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Review

Adipose-derived stem cells: Effectiveness and advances in delivery in diabetic wound healing

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ABSTRACT

With the increasing global prevalence of diabetes mellitus, a significant rise in the number of patients suffering from non-healing wounds is expected. However, available treatments, such as revascularization surgery and foot care education are often insufficient to ensure satisfactory wound healing. One therapeutic strategy that has been identified as particularly promising utilizes adipose-derived stem cells (ADSCs). Through a comprehensive literature search of published and ongoing studies, we aimed to provide an overview of the experimental basis, the scientific background, and advances in the delivery of ADSCs for treating non-healing diabetic wounds. ADSCs have the capacity to differentiate into multiple cell lineages and are considered an alternative to bone marrow–derived mesenchymal stem cells. They can be easily extracted from the adipose tissue and are capable of in-vitro expansion. The reviewed experimental studies showed that ADSCs can enhance diabetic wound healing through increasing epithelialization and granulation tissue formation, anti-inflammatory and anti-apoptotic effects, and release of angiogenic cytokines. Moreover, few small clinical trials showed that ADSCs treatment in patients with diabetic ulcers caused enhanced ulcer evolution, lower pain scores, and improved claudication walking distances with no reported complications. In conclusion, ADSCs have a promising potential in the regenerative therapy of chronic diabetic wounds. However, larger studies should confirm their efficacy and long-term safety in diabetic patients.

1. Introduction

Diabetes mellitus (DM) is a pandemic chronic disease, expected to reach a global prevalence of 592 million individuals by 2035 [1]. Foot ulcers affect 6.3% of diabetic patients globally [2] with an attributable cost of £580 million over two years in the UK National Health Service [3]. Furthermore, foot ulcers have a significant influence on the patients' quality of life, causing more pain, less vitality, and restriction of social functions [4]. With the increasing prevalence of DM, poorly-healing or non-healing wounds are becoming a serious global health issue.

Hyperglycemic states can impair wound healing through different mechanisms. Neuropathic lack of sensation may aggravate the traumatic tissue loss, while deficient epithelialization (due to impaired cellular proliferation and resistance to growth factors) can delay wound healing [5,6]. Moreover, impaired macrophage migration and deficient release of signaling molecules in DM inhibit new vessel formation [7]. Lobmann et al. showed that diabetic wounds have a higher activity of

Abbreviations: ADSCs, adipose derived stem cells; Ad-MSCs-SF, silk fibroin patches cellularized with human adipose-derived MSCs; BMSCs, bone marrow mesenchymal stem cells; CXCR-4, C-X-C chemokine receptor type-4; D-Ad-MSCs-SF, silk fibroin patches decellularized with human adipose-derived mesenchymal stem cells; DM, diabetes mellitus; ECM, extracellular matrix; EGF, epithelial growth factor; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; Mif, macrophage migration inhibition factor; MMP, matrix metalloproteinases; PI3K, phosphoinositide 3-kinase; PLGA, poly (L-glutamic acid)/chitosan scaffold; SDF, stromal derived factor; SVF, stromal vascular fraction; TGF-β, transforming growth factor-Beta; vWF, Von-Willebrand factor; VEGF, vascular endothelial growth factor

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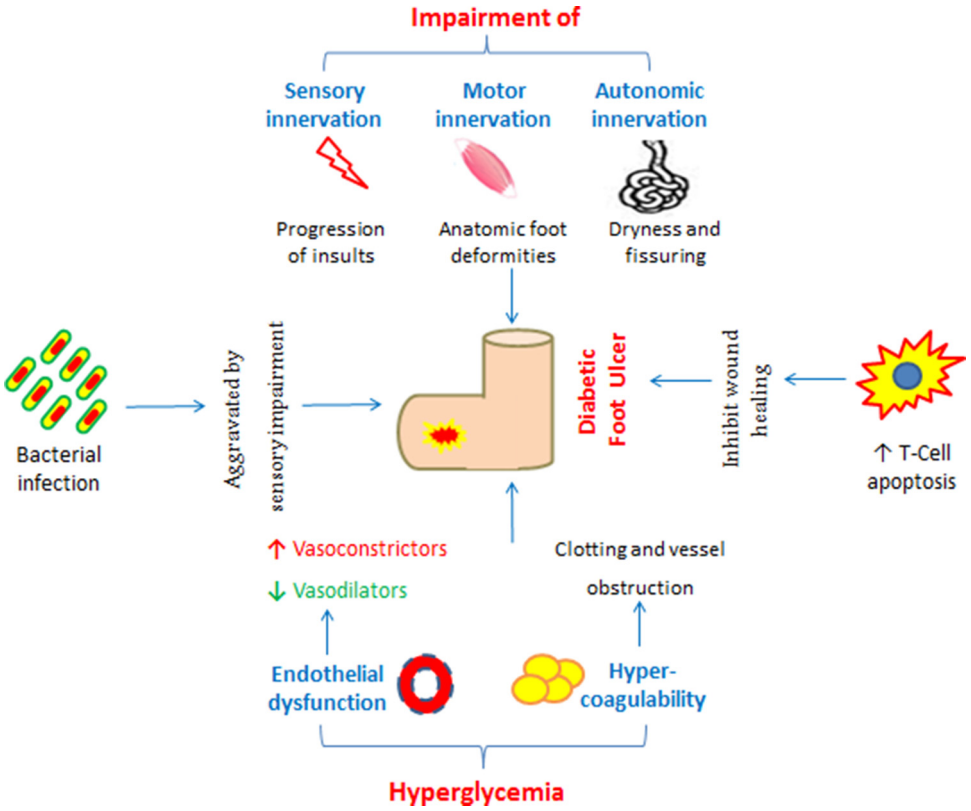

Fig. 1. shows a summary of the pathogenic mechanisms, involved in the development of diabetic foot ulcer.

matrix metalloproteinase (MMP) enzymes than healthy wounds; therefore, collagen fibers are destroyed at a faster rate than their secretion, delaying the formation of adequate granulation tissue [8]; Fig. 1.

Standard treatments for diabetic wounds include debridement of necrotic tissue, revascularization surgery, infection control, mechanical offloading, control of blood glucose, foot care education, and limb elevation. However, these treatments are often insufficient to ensure satisfactory wound healing and are associated with high rates of limb amputation [9]. One therapeutic strategy that has been identified as particularly promising utilizes adipose-derived stem cells (ADSCs). These cells have the capacity to differentiate into multiple cell lineages and are considered an alternative source to bone marrow–derived mesenchymal stem cells (BMSCs). Through a comprehensive literature search (updated in February 2018) of published (Medline, SCOPUS and Cochrane Central) and ongoing studies (Clinicaltrials.gov), we aimed to provide an overview of the experimental basis, the scientific background, and possible clinical applications of ADSCs in diabetic wound healing.

2. Adipose-derived stem cells (ADSCs)

The adipose tissue has traditionally been regarded as an energy-storing tissue, composed of adipocytes (11.8%), endothelial/hematopoietic cells (60.7%), fibroblasts/others (27.5%) and nurtured by an intermingling vasculature. ADSCs can be isolated from the human adipose tissue in large amounts with minimal donor morbidity, then cryo-precipitated and preserved for over six months [10]. They can be isolated from the patient/animal himself, in which case they are called "Autologous ADSCs". These cells are isolated from the subcutaneous adipose tissue, either from the inguinal [11–15] or abdominal areas [16,17]. They can also be obtained from another individual in the same species "Allogenic" or from a different species "Xenogenic ADSCs" [18–21].

The usual method of ADSCs isolation starts with extraction of a liposaspirated tissue (1 gm contains 3.5×10^5 to 1×10^6 ADSCs), which is subsequently processed by collagenases and centrifuged to obtain a stromal vascular fraction (SVF); a high density fluid with multiple components, such as primary adipocytes, pericytes, macrophages, and ADSCs. To obtain purified ADSCs, subculturing is usually performed [22]. Recently, SVF has been used more frequently in experimental studies than the purified ADSCs because the multiple components of SVF are thought to act synergistically to enhance the regenerative potential of ADSCs [23]. This concept was challenged by Bai et al. who showed that both SVF and purified ADSCs had the same efficacy when investigated in the mouse model of myocardial infarction [24]. The distinction between both modalities is still to be investigated.

The characterization of ADSCs requires fulfilling both the immune-phenotypic and differentiation capacity criteria. The immune-phenotypic analysis, performed by flow cytometry with specific antibodies, must confirm the heterogeneity of the freshly isolated SVF (CD34 and CD45 as hematopoietic markers, CD29, CD44, CD73, CD90 and CD105 as mesenchymal markers, CD31 and CD34 as endothelial cell markers, and CD117 as a stem cell marker) [25]. After subsequent in-vitro culture and homogenization, independent investigations identified highly consistent, yet non-identical expression profiles of surface markers on ADSCs, including CD9 (tetraspan protein), CD10 (neutral endopeptidase enzyme), CD13 (aminopeptidase), CD29 (integrin β1), CD49 (integrin α4), CD54 (intracellular adhesion molecule-1), CD105 (endoglin), and CD106 (vascular cell adhesion molecule). Typical ADSCs have a fibroblastic morphology, containing a large nucleus and a large endoplasmic reticulum [26]. As multi-potent progenitors, ADSCs can give rise to osteoblasts, chondrocytes, and adipocytes. As a part of the differentiation criteria, ADSCs must generate at least two of these lineages to prove multi-potency [25].