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A Review of Diabetic Wound Healing Methods Based on Using Stem Cells

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Abstract

Diabetic foot and diabetic foot ulcer are still a major cause of disability in diabetic patients, and despite many advances in the diagnosis and treatment of diabetes, the problem of diabetic foot has not yet been resolved Researchers have succeeded in treating diabetic foot ulcers with new therapies, including cell therapy. Autologous stem cells derived from peripheral blood mononuclear cells (*CD34*) are effective in healing diabetic foot ulcers and preventing limb amputation. Several interventional studies have shown that bone marrow aspiration stem cells or peripheral blood mononuclear cells (*CD34*) can lead to angiogenesis and improve tissue activity in ischemic tissue and help wound healing. Stem cells can also be used which is extracted from adipose tissue, treated diabetic foot ulcers. In this method, induced pluripotent stem cells are used. In another method, a special type of modified blood cells from the umbilical cord called EPC can be used, which Used to speed up the healing and healing of diabetic wounds.

Keywords: Diabetic foot; Diabetic patients; Stem cells; Diabetic wounds; Cell therapy

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Introduction

Diabetic Foot Ulcers (DFU) is a common and severe complication of diabetes. Chronic ulcers that do not respond well to treatment [1,2]. In patients with diabetic foot ulcers, the quality of life is severely reduced, and in addition to this complication, which is more common in developing countries than in developed countries, it also incurs back-breaking costs for patients and the country's health care system. And yet in many cases the therapist is forced to amputate the patient [3].

In a study conducted in the United States, the cost of treating patients with diabetic foot ulcers was estimated at $ 13-9 billion annually, which is covered by patients or insurers [4]. Previous research has shown that diabetic vasculopathy and ischemia in the limb are a major cause of chronic ulceration [2]. In molecular studies of wound fibroblasts, researchers observed a significant difference between diabetic wound fibroblasts, or Chronic Wound Fibroblasts (CWF), compared with normal fibroblasts in normal individuals [5,6].

One study found that these two types of fibroblasts differed in the expression of 118 genes, including those related to cell cycle and aging, cytoskeleton, oxidative stress, inflammatory response, proteases and protease inhibitors, extracellular material production, and growth factor signaling. Of these, 118 genes and 53 genes are expressed in CWF more than normal fibroblasts and 65 genes less than that. The study also found that 22 genes in NF were twice as expressed as CWF, of which six members of the CXC chemokine family and several proteases including *MMP1* and *MMP12* were significant. And of them 4 genes related to the activity of growth factor or cytokines and hyaluronan synthase 1 are significant [6].

In this study, it was found that CWF produces more superoxide than NF and it was also found that CWF performs poorly in the production of CXCs 1, 2, 3, 5, 6 and 12 and it was further found that CWF performance shows a delay in neutrophil recall. This finding is consistent with the findings of another study that discussed the association of leukocyte and cytokine accumulation at the wound site with delayed wound healing at DFU. In this experiment it was shown that the number of leukocytes and the frequency of

IL6 at the site of chronic diabetic wound in the delayed phase are significantly lower than the control group and we see less inflammatory response in the delayed phase of wound healing in the diabetic group [7].

Studies have shown that in hyperglycemic conditions (as seen in diabetes), the rate of fibroblast mitosis (normal or diabetic) decreases, which is more dramatic in the case of chronic wound fibroblasts. Also in morphology, CWF, with its large appearance, can be easily distinguished from normal fibroblasts by its spindle appearance [8].

In another study, these two types of fibroblasts were compared and it was shown that the migration capacity of diabetic fibroblasts is much lower than healthy fibroblasts. Examination of the amount of VEGF produced by fibroblasts at the wound site showed that healthy fibroblasts produced more VEGF in both standard oxygen pressure and hypoxia. Interestingly, in this study, researchers could not even stimulate diabetic fibroblasts with hypoxia cause a significant increase in the production of VEGF by these cells [5].

The above studies as a whole showed the importance of changes in wound fibroblasts as one of the factors delaying wound healing in patients with DFU. On the other hand, stem cells, due to their regenerative properties (meaning to give new life) and the ability to produce cytokines and various growth factors, in recent years have shown clear horizons in vascular repair and disease recovery [9].

Many studies, including [10], have discussed the ability of mesenchymal stem cells to become human umbilical vein endothelial cells and the secretion of VEGF, which is effective in angiogenesis. Various studies have examined the effectiveness of adipose-derived stem cells in secreting growth factors, neovascularization, rapithelization, granulation tissue formation, or the treatment of diabetic foot ulcers.

In an *in vitro* study of stimulated splenocytes and the ability of ASC cytokine secretion, the immunomodulatory effect of these cells was due to increased secretion of IL13, TGF-B, IL4, IL10 and decreased secretion of IFN-Y, IL2, IL17 by Stimulated splenocytes were demonstrated in comparison with the control group. MO6 stimulated and the ability to secrete cytokine ASC was assessed, the immunomodulatory effect of these cells due to increased secretion of IL13, TGF-B, IL4, IL10 and decreased secretion of IFN-Y, IL2, IL17 by splenocytes stimulated Proved [11].

In other studies, in the simultaneous use of ASC and low level laser therapy, we saw an increase in growth factors such as VEGF, Beta-FGF, HIF-1 alpha, NGF at the wound site. MO3, MO4 were also shown to adapt to hypoxia conditions, increase the number of vessels and blood flow at the wound site, as well as increase rapitilization and granulation tissue formation [12,13].

Research has shown that one of the problems with using stem cells is their short lifespan. To solve this problem, the researchers examined the use of stem cells along with other treatments. Examples of their success have been reviewed in [12,13,14] articles which have succeeded in increasing the effectiveness of this treatment with low level laser therapy methods and the use of photomodulin. More accompanying therapies are being explored by researchers.

Another problem is the decreased efficiency of stem cells in the hyperglycemic environment. Inhibits MSC and in addition increases MSC differentiation into human umbilical vein endothelial cells and its paracrine VEGF secretion [10]. Insulin use has also been shown to be effective in angiogenesis by releasing NO and inducing migration of endothelial progenitor cells to the wound site, as well as stimulating the secretion of stromal derived growth factor 1 (SDF-1) and thus increasing *MMP9* and modulating *TIMP1* [15]. Further research showed that negative pressure wound therapy can also increase angiogenesis at the site of injury by invoking EPC cells and increasing growth factors [16].

Literature Review

Mesenchymal Stem Cell (MSC)

ost accessible method that increases blood flow to the wound area [17]. Histological examination shows that injection of growth factor and stem cells into the wound site causes the accumulation of stem cells around the small luminal space with endothelium and at other times causes new angiogenesis at different stages of growth [18]. Also, failure to heal foot ulcers in diabetics may be related to growth factor, which is essential for angiogenesis, or may be associated with lymphopathy [19]. Also, in the presence of an exome of stem cells, it induces some genes related to the cell cycle, myc-c (cyclin A1, cyclin D2) Growth factors *(HGF, IGF1, NGF, SDF1*) and increases IL-6 cytokines In addition, exosomes extracted from stem cells increase the ability of healthy and diabetic(less than healthy fibroblasts) fibroblasts to grow. They also increase the migration ability of fibroblasts [20].

In the injection of mesenchymal stem cells with cm (conditional media) we saw a local increase in skin temperature [21] Epithelialization was also improved and signs of angiogenesis were seen at high doses. However, this stimulation had no effect on the deposition parameter (coagulation) and the pallet count parameter after and before stimulation and remained constant [22]. Stem cell therapy also increases blood flow, reduces the process of cell apoptosis and reduces the (stress oxidative) at the wound site [23].

In the study, the therapeutic effect of stem cells, mesenchymal bone marrow and their secretions on chronic wounds of mice was investigated. These materials were applied topically in combination with fibrin adhesive. In the FG+CM and FG+SC groups, thick groups of collagen were networked in different directions. FG+CM and FG+SC groups had better conditions than other two groups in terms of water retention and endurance of repaired skins [24].

Finally, SCT (autologous Stem Cell Therapy), has better results than PTA (Perataneous Transluminal) for patients with CLI (Critical Limb Ischemis) and people with diabetic foot [25].

Umbilical Cord-Stem Cell (UC-SC)

Human umbilical cord mesenchymal stem cells were extracted using a retroviral vector that caused overexpression of Wnt7a was measured in them and the results showed that the use of WNT-conditioned medium (wnt-cm) as subcutaneous injection around the wound compared to MSC-CM and the control group accelerated the wound closure process. Also in groups WNT-CM and MSC-CM compared to the control group, there were more ECM proteins like SMA α and collagen 1 and 3. Importantly, WNT-CM accelerates the migration of fibroblasts to the wound site compared to the other two groups. In addition, the CM-WNT-treated group showed regeneration of hair follicles in the repaired wound. Also CM-WNT By expressing MYC-C directly, it reduces the ability of keratinocytes to move, but on the other hand, by increasing the effect on fibroblasts, it increases this ability and also increases the expression of cytoskeletal proteins [26].

Examination of patients injected with umbilical cord mesenchymal stem cells showed significant increase in skin temperature and ankle-brachial index, intermittent lameness, pain, and numbness after stem cell treatment [27]. We also saw an increase in approximate transcutaneous oxygen pressure. In addition, angiography around the lower limb ulcer in two patients showed bilateral angiogenesis [28].

On the other hand, injection of umbilical cord mesenchymal stem cells improves skin color and increases exudate after one week of injection. This injection shows an increase in cytokines and etherloquins, which causes the arteries to dilate and the skin temperature to rise [29].

Finally, umbilical cord mesenchymal stem cell transplantation, after angioplasty, is an effective treatment for severe diabetic foot [30,29].

Bone Marrow Mesenchymal Stem Cell (BM-MSC)

Numerous studies have been performed on the use of bone marrow mesenchymal stem cells in wound healing [31]. The use of BM-MSC autologous suspension in the form of several intramuscular injections into different parts of the injured foot to significantly improve symptoms after one month, including: pain, intermittent lameness, localized cold, ankle-brachial index and lower extremity blood flow [32]. Bone marrow stem cells have been used to treat refractory wounds and histological effects including: enlarged tissue vessels, thickened dermis, and increased dermal connectivity have been observed [33]. Examination of paracrine factors in allogeneic acelullar derivatives BM-MSCs in comparison with allogeneic BM-MSCs showed that the concentration of proteins and growth factors CoL-1, KGF, MPP-1 and Ang-2 is at high levels and it seems that the effect of paracrine secretions of cells Stem more than the ability of these cells to proliferate and differentiate can heal wounds [34]. BM-MSCs, through paracrine and expression of VEGF-α and Ang-1, increase capillary density and create new vessels at the wound site, which maintain granulation tissue and keratinocyte survival [35]. BM-MSC has significantly higher growth factors than EGF, KGF, IGF-1, VEGF-a, EPO, SDF-1, as well as angiopoietin and macrophage-absorbing factors such as MIP-1a and MIP-1b in BM-MSC compared to dermal fibroblasts. Secrete [36]. Exosomes secreted by fibrocytes can also increase the migration and proliferation of keratinocytes in diabetics, increase the proliferation of cutaneous fibroblasts, and proliferated endothelial cells and regenerate in a dose-dependent manner [37]. The positive effect of bone marrow mesenchymal stem cells on skin grafting has also been confirmed. BM-MSC injection at the same time as skin flap increases the total number of mast cells, dramatically increases angiogenesis and expression of cd105 and cd90 genes, and ultimately improves the operation and reduces the area of necrosis viability [38]. The skin flap increases after the simultaneous use of Chicken embryo extract and BM-MSC due to its associated growth factors and induction of the effect of endothelial differentiation [39,40]. Concomitant use of bone marrow mesenchymal stem cells and other wound healing therapies has also yielded promising results. Examination of the effect of Low Level Laser Therapy (LLLT) and human bone marrow stem cell mesenchymal cells (hBM-MSCs) showed that each of these methods alone increases the viability of fibroblasts and the combination of these two methods also has a synergistic effect [41]. Three-dimensional culture of bone marrow stem cells with fibrin adhesive strongly stimulates their differentiation into Insulin-Producing Cells (IPC) and dramatically increases the incidence of *PDX1, GLUT2,* Insulin, MafA, and Pax-4 [42].

Adipose Derived Stem Cell (ADSC)

Due to the benefits of adipose tissue as a source of stem cells, several studies have been performed on the use of ADSC in wound healing [43,44]. Intramuscular injection of Adipose-Derived Stem Cells (ADSC) in combination with platelet-rich plasma into blocked arteries in diabetic foot ulcers reduces the rate of amputation [45]. The rate of apoptosis in Endothelial Progenitor Cells (EPCs) and the production of inflammatory factors IL-1β, IL-6 and TNF-α are significantly reduced by the presence of exosomes secreted by ADSCs and increased wound closure rate, increased angiogenesis and expression Looks for growth factors. Also, after overexpression of *Nrf2* factor by ADSC, these effects are amplified [46]. Concomitant use of Keratinocyte-Like Cells (KLCs) derived from ADSC and Platelet-Rich Plasma (PRP) accelerates wound closure as well as increases the expression of collagen 1 (COL1α2) and growth factors such as EGF, VEGF-α, FGF-2 becomes TGF-β1. The expression level of MCP-1, which is an inflammatory marker, also decreases [47]. Adipose Tissue Stem Cells (ATSC-Ex) extract-free and cell-free substrates increase the proliferation of dermal fibroblasts in a dose-dependent manner and also increase the ability of fibroblasts to migrate and produce type 1 collagen and MMP-1 [48]. The ability of keratinocytes to migrate and proliferated increases with the use of ADSCs as well as VEGF secretion, and the concomitant use of Exendin-4 and ADCS with a synergistic effect can accelerate wound closure [49]. The effect of mesenchymal stem cells extracted from adipose tissue on skin grafting has also had promising results. Injection of adipose-derived stem cells into the distal pike of the wound, like bFGF, can dramatically induce angiogenesis and increase flap survival [50]. Topical administration of ADSC in hypoxic

conditions in diabetic rats results in increased production of VEGF and hif1, a marked increase in blood flow at the transplant site, and neovascularization, which increases the chances of successful skin flap surgery [51,52]. The source of adipose tissue for ADSC preparation must be selected correctly. If the donor of adipocytes is diabetic, diabetic adipose tissue-derived stem cells have a much poorer performance compared to ADSC in terms of angiogenesis and proliferation, resulting in wound healing [53]. A similar study showed a reduction in angiogenic factors including *IGFBP3, MCP-1, SDF-1*, osteopontin in ADSCs taken from diabetic rats compared to healthy ADSCs and their ineffectiveness in protecting retinal vessels against vessel dropout in retinopathy proven to have diabetes [54]. To confirm the results obtained in larger animals, the effects of ADSC on the treatment of diabetic ulcers in diabetic swine were studied and it was shown that the use of ADSC and endothelial-differentiated ASCs increases angiogenesis and reduces acute inflammation [55].

Study of the effect of different substances and their mechanism on the healing of diabetic wounds and angiogenesis

Based on the study of different resistances in diabetic patients, the function of EPCs and as a consequence, the ability of wound healing and angiogenesis of these cells becomes impaired. In people with HbA1c in the diabetic and pre-diabetic ranges, EPCs expressing OCN, which is a marker of osteoblast, appear to be significantly higher than in normal individuals, so it may be associated with vascular classification and vascular injury in these individuals [56]. Increasing the number of EPCs in circulation and VEGF levels in PAMA were observed in diabetic patients with critical ischemia of the foot compared to those with diabetes mellitus without lower extremity vascular disease and healthy individuals, but a significant problem is the lack of natural migration of these cells resulting in Zam's inability to repair and regenerate [57]. Also, in patients with diabetes, a defect in the 1-HO-adiponectin axis leads to oxidative stress and an increase in inflammatory cytokines such as 6-TNF-α, IL and 1-MCP, resulting in a decrease in colony formation, EPC survival and the number of EPCs are circulating [58]. To treat this problem, studies have been conducted on the effectiveness of various methods and materials to improve angiogenesis and wound healing in diabetic patients. In the following some of them are found:

Aliskiren improves the angiogenesis of diabetic EPCs by increasing the expression of SDF-1α, VEGF, and (p) RR in diabetic EPCs, and possibly by activating (P) RR-associated pathways (VEGF/SDF-1α regulation) [59]. Crocetin is mediated by repairing and activating the -PI3K/AKT eNOS pathway and suppressing the ROS pathway to increase No bioavailability as well as improving cell proliferation, inhibiting apoptosis, and increasing the migration capacity of diabetic EPCs from bone marrow in diabetic animals [60]. Subcutaneous SP increases the activation of YAP and consequently increases cell proliferation, including increased myofibroblasts of αSMA-positive cells, as an effective factor in wound contraction. Therefore, through increased angiogenesis, cell proliferation, and wound contraction, wound healing accelerates in type 2 diabetic mice [61].

The protective effects of vasodilation on the treatment of sinusitis are probably due to the increase in NO stimulation and the regulation of eNOS activity. Results In STZ-induced diabetic mice, niacin increased bone marrow-derived EPCs and their differentiation into endothelial cells, improved blood flow and Increased new vascular formation, improved glucose-induced oxidative stress, decreased cell apoptosis, and aging in lower extremity ischemia [62].

T2DM patients stimulate the production of NO and eNOS by activating AMPK and increasing the mobilization and function of EPCs. Treatment with GLIMET compared to MET, in increasing the number and function of circulating EPCs, decreasing MDA oscillation concentration and increasing SOD, migratory capacity, decreasing serum TC levels and finally in improving cardiovascular risk factors which are inversely related with EPC amount are more effective [63].

Glutamine use also increases HIF-1, SDF-1, VEGF and MMP-9 in diabetic rats compared to the control group as well. It lowers blood sugar and oxidative stress, which results in an increase in the percentage and mobilization of EPCs, which can accelerate the repair of vascular endothelium in mice [64]. Diabetic patients undergo ischemia Topical intraosseous injection of simvastatin increases APN and 1-SDF levels in the peripheral circulation and decreases their surface in bone tissue, so local intraosseous injection of simvastatin through the 1-APN/SDF pathway, which plays a regulatory role on the CXCR4/1-SDF axis, can increase the migration and motility of EPCs, followed by improved angiogenesis, increase in the quality of Granulation tissue and Increased in sedimentation in granulation tissue and accelerated wound healing in diabetic rats [65].

In case of using insulin with metformin we will see the increase in the number of circulating EPCs, the adjustment of the ratio of 2-pTie-2/Tie and pAKT/AKT, the increase of angiogenic factors such as 1-VEGF, SDF as well increased migration capacity, tubulogenesis of EPCs compared to only metformin use [66]. Transfer of 1-Ang gene to diabetic mice and increasing its expression increases 9-MMP and SCF, so 1-Ang exerts its effects through two factors: 9-MMP and SCF, and through this causes increased proliferation and migration of EPCs from the bone marrow to the site of injury [67]. The effect of QQc on diabetic EPCs in diabetic mice with controlled glucose levels is by increasing the expression of growth factor genes such as endothelial growth factor and 2-fibroblast growth factor and angiogenesis-related genes such as vWF and *CD29* in these cells. It also increases the ability to form tubules in diabetic KSLs at the wound site [68].

Use of IFR increases the activity of p-38 MAPK, p-ERK, Akt, eNOS, VEGF production, bioavailability and reduces oxidative stress in EPCs in diabetic rats. Following these changes, improved performance, increased mobility, delayed aging process and Increased circulating EPCs in diabetic patients result in increased capillary density, new vascular formation, and ischemic blood flow in diabetic mice [69]. Procyanidin B2 enhances antioxidant capacity, reduces ROS accumulation and inhibits by activating the *Nrf2* signaling pathway 2 Expression of oxidative markers (NT and HNE-4-3) in diabetic EPCs resulting in loss of oxidative stress;

Therefore in this way, *PCB2* causes Maintenance of angiogenesis function, prevents apoptosis and increases the migration of diabetic EPCs and accelerates the healing of diabetic wounds [70].

Expression of miRNA-221-3p from exomes derived from EPCs increases the level of VEGF, which is one of the factors influencing angiogenesis, and also increases the level of Ki67, which is effective in cell proliferation. MiRNA-221-3 p inhibits the AGE-RAGE signaling pathway and subsequently reduces the level of proteins in this pathway such as 3-aspase, which results in a reduction in oxidative stress. On the other hand, miRNA-221-3p can reduce dependent kinase inhibitors. Cyclin, including p27 and p57, can therefore be expected to increase cell proliferation and generally promote wound healing in mice. It becomes normal and diabetic [71].

In diabetic mice, the use of oxygen therapy with pressure (HBO) increases the motility of EPC cells in the environmental blood. On the other hand, topical application of (Stromal cell-derived factor-1) *SDF1* induces EPCs to the wound site and concomitant use of HBO and *SDF1* showed satisfactory results in wound healing [72]. Topical administration of VEGF in diabetic rats increases the rate of upregulation in PDGF-B and 2-FGF and recall of BM-derived Endothelial Progenitor Cells (EPCs) to the wound site [73]. The effect of Low Level Laser Therapy (LLLT) on the amount of factors secreted by gingival fibroids indicates that the rate of proliferation Fibroblasts and production of bFGF as well as 1-IGF factors were significantly increased in the LLLT groups compared with the control group, while the level of IGFBP3 factor did not show a significant increase [74-77].

Discussion and Conclusion

In diabetic rats with growth factors such as VEGF and TGF-1β at the wound site It was significantly reduced in the normal group, increased after treatment with viscous, and viscous caused a significant decrease in -iNOS, COX-2, NF factors. KB, which is increased in diabetes, becomes normal even compared to the control group. EGE entices the production of clinidine and integrin B1 and the joining of the two to it also makes it easy. We suspect that one of the signaling pathways for wound healing is EGF-Kindlin-1-integrinB1-FAK. EGF also changes the cell skeleton by acting on actin, although the presence of kindline is essential for this effect and can be said to be effective in wound healing.

Atrocarpine causes growth and migration of fibroblasts in laboratory conditions based on signaling in the pathway of JNK and P38. Also, *vivo* increases the cell marker for keratinocytes and the marker for cell division, and it can generally be concluded that atrocarpine has an effect on wound healing and does not affect events such as fibrosis and scarring.

Finally, for the treatment of diabetic wounds, new stem cell-based therapies can be used, which have been the subject of much research. This article introduces and briefly reviews new stem cell-based therapies.

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