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# Stem Cells In Diabetic Wound Healing

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## Abstract:

Mesenchymal stem cells (MSCs) transplantation seems to be a promising new therapy for diabetic wound healing (DWH) and currently, arrays of MSCs from various sources ranging from umbilical, adipose to dental sources are available as a treatment modality for this disease. However, it now appears that only a fraction of transplanted cells actually assimilate and survive in host tissues suggesting that the major mechanism by which stem cells participate in tissue repair are most likely related to their secretome level. These include a wide range of growth factors, cytokines and chemokines, which can be found from the conditioned medium used to culture the cells. Basic studies and preclinical work confirm that the therapeutic effect of conditioned media (CM) is comparable to the application of stem cells.

## Introduction:

Diabetes is a serious debilitating disease and it is on the rise. In 1980 an estimated 108 million people were living with diabetes and the number ballooned four-fold in just 35 years to over 422 million diabetes patients in 2014 (World Health Organisation, 2017). The number of diabetes patients may be more than 360 million in 2030. In 2015 alone, it was the direct cause of death of 1.5 million patients . Diabetes is also one of the major culprits that lead to other complications such as cardiac ischemia, cerebral ischemia, renal failure, amputation and neuropathy. Among these complications, lower extremity amputation caused by diabetic ulcers is 20 times higher in diabetic patients as compared to non-diabetic patients this translates to a higher wound management cost as well; this has become a major global health burden. For example, in the United Kingdom alone, its National Health Service report shows that annually up to 5 billion pounds were spent for diabetic wound treatment.

A wide range of treatments are currently available in diabetic wound management and these are mainly based on the different stages of the wound. For example, customized dressings are used for different types of chronic wounds within 12 weeks of onset whereas surgical debridement, negative pressure wound therapy and hyperbaric oxygen were commonly used for diabetic wounds that persist more than 12 weeks. This is because necrotic tissues are formed beyond this time frame and the tissues require debridement prior to any treatment. While novel modifications of current treatments such as the usage of maggots as bio-surgical debridement to replace classical method of current treatment have now been proposed, the complexity of the mechanisms underlying diabetic wound often contribute to indifferent results as it lacks a holistic approach in resolving the problem. In order to improve results in diabetic wound treatment, advanced therapy such as topical application of growth factors, human dermal allografts, bioengineered cellular therapies, and stem-cells therapy are being investigated. Among these, stem cell therapy has become the focus of attraction in treating diabetic wound due to their ability to home towards the wound and release potent bioactive factors which can enhance the wound healing process.

MSCs are a type of stem cells that can be isolated from connective tissues of different tissues or organs including bone marrow, adipose tissue, cartilage, umbilical cord blood and Wharton's Jelly. As MSCs can be isolated easily with less ethical concerns and can be expanded in great numbers, they have been the focus of many studies regarding their usefulness in regenerative medicine in general and wound healing in particular. However the unexpected failure of several RCTs to demonstrate efficacy have led to a rethinking about the strategies of using MSCs including the delivery systems, dosages and specific types of MSCs used. Consequently, researchers have started to move towards a cell-free therapeutic strategy by incorporating the conditioned media (CM) of MSCs to overcome the problems faced by cell therapy To date, accumulated data indicates that MSCs secretome from the CM is the major mechanism that MSCs use to exert their functions on adjacent cells. The MSC secretome regulates a number of different cellular responses including cell survival, proliferation, migration and gene expression. Though, studies utilizing MSCs-CM seem to be promising and safe, research that has been conducted in the past few years have yet to determine the underlying mechanism of action of the CM, the components in the CM, a standard protocol of CM production and the dosage used in treatment. Thus, in this review, the underlying mechanism of MSCs-CM in treating diabetic ulcers will be discussed in details to find a feasible way of utilizing MSCs-CM in diabetic ulcers treatment.[(1)]

In a study done in 2014, BM-MSCs were able to restore cell viability of keratinocytes in wounded sites, elevate expression of EGF and IGF-1 enhance migration of keratinocytes through upregulation of MMP-2 and at the same time decrease level of MMP-9 in rats' diabetic foot ulceration. In another unrelated study, bone marrow (BM)-MSCs were postulated to work on promoting migration, angiogenesis and reepithelialisation process whereby they express higher amount of VEGF which thicken the granulation tissue in diabetic rodent model.[(5)]

On the other hand, in 2015 another study reported that the transplantation of adipose tissue- derived MSCs (AD-MSCs) was able to accelerate skin regeneration in a vivo wound model of Type 2 diabetes rats through secretion of angiogenic growth factors. They further postulated that the cells may differentiate into perivascular

cells to support the neo-vascularization process. Additionally, silk fibrion cellularized with AD-MSCs demonstrated a significant effect on improving skin healing in diabetic mice through upregulating the expression of genes which are involved in angiogenesis, tissue regeneration and ECM deposition. It was proven that the increment of growth factors such as VEGF, FGF2, TGF-beta and EGF have played an important role in wound angiogenesis and cell migration **t**ransplantation of umbilical cord blood (UCB)-MSCs in diabetic foot ulceration rats also enhances collagen and glycosaminoglycan (GAG) synthesis in diabetic fibroblasts.[6]

This review describes in detail the wound healing process in diabetes and the cellular and biological factors which influence the process.

## Materials And Methods:

The last study which involved intravenous infusion of MSCs to mice with liver ischemia-reperfusion injury. The MSCs which were injected through tail vein were found to be viable in the lungs within the first 24 hours, but disappeared after 24 hours with no trace found in other organs including blood, liver, spleen, kidneys and bone marrow suggesting the short viability period of infused MSCs and that the delivery of MSCs to the site of injury is not necessary required to harness a therapeutic effect.[6]

## Results:

These observation leads to the notion that the main therapeutic effect of MSCs transplantation are related to their paracrine activity on resident cells which then enhance angiogenesis and cell survival.

## Discussion:

Diabetes wound Diabetes mellitus (DM) is a chronic disease where the pancreas produces insufficient insulin or ineffective use of insulin by the body. Type 1 diabetes is a chronic autoimmune disorder in genetically susceptible individuals whereby the body own immune system attack and destroy the beta-cells and eventually eliminate insulin production. On the other hand, Type 2 diabetes is characterized by defects of insulin secretion by β-cell or insulin resistance which in most of the cases are strongly associated with patients' lifestyle and diet habits. Diabetes patients generally have dysregulated immune response in which the inflammatory cells fail to response to chemotaxis gradient, malfunction and inactive which delay or prolonged the wound healing process.[(2)]

A large number, supposedly over 100, physiologic factors are responsible for poor wound healing in diabetes. These affect a wide variety of molecular mechanisms including impaired growth factor production, impaired angiogenic response, macrophage function and collagen formation among others. A study which examined epidermal biopsies from diabetic patients suggested that there is overexpression of c-myc and nuclear localisation of Beta catenin. Wounds can be generally categorized as acute or chronic wounds. Acute wounds typically heal in a well-organized process in which the tissue repair progress is predictable. An example of common acute wound is a clean and uninfected surgical incisional wound with surgical sutures. In contrast, chronic wounds develop when the controlled sequence of events of a natural wound healing become stalled and show no signs of effective healing within three months after the tissue injury .

Chronic wounds can be assigned to three main categories: vascular ulcers, diabetic ulcers, and pressure ulcers. In general, all these chronic wounds categories share certain common features such as excessive levels of pro-inflammatory cytokines, proteases, reactive oxygen species (ROS) and senescent cells with persistence infection, formation of drug-resistant microbial biofilms as well as deficiency of functional epidermal cells. In the case for diabetes patients, they suffer from overall impaired healing even with a slight skin abrasion or scratch and are prone to develop

chronic wounds such as diabetic foot ulcers . One of the common syndromes that accompany diabetes is diabetic foot disease (DFD). DFD includes diabetic peripheral neuropathy which is a loss of sensory function due to axonal and microvascular damage. In peripheral neuropathy arteriovenous shunts form in the subcutaneous tissue directing more blood to the deeper layers resulting in overheating of the skin. In consequence, the skin becomes dried out and easily injured. Peripheral arterial disease (PAD) is another common syndrome that causes ulceration in diabetic patients. Hyperglycemia and insulin resistance in diabetic patients causes derangements in the vessel wall through promotion of vascular inflammation and endothelial cell dysfunction and eventually foster development and progression of PAD. Diabetes patients with PAD are prone to develop ischemic necrotic ulcers due blockage in the arteries that supply blood to the extremities. The inner linings of the arteries wall become narrower due to accumulation of lipids, thus, minimizing the blood supply, delivery of oxygen nutrition and antibiotics to the limbs.[(3)]

**MSCs in diabetic wound healing** stem cells can be divided into embryonic stem cells (ESCs) and adult stem cells (ACSs). Due to the moral and social controversy surrounded the former, the latter has been extensively exploited for many anticipated clinical potential. Mesenchymal stem cells, a subset of adult stem cells has been chiefly isolated from bone marrow (BM) and later isolated from other tissues such as adipose, umbilical cord, cord blood and dental pulp. In in vitro condition, MSCs from these tissues could be grown for long term and exhibited the capacity of prolonged self-renewal and differentiation along with mesoderm cells though there are some extend of variability in terms of frequency and degree of differentiation.[(4)]

The soluble factors and exsosomes are major factors mediating MSCs' therapeutic effects. Since the protocols for isolation, in vitro expansion, phenotyping, dosing, and administration are not well documented, it can manifest different outcome in animal models versus human trials which makes efficacy and therapeutic potential hard to reproduce.

MSC-CM is cell free therapeutics that will help to mobilize homogenous MSCs as they are rich in pro-angiogenic and trophic factors and the collection method has less ethical issues.[6]

## Conclusion:

Diabetes is a common disease that lead to complication.Unfortunately traditional stem cell therapy has became the focus of attraction for treating diabetic wounds.It is concluded that diabitic wounds can be effectivly healed by useing MSC from varius sources. Basic studies and preclinical workt confirm that the theraputic effect of conditioned media is comparable to the application of stem cells.

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