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Mesenchymal Stem Cells (MSCs) Therapy for Pressure Ulcers: A Literature Review

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ABSTRACT

Pressure ulcers or injuries, arise from ischemic damage to soft tissues induced by unrelieved pressure over a bony prominence. They are usually difficult to treat with standard medical therapy and often they recur. Promising alternative methods for treatment are now developing in the search for better treatment choices. Within the field of regenerative medicine, ongoing research on advanced therapies seeks to treat pressure ulcers with mesenchymal stem cells (MSCs). This review was synthesized and obtained from various online databases. Scientific articles were selected based on the inclusion criteria. MSCs have anti-inflammatory capabilities, they are very helpful for treating chronic wounds such as pressure ulcers because they can restart healing infected wounds by moving the wound through a chronic inflammatory state and into the subsequent stage of healing. The research indicates that MSCs produce soluble compounds that promote the proliferative and migratory behavior of the dominant cell types in the wound. MSCs promote wound closure with promoting angiogenesis, granulation tissue production, and faster epithelialization. Additionally, it was discovered that the cells create bioactive chemicals that appear to accelerate the regeneration process. These findings show that MSC therapy affects all stages of wound healing, including inflammation, epithelialization, development of granulation tissue, and tissue remodeling. Although there are many medications to treat pressure ulcers, there are surprisingly new therapies that take use of MSCs' positive benefits and crucial for wounds that are difficult to heal.

KEYWORDS: Mesenchymal Stem Cells (MSCs), Pressure Ulcer, Wound Healing

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INTRODUCTION

Pressure injuries, also known as pressure ulcers (PU), are classified as localized lesions to the skin and/or underlying tissues (epithelial, dermal, and subcutaneous tissues, such as fat or muscle).[1] They typically result from intense and/or persistent pressure, perhaps including shear and friction pressures, and commonly develop over a bony prominence or at the location of medical equipment (or others). According to the pathophysiological theory, persistent external pressure reduces blood flow, which causes local tissue ischemia and ultimately necrosis in the affected area. Reperfusion of the damaged tissue normally occurs after a ischemic episode (once external pressure stops).[2]

Pressure injury management is one of the most challenging clinical problems in hospitals. The risk of developing PU is increased by limited mobility and/or tactile sensation, frequently associated with poor nutrition and subsequent loss of muscle and body mass. This determines a high prevalence and burden of PU in older adults and patients in intensive and long-term care settings.[3]

According to accumulated data, extracellular matrix (ECM) proteins and particular growth factors produced by the skin, as well as active epithelial cells, fibroblasts, and mesenchymal stem cells (MSCs), should all be present in wound-care solutions. Recently, methods using bioengineered dressings and cell-based products have become widely used in clinical settings; yet, their effectiveness remains subpar since chronic wounds continue to be a significant unmet medical need.[4] The introduction of MSCs is a viable treatment option for nonhealing wounds since MSCs are present in healthy skin and play a crucial role in wound healing.[5]

In this review, the role of MSCs in wound healing is examined, specifically for pressure ulcers. In particular, the important role MSCs have in each phase of the wound-healing process is described. The mechanisms of MSCs in

pressure ulcers healing and evidence of MSC importance in pressure ulcers healing is also described.

METHODS

The NCBI, Google Scholar, Science Direct, Elsevier, Springer Nature, Wiley Online Library, World Health Organization databases were searched on May 18, 2023. The keywords used in the literature searching were Pressure Ulcers or Decubitus Ulcers, Wound Healing, Therapy for Decubitus Ulcers, and Mesenchymal Stem Cell(s). Scientific articles were selected based on the following inclusion criteria: (1) The journal can be freely accessed, (2) Publication year of journal is not less than 2013, and (3) Matched with the material discussed in this literature review. Each selected work of literature is reviewed, and the data is then analyzed and put together into a logical flow of ideas.

RESULTS

There are few studies that considered eligible for inclusion criteria in the Table 1.

ID	Pressure ulcers	Mesenchymal stem cell	Recipient	Outcome
Chen 2019[6]	On the back of D-galactose induced aging mice.	Human embryonic stem cell-derived exosomes	Mice	Accelerating wound healing in aged mice.
Feldman 2018[7]	Full-thickness wound	Mesenchymal stem cells combine with TGF-β3 and albumin based scaffold	Rabbit	The combined treatment showed the greatest increase in healing rate, particularly for the epithelialization rate
Lanci 2019[8]	A superficial pressure sore developed on the left hock	Heterologous Wharton's Jelly Derived Mesenchymal Stem Cells	Human	The wound was completely healed
Iacono 2015[9]	Spontaneously arisen pressure sores	Amniotic fluid mesenchymal stem cells in carboxymethyl cellulose gel	Horse	The local application of mesenchymal stem cells isolated from amniotic fluid, using CMC as scaffold, could be considered as an effective treatment of deep sores in hospitalized neonatal foals
Dulamea 2015[10]	Two stage IV PUs on the lateral left malleolus (8/7 cm) and on lateral side of thigh (3 cm) respectively and a stage III PUon right calcaneum and Neuromyelitis optica	Autologous mesenchymal stem cells	Human	For 6 years the patient was free of relapses and showed an improvement of disability (from EDSS 9 to EDSS 3.5)
Motegi 2017[11]	Pressure ulcers with Cutaneous ischemia-reperfusion mice model	Mone marrow-derived mesenchymal stem cell	Mice	The injection of MSCs might protect against the development of PUs after cutaneous I/R injury by reducing vascular damage, oxidative cellular damage, oxidative stress, ER stress, and apoptosis.
Yoon 2018[12]	Pressure ulcer wound in a mouse model.	Fibroblasts Differentiated from Human Embryonic Stem Cell-Derived Mesenchymal Stem Cells	Mice	ESC-MSC-Fbs might have clinical applications as a source of cells for the treatment of pressure ulcers.

DISCUSSION

Decubitus ulcers

Definition

Decubitus ulcers are skin and soft tissue lesions that develop as a result of continuous or prolonged pressure to the skin. They are also known as bedsores or pressure ulcers. These ulcers develop at the ischium, greater trochanter, sacrum, heel, malleolus (lateral than medial), and occiput which are bony area of the body. Most often, these lesions affect persons who struggle to change their posture due to disorders that limit their movement.[13]

Etiology Decubitus ulcer growth is complicated and multifaceted. The most significant factors to contribute the development of these ulcers are loss of sensory perception, locally and generally impaired loss of consciousness, along with restricted movement because patients are unaware of

their suffering and do not alleviate the pressure.[14] These ulcers are the result of simultaneous internal and environmental variables. The development of these lesions is sped up by internal and external causes like fever, starvation, anemia, and endothelial dysfunction.[15]

A decubitus ulcer can form in a patient who is bedridden or having surgery after as little as two hours of immobility.[15] The development of these ulcers may in part be attributed to the malfunctioning of nerve regulatory systems that control local blood.[16] Long-term pressure on tissues can result in capillary bed blockage, which lowers the area's oxygen levels. The ischemic tissue starts to build up harmful compounds over time. The result is tissue necrosis and ulceration.

The following medical conditions put patients at risk for developing decubitus ulcers: (1) Neurologic disease, (2) Cardiovascular disease, (3) Prolonged anesthesia, (4) Dehydration, (5) Malnutrition, (6) Hypotension, (7) Surgical patients.

Epidemiology

Many thousand people are impacted by decubitus ulcers each year, which is a serious medical issue on a global scale.[13] Their annual management expenses in the billions of dollars stress the already underdeveloped health economy. Two-thirds of sacral decubitus ulcers in individuals over 70 years old, as previously mentioned, occur in older people. According to research, 83% of hospitalized patients who had ulcers did so within five days of being admitted.[15] According to a study conducted in a Turkish medical research center, 360 out of 22834 hospitalized patients acquired one or more pressure ulcers. The intensive care unit (ICU) was the place where the majority of patients with pressure ulcers were placed.[17]

Pathophysiology

Although the external and internal causes that contribute to the development of decubitus ulcers are numerous, they all have a basic pathway that leads to ischemia and necrosis. Although tissues are capable of surviving unusually high external pressure, sustained pressure over an extended period of time is the main problem. In order to restrict blood flow, external pressure must be higher than the arterial capillary pressure (32 mmHg), and it must also be higher than the venous capillary closure pressure (8–12 mmHg) in order to restrict the return of venous blood. If the pressure remains over certain levels, it results in tissue ischemia and then tissue necrosis.[18] Any hard surface that the patient comes into contact with while being compressed by a hard mattress, hospital bed railings, or both might cause this extreme pressure. By causing wounds in the skin's superficial layers, friction from the skin rubbing against things like clothing or bedding can also cause ulcers to form. Through tissue breakdown and maceration, moisture can both initiate ulcers and exacerbate pre-existing ulcers.

Evaluation

A thorough history is required for the initial evaluation of patients with pressure injuries, and the following information should be gathered by the clinician: (1) Duration of immobility or being bedridden. (2) Duration of hospital stay. (3) ssociated medical cause that has caused the injury (e.g., paraplegia, quadriplegia, stroke, road traffic accident (RTA) that might have resulted in immobility. (4) The natural history of the injury; the site at which it first developed. Did it increase in size? How long has the injury been present?. (5) brief history of any systemic diseases is also necessary. Diseases like diabetes mellitus, peripheral vascular disease, and malignancy prevent or slow down wound healing. (6) If the patient recognizes the location of the ulcer or any discomfort that may be there because most of the time, ulcers are painful but the patient is unaware of this because he is paralyzed or in a serious situation. (7) Is there any discharge or foul odor from the ulcer site? These may specify the worsening of the lesions.

Differential diagnosis

The differential diagnosis of sacral decubitus ulcers include: Diabetic ulcers, Venous ulcers, Pyoderma gangrenosum, Osteomyelitis.[14]

Staging

Sacral decubitus ulcers can be staged in a variety of ways. The National Pressure Ulcer Advisory Panel (NPUAP) system is the most commonly used classification scheme. It categorizes these ulcers based on ulcer depth.[15]

The stages are as follows:

A. Stage I: The skin is intact with the presence of non-blanchable erythema.
B. Stage II: There is partial-thickness skin loss involving the epidermis and dermis.
C. Stage III: There is a full-thickness loss of skin that extends to the subcutaneous tissue but does not cross the fascia beneath it. The lesion may be foul-smelling.
D. Stage IV: There is full-thickness skin loss extending through the fascia with considerable tissue loss. There might be possible involvement of the muscle, bone, tendon, or joint.

Prognosis

The majority of the time, lifetime therapy and preventative measures are required for these patients, despite the fact that outcomes have been difficult to research. The probability of a recurrence is very significant in patients with sacral decubitus ulcers.[19]

Complications

With decubitus ulcers, complications may appear. The most typical issue is infection. Grade III and IV ulcers need to be treated carefully since their consequences might be life-threatening. Aerobic and anaerobic bacteria are both present in the lesions, according to microbial studies.[20] Periostitis (infection of the layer covering the bone), osteomyelitis (infection of a bone), septic arthritis (infection of a joint), and sinus development (abnormal space produced by tissue loss) can occur if the infection progresses to deeper tissues and the

bone. Because septicemia is difficult to treat in a patient who is already insufficient, the invasion of the infectious agent has fatal implications. These wounds are catabolic, which means they consume a lot of energy. Due to the catabolic nature of these ulcers, significant protein and fluid loss occurs, which may cause hypoproteinemia or malnutrition. An ulcer that is draining might cause daily protein losses of up to 50 grams.[20] Chronic decubitus ulcers may result in secondary amyloidosis or chronic anemia. Anemia can also develop as a result of ongoing bleeding and water loss.[20] Inadequate postoperative care can lead to difficulties after reconstructive surgery. These include the development of hematomas or seromas, wound dehiscence, the growth of abscesses, or postoperative wound sepsis.

TREATMENT OF DECUBITUS ULCERS

Decubitus ulcers are challenging to cure since there is no set treatment plan or strategy. Once it has manifested, treatment should not be delayed, and treatment should begin immediately.[21] The type of treatment depends on the location, stage, and ulcer-related problems. All of the many treatment approaches aim to keep the ulcer as aseptic or least septic as possible by reducing moisture, pressure, and contact between the ulcer and a hard surface. The type of treatment to be used should depend on the ulcer's stage or grade as well as its intended goals (e.g., reducing moisture and removing necrotic tissue, or controlling bacteremia).[22] Decubitus ulcer treatment is thus based on Prevention of additional ulcers, Decreasing pressure on the wound, Wound management, Surgical intervention, Improving the nutritional status. Stage I and II ulcers typically don't need to be operated on. Ulcers in stages three and four can need surgery. Several reports on the therapeutic efficacy of laser sessions, ultrasound, recombinant platelet-derived growth factors, and hyperbaric oxygen have shown some improvement in the healing of pressure injuries, especially stage III and above. Because different types of wounds have different molecular and cellular pathways, there is currently no one therapy strategy that will fully cure a wound. The field of wound healing research today has a much greater understanding of evaluation and treatment approaches because to recent technological improvements and advancements. The advancement in this field has led to a paradigm change from dry dressings to moist dressings, stimuli responsive dressings, growth factor-based therapy, tissue engineered skin, bioengineered human skin substitutes, gene therapy, nanotherapeutics, and stem cell therapy. The stem cells therapy has revolutionized the development in this field.

THE MECHANISMS OF MSCS IN PRESSURE ULCERS HEALING

MSCs have varying roles in each of the three stages of wound healing. Additionally, they affect the wound's ability to go past the inflammatory stage and avoid regressing into a chronic wound condition. The direct attenuation of inflammatory response by MSCs is an important part of their mode of action. MSCs have been demonstrated to reduce the secretion of the proinflammatory cytokines TNF-α and interferon (IFN-γ) while enhancing the secretion of the antiinflammatory cytokines interleukin-10 (IL-10) and IL-4 during an active immune response.[23] Because MSCs have anti-inflammatory capabilities, they are very helpful for treating chronic wounds such as pressure ulcers because they can restart healing infected wounds by moving the wound through a chronic inflammatory state and into the subsequent stage of healing.

Growth factors, cytokines, and chemokines, specifically VEGF, PDGF, bFGF, EGF, keratinocyte growth factor (KGF), and TGF-β, are among the known mediators of tissue repair that are secreted by MSCs, according to analyses of MSC-conditioned medium.[24] [25] A number of diverse physiological responses, such as cell survival, proliferation, migration, and gene expression, are regulated by MSC paracrine signaling, including those of epithelial cells, endothelial cells, keratinocytes, and fibroblasts, according to studies.[26] In vitro, macrophages, endothelial cells, epidermal keratinocytes, and dermal fibroblasts respond to MSC-conditioned media as chemoattractants.[25] [27] Dermal fibroblasts have been demonstrated to be stimulated by MSCs or MSC-conditioned media to accelerate wound healing.[28]

Overall, the evidence shows the release of soluble substances by MSCs that encourage the proliferation and migration of the wound's predominate cell types. Additionally, the production of VEGF and hepatocyte growth factor (HGF) as well as the maintenance of the correct ratio between TGF-β1 and TGF-β3 are two additional ways that MSCs' paracrine signaling exhibits antiscarring effects.[29-31]

EVIDENCE OF MSC IMPORTANCE IN PRESSURE ULCERS HEALING

Exogenous MSCs are advantageous for the therapy of wounds, as shown by in vivo investigations. According to numerous studies, administering MSCs to diabetic or acute wounds in rodents promotes wound closure by promoting angiogenesis, granulation tissue production, and faster epithelialization. In a skin defect model, MSCs plus bFGF may speed up wound healing, according to Nakagawa et al.[32] who also demonstrated that human MSCs transdifferentiated into the epithelium in rats. MSC transplantation on the surface of deep burn wounds in rats lowered inflammatory cell infiltration and sped up the development of new vasculature and granulation tissue, according to research by Shumakov et al.[33] Additionally, it was discovered that the cells create bioactive chemicals that appear to accelerate the regeneration process. These findings show that MSC therapy affects all stages of wound healing, including inflammation, epithelialization, development of granulation tissue, and tissue remodeling.

Clinical outcomes using MSCs to speed up wound healing have also been encouraging, Badiavas and Falanga[34]

demonstrated that direct administration of bone marrow-derived cells can result in wound closure and tissue reconstruction in a human study of chronic nonhealing wounds. In one investigation of chronic diabetic foot ulcers, autologous fibroblasts and MSCs were mixed on a biodegradable collagen membrane by Vojtassa k et al.[35] On days 7 and 17, MSCs were also injected into the wound's edges as part of the same investigation. The wound's dermal thickness and vascularity grew as the wound's size decreased. Falanga et al.[36] examined a special delivery method employing fibrin glue in both acute and chronic wounds.

The study also discovered a correlation between the MSCs' surface density and the reduction of ulcer size. Twenty patients with diverse non-healing wounds were treated with autologous bone marrow-derived MSCs cultivated on a collagen sponge in one of the largest studies by Yoshikawa et al.[37] When wounds were treated with the cell composite graft, 90% of them healed fully, and the addition of MSCs enhanced tissue regeneration.

Chronic wound healing has also been seen to be improved by systemic delivery of MSCs, particularly when other underlying conditions like diabetes and other systemic illnesses are present. In a randomized controlled study by Dash et al.[38] the researchers gave cultured autologous bone marrow-derived MSCs topically to the ulcer and intramuscularly to 24 patients with nonhealing ulcers of the lower limbs. Within 12 weeks, the MSC-treated group outperformed the control group in terms of both pain relief and wound size reduction (72% versus 25%). A randomized controlled research by Lu et al.[39] also revealed a clinical advantage of systemic delivery of MSCs.

Briefly, fresh nonculture bone marrow-derived mononuclear cells or cultured autologous bone marrow-derived MSCs were injected intramuscularly into one of the patient's limbs. Each subject received a standard saline injection in the opposite leg as a control. Both MSC and mononuclear cell injections improved pain-free walking at 24 weeks and significantly increased the rate of ulcer healing when compared to control groups. Additionally, compared to the group that received mononuclear injections, the MSC-treated group showed a considerably larger increase in ulcer healing rate.

CONCLUSION

The coordinated interaction of ECM, growth factors, and cells is crucial for the complex process of wound healing. Particularly MSCs have an essential role in modulating the inflammatory, proliferative, and remodeling stages of the wound-healing process in pressure ulcers. As a result, numerous preclinical and clinical investigations have shown that MSCs are beneficial for pressure ulcers. A number of processes, such as anti-inflammatory and antibacterial, immunomodulative, and tissue reparative activities, are implicated in MSC-mediated wound healing. Although there are many medications on the market right now to treat pressure ulcers, there are surprisingly few therapies that take use of MSCs' positive benefits, which are crucial for wounds that are difficult to heal. It is crucial to take MSCs into account while developing new bioengineered wound-healing products because of their significance to the healing process.

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