrene covering the entire leg

Mesenchymal Stem cells (MSCs) in Diabetic Foot Ulcers

Wound healing is a complex and dynamic process. The relationship between cells and the extracellular matrix (ECM) is essential in healing. This process involves various vital events such as angiogenesis, neovascularization, and the release of growth factors. Currently, standard therapy used to treat diabetic foot ulcers includes glucose control, infection control in the foot, ischemic control, debridement, and wound care. However, diabetic foot ulcers require a long time to heal. The majority of patients with ulcers experience failure in the healing process, which ultimately causes gangrene, necrosis, and amputation. Current therapies aim to maintain wound moisture so tissue regeneration is expected to occur, but cannot repair a damaged microcirculation system. Thus, other effective methods are needed to help heal diabetic foot ulcers. *Stem cells* are currently being considered as a therapy for diabetic foot ulcers, and research is currently continuing on animals and humans.¹⁰ Research conducted by Zhao et al. (2020) on 12 diabetic foot ulcer patients showed that administering *umbilical cord mesenchymal stem cell (UCMSC)*, injections could speed up the healing process of chronic wounds.¹¹

Stem cells can differentiate and replenish themselves. Thus, they may assist diabetic foot ulcer patients in curing chronic wounds by regenerating tissue around wounds. BM-MSCs and ASCs are two adult stem cell types that may help heal chronic wounds. *Mesenchymal stem cells* are found in all body organs, especially in the perivascular area, with the highest content in the umbilical cord, bone marrow, and adipose tissue.^{5,12}

Mesenchymal stem cells have the potential to renew themselves and differentiate into cells that play a role in the formation of new tissue, such as osteoblasts, adipocytes, chondrocytes, tenocytes, and myocytes. MSCs can secrete paracrine, modulating the surrounding environment and stimulating wound healing.¹³ MSCs express *CD markers* such as CD44+, CD73+, CD90+, and CD105. Specifically, MSCs can reduce the production of proinflammatory cytokines in the acute phase and increase them in the subsequent regeneration phase. MSCs contain various cytokines and chemokines, such as IL-8, IL-6, TGF- β , and VEGF, which play a role in wound healing. MSCs play a role in increasing the processes of angiogenesis, re-epithelialization, and granulation tissue formation.^{5,14}

Mesenchymal Stem Cells work through 5 main pathways: 1. Increasing the extracellular matrix remodelling process by increasing collagen, elastic fibres, and fibroblasts and reducing MMP-1 production; 2. Immunomodulatory capabilities by suppressing the migration of inflammatory cells, suppressing IL-1 production, TNF- α , ICAM1, and increasing the production of SOD, GPx, IL-10, 3. Skin regeneration is increased by increasing the thickness of the regenerated epidermis and completing lost skin structure. 4. Increasing the angiogenesis process by increasing the production of VEGF and HGF and increasing vessel density blood, 5. Increase the migration of fibroblasts and keratinocytes, thereby accelerating wound closure.¹⁵ The mechanism of wound healing by *Mesenchymal Stem Cells* can be seen in Figure 1.

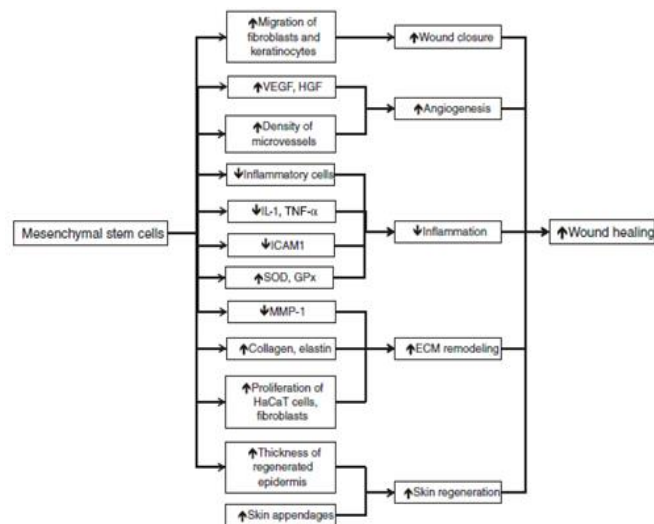


Figure 1. Mechanism of wound healing by *Mesenchymal Stem Cells*¹⁵

Administration of mesenchymal stem cells to diabetic Goto-Kakizaki rats participated in the angiogenesis process through the secretion of pro-angiogenic molecules, such as VEGF, bFGF, IGF-1, *transforming growth factor- β* (TGF- β), and *hepatocyte growth factor* (HGF).¹⁶ Another study also conducted by Yang J et al. (2020) showed that the administration of a combination of *human umbilical cord MSC* (hUCMSC)- *derived exosomes* (hUCMSC-expos) and Pluronic F-127 (PF-127) *hydrogel* could improve wound healing by how to accelerate the rate of wound closure, increase the expression of CD31 and Ki67, increase the regeneration of granulation tissue and increase the expression of vascular endothelial growth factor (VEGF) and transforming growth factor beta-1 (TGF β -1).¹⁷

CONCLUSION

Stem cells have the potential to cure diabetic foot ulcers, according to studies. Using paracrine signals, Mesenchymal Stem Cells (MSCs) promote extracellular matrix remodeling, angiogenesis, wound closure, skin structure and function regeneration, and extracellular matrix remodeling; this may reduce the risk of complications such as amputation, shorten the healing period, and expedite tissue regeneration.

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