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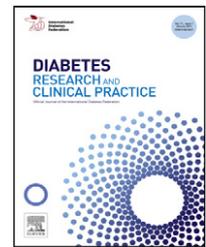
Review

Progress in stem cell therapy for the diabetic foot

Xiao-Yan Jiang, De-Bin Lu, Bing Chen *

Department of Endocrinology, Southwest Hospital, Third Military Medical University, Chongqing 400038, China

ARTICLE INFO

ABSTRACT

The diabetic foot is a common and severe complication of diabetes comprising a group of lesions including vasculopathy, neuropathy, tissue damage and infection. Vasculopathy due to ischemia is a major contributor to the pathogenesis, natural history and outcome of the diabetic foot. Despite conventional revascularization interventions including angioplasty, stenting, atherectomy and bypass grafts to vessels, a high incidence of amputation persists. The need to develop alternative therapeutic options is compelling; stem cell therapy aims to increase revascularization and alleviate limb ischemia or improve wound healing by stimulating new blood vessel formation, and brings new hope for the treatment of the diabetic foot.

Contents

1. Introduction

The incidence of diabetes mellitus is increasing globally and diabetic foot disease represents one of the most common and severe complications, affecting 15% of those with diabetes. Based on the World Health Organization definition, the diabetic foot (DF) includes infection, ulceration, and/or destruction of deep tissue associated with various degrees of peripheral vascular disease, neurologic abnormalities, and/or metabolic complications in the lower limb. Diabetic vasculopathy is typically a multi-segmental diffuse lesion and many blood vessels may be affected. Complications associated with diabetic

vasculopathy are commonly grouped into two categories: macrovascular and microvascular lesions, and are the major causes of morbidity and mortality in patients with DF.

Those with diabetes have a 12–25% lifetime risk of developing a foot ulcer [1,2], with 5–8% requiring major amputation within 1 year [3–5]. Foot ulceration precedes approximately 85% of lower extremity amputations [6,7].

Numerous factors such as repeated trauma, ischemia and infection, and intrinsic factors that lead to impairment of wound healing may result in the development of diabetic foot ulceration. It is estimated that ischemia may contribute to 30–40% of diabetic foot ulcers (DFUs). Diabetic patients with ischemic foot ulcers have the worst prognosis of all chronic skin wound patients. Consequently, improvement of blood supply to the ischemic limb is a treatment for DFUs.

General surgical procedures to improve lower-extremity ischemia in diabetics have been extensively practiced; however, has limitations. This is because of the widespread and distal location of vascular obstruction, in addition to the presence of multiple comorbidities. Bypass surgery and endovascular interventions are complementary techniques for revascularization in diabetic patients with non-healing ulcers [8]. By-pass graft surgery is used for long occlusions and is performed on distal arteries, such as the dorsalis pedis artery, since atherosclerosis mainly affects the infra-popliteal arteries [9,10]. According to a national vascular registry-based survey with more than 5000 patients, patency rates after crural and pedal bypass are similar for diabetic and non-diabetic individuals, whereas leg salvage rates are worse in those with diabetes [11]. Many patients with DFUs experience amputation more than once in their lifetime due to lack of effective interventions. Therefore, there has been an increased interest in novel therapies for the treatment of DFUs that have been refractory to standard treatment.

The potential use of stem cell-based therapies represents a promising therapeutic approach for DF. The DF is ischemic, and poor arterial flow reduces the blood supply to the ulcerated area resulting in reduced oxygenation, nutrition and healing. Autologous stem cell transplantation is a mechanism whereby stem cells can preferentially locate at damaged tissue sites to induce angiogenesis, and regenerate the epidermis. Healing of DFUs will be enhanced and the pain induced by tissue ischemia may be relieved. In the short-term, patients can avoid amputation or reduce the extent of amputation. Long-term effects may include a decrease in recurrence of ulceration and improvement in quality of life.

Here, we review the potential role of stem cells as new therapeutic agents in the treatment of DF.

2. The theory of stem cell therapy in DF

Stem cells and progenitor cells have a potential therapeutic role to induce angiogenesis and improve vascularisation of the ischemic limb so that perfusion increases sufficiently for wound healing to occur, relieving pain, and ultimately saving the limb.

2.1. Characteristics of stem cells

Self-renewal and multi-differentiation potential are two main characteristics of stem cells. In vitro, stem cells and progenitor cells possess the ability to self-renew and differentiate into organ-specific cell types; in vivo, transplantation of these cells may reconstitute an organ system. These two functional characteristics of stem cells show great promise for use in a variety of cell-based therapies, including diabetic foot disease. The self-renewal of stem cells means that they can maintain their characteristics after generating daughter cells through mitosis. Their plasticity means that stem cells could differentiate into various functional cells in a different microenvironment or regulatory system, and can repair damaged or dysfunctional tissues. Theoretically, vascular regeneration based on stem cell implantation could be an effective strategy to treat diabetic foot disease. This possibility is being evaluated through experimentation and medical practice.

2.2. Types of stem cells

There are two types of stem cell: embryonic stem cells (ES cell) and post-natal (or adult) stem cells. ES cells, as their name suggests, are derived from the embryo, more specifically, from the blastocyst's inner cell mass. ES cells are totipotent stem cells with the ability to differentiate into all types of cells, making them more suitable for the treatment of the complicated pathological changes that occur in DF. In addition, these cells tend to have a strong proliferative capacity and a low differentiation maturity. However, tumor cell lines are also easily created, having the characteristics of rapid proliferation and low differentiation. Further, immune rejection and ethical issues are real obstacles facing clinical application of these techniques. Therefore, embryonic stem cell therapy for DF is rarely carried out at present.

Adult stem cells thus are the preferred candidates for therapeutic approaches, particularly as there is no ethical controversy and the cells can be isolated in appropriate amounts from several sources. According to their tissue origin, adult stem cells can be divided into hematopoietic stem cells (HSCs), mesenchymal stromal stem cells (MSCs), neural stem cells, muscle stem cells and so on [12]. Adult stem cells exist in many tissues and vary in their potential to differentiate, thus representing an important therapeutic opportunity in regenerative medicine.

2.3. Sources of stem cells

The source of stem cells should be considered according to their intended purpose, that is, for experimental or therapeutic use. Currently, bone marrow is considered to be the most accessible and enriched source of stem cells for widespread medical treatments. It has previously been shown that a combination of bone marrow stroma-derived hematopoietic (HSC) and mesenchymal (MSC), stem cells can accelerate chronic wound healing in patients with DF [13].

2.4. Stem cells and the DF

Promising results in the treatment of DF have been achieved by administering stem cells either via intramuscular or intra-arterial injection into the diseased lower limb or by direct application over the wound [14]. Many human trials have shown intramuscular injection to be the preferred mode of

Table 1 – Selected clinical studies using stem cells in the treatment of diabetic foot disease.

Reference	Condition	Cell type	Approach administration	Dosage	Outcome
Gabr [44]	CLI	BM-MNCs	Intramuscular injection	1.11×10^9	Limb perfusion↑ ABI↑
Kawamura [46]	CLI and DFUs	PB-MNCs	Intramuscular injection	$3.6 \pm 2.9 \times 10^7$ or $4.8 \pm 4.2 \times 10^7$	Blood flow↑ Ischemic limb rescue↑
Huang [47]	CLI	PB-MNCs	Intramuscular injection	3×10^9	Blood flow recovery↑ New vessels formation↑
Bartsch [45]	DFUs	BM-MNCs	Intraarterial and intramuscular combined injection	157×10^6	Ulcer healing Walking distance↑ Blood circulation↑
Vojtassak [60]	DFUs	BMSCs	Topical application	3×10^6	Ulcer healing

CLI, critical limb ischemia; BM-MNCs, bone marrow mononuclear cells; ABI, ankle brachial index; DFUs, diabetic foot ulcers; PB-MNCs, peripheral blood mononuclear cells; DF, diabetic foot; BMSCs, bone marrow-derived mesenchymal stem cells.

administration for diabetic critical limb ischemia (CLI), while topical application [15] and injection into the wound periphery [16] may be safer and more appropriate for ultimate wound closure in patients with DFUs (Table 1). In addition, stem cells combined with an appropriate scaffold are another choice for ischemic refractory skin ulcers. For example, using collagen matrix impregnated with bone marrow stem cells as a scaffold biomaterial for regeneration has been shown to promote the repair of chronic and acute wounds, especially if treated at early stage [17–19].

Numerous stem/progenitor cell populations from a variety of sources have been proposed for the treatment of DF. Both unselected bone marrow-derived mononuclear cells (BM-MNCs), which include stem/progenitor cells and several other cell types, and endothelial progenitor cells (EPCs), a subpopulation of BM-MNCs, display regenerative potential in ischemic tissue and could potentially be used to treat DF.

EPCs aid neovascularization by secreting angiogenic growth [20,21]. In some pathological conditions including diabetic foot ulceration, ischemic stimulation causes proliferation, migration, and mobilization of EPCs. EPCs isolated from the mononuclear-cell fraction of human peripheral blood [21] and have been incorporated into the focus of neovascularization. EPCs display an endothelial-like phenotype and these cells appear to be particularly well suited for therapeutically modifying the microcirculation in ischemic tissues. Because EPCs target sites of damage and promote vascular integrity, they not only mediate repair of injured tissue but also bring about reperfusion of ischemic regions [22]. Accumulating evidence shows the ability of mobilized EPCs to repair injured vessels in animal models [23–26]. Kalka et al. transplanted ex vivo-expanded human EPCs into athymic nude mice with hind limb ischemia and showed recovery of blood flow, enhanced capillary density, and 60% limb salvage, compared with 7% in controls [27]. These experimental findings indicate that both cultured and freshly isolated human EPCs have therapeutic potential in peripheral vessel disease. However, research suggest that frequency of EPC mobilization of bone marrow depends on aging or concomitant disease [28]. It has been reported that there is a decrease in the number of EPCs, and functional impairment in proliferation, adhesion and angiogenesis of EPCs in diabetic patients. As a consequence, EPC dysfunction may produce fewer endothelial cells and reduce vascular regenerative potential [29–31]. Specifically, EPCs of diabetic origin have shown a reduced ability to integrate into

endothelial cell tubes in vitro compared with EPCs of non-diabetic origin [32]. EPCs isolated from diabetic patients for autologous cell transplantation may retain their dysfunctional characteristics in vivo and as a consequence display a reduced capacity to improve neovascularization [33,34]. This makes diabetic patients with peripheral vascular complications more difficult to treat with EPCs.

Unselected BM-MNCs, which include several stem/progenitor cell populations as well as many other cell types, have also been used successfully in the treatment of ischemic limb disease. Local autologous BM-MNC implantation has been demonstrated to induce therapeutic angiogenesis in experimental ischemic limb models [35–37]. With intra-arterial administration of BM-MNCs, stem cells can reach the border zone region of maximum ischemia [38–40]. Stamm et al. found that BM-MNCs could promote reconstitution of local blood vessels and capillaries following transplantation into the infarcted limbs [41]. Interestingly, BM-MNCs derived from diabetic rats also showed good potency in the production of angiogenic factors and endothelial differentiation. Hirata et al. examined the angiogenic effect induced by autologous bone marrow cell implantation in the ischemic hindlimbs of diabetic and non-diabetic rats. They found no difference between diabetic and non-diabetic rats in the release of angiogenic factors or endothelial differentiation from bone marrow cells in vitro [42]. Therefore, therapeutic angiogenesis induced by bone marrow cell implantation could be a safe and effective treatment for ischemic limb disease in diabetic patients.

On the basis of these results in animals, Tateishi-Yuyama started the first clinical trial to test cell therapy using autologous BM-MNCs in patients with ischemic limbs. The initial pilot study was a randomized controlled trial involving 25 patients with unilateral limb ischemia; the patients were considered unsuitable for surgical revascularization and therefore treated with autologous BM-MNC injections in the gastrocnemius of the ischemic leg. After 24 weeks, a significant increase in transcutaneous oxygen pressure (TcO_2) and ankle-brachial pressure index (ABI), relief from rest pain, and pain-free walking time without any important adverse reaction were recorded in all patients. The second part of the study was a randomized controlled trial in 22 patients with bilateral limb ischemia who were randomized to receive BM-MNC implantation in one leg and peripheral blood mobilized mononuclear cells (PB-MNCs) as a control in the other. Symptoms improved significantly in the BM-MNC-injected leg and a slight clinical improvement was

also seen in the control leg [43]. Subsequently, many researchers have reported a therapeutic effect of mononuclear cell transplantation of autologous bone marrow in ischemic lower extremity vascular disease. More recently, a prospective pilot clinical trial reported that BM-MNCs obtained by aspiration of 300 ml of bone marrow and injected intramuscularly into affected muscles significantly improved the clinical symptoms of the patients with limb ischemia [44].

Autologous BM-MNC transplantation has yielded encouraging results not only in the treatment of peripheral arterial disease, but also in patients with DF. Bartsch et al. reported rapid healing of therapy-refractory DF using transplantation of autologous bone marrow stem cells. After administration of BM-MNCs, the ulcer healed completely within 8 weeks and, after 6 months, walking distance increased by >100%, arterial blood circulation at rest increased by 23% and reactive hyperaemia by 56%. This case confirmed the regenerative potential of adult BM-MNCs in patients with DF [45].

Autologous PB-MNC transplantation has also been used in clinical trials in the treatment of critical lower limb ischemia of diabetic patients [46,47]. Huang et al. showed a significant improvement in many clinical manifestations [47], including lower limb pain, pain-free walking distance, diabetic foot ulcers and angiographic scores. Surprisingly, they also found that transplantation of PB-MNCs mobilized granulocyte colony stimulate factor (G-CSF) and this may improve blood glucose metabolism. The level of plasma glucose after cell transplantation was decreased in the transplant group of patients compared with controls.

Studies into stem cell therapy for the diabetic foot have been increasingly and based on a PubMed literature search, there are now more than one hundred papers describing this treatment. These studies show that stem cell therapy has a significant therapeutic effect with general remission of cold sensation and pain (83–100%), improvement of ABI (44–92%) and preservation of limb (78–85%). BM-MNC and PB-MNC transplantation derived from adult autograft are both suitable adoptive methods in the treatment of the DF.

MSCs are a stem cell population found in nearly all adult tissues and organs, including bone marrow, adipose tissue, umbilical cord blood, peripheral blood and other solid organs, such as liver, spleen and lung [48–50]. MSCs resemble multipotent adult stem cells that are able to differentiate into various mesodermal cell lineages, including osteocytes, chondrocytes and adipocytes. MSCs are also able to induce angiogenesis both in vivo [51] and in vitro [52]. Kinnaird et al. demonstrated that MSCs secrete a large number of arteriogenic and angiogenic cytokines that contribute to collateral remodelling of the ischemic limb via paracrine mechanisms [53]. Reyes et al. reported that mesenchymal stem cells from human postnatal bone marrow had the ability to differentiate into angioblast and vascular endothelial cells and then form blood vessel-like structures, giving them the ability to function as mature endotheliocytes, which can contribute to neoangiogenesis in vivo in wound healing [54]. Al-Khaldi et al. reported the ability of autologous MSC implantation to promote collateral formation and surrounding tissue repair in an animal model of chronic limb ischemia [55]. These examples of experimental medicine have set the foundation for further clinical practice with MSC's.

BMSCs are multipotent stem cells capable of differentiating into numerous cell types, including fibroblasts, chondrocytes, osteoblasts, adipocytes, cardiomyocytes, vascular endothelial cells, neurons, hepatocytes, epithelial cells and other tissues of mesenchymal origin. BMSCs also secrete a large number of growth factors and cytokines that are critical to repair the injured tissues, making them attractive as therapeutic agents for DF. Treatment with BMSCs either systemically or locally at the wound site improves healing of diabetic wounds in rats [56]. Intravenous injection of BMSCs has been shown to significantly increase collagen levels in diabetic wounds and increase wound-breaking strength [56]. Injection of BMSCs has also been shown to increase transforming growth factor (TGF-beta), keratinocyte growth factor (KGF) epidermal growth factor (EGF), platelet-derived growth factor (PDGF-BB) and vascular endothelial growth factor (VEGF) [56]. In addition to these paracrine effects, BMSCs can help to heal diabetic wounds through their ability to differentiate [57] and regenerate damaged epithelium through differentiation and fusion [58]. Although BMSCs were not found in the vascular structures of diabetic wounds, it was reported that, after BMSC treatment, there was increased capillary density, suggesting that BMSCs play a very important role in promoting angiogenesis related to successful wound healing [57,58]. Another rat diabetic skin wound model suggested that transplanted BMSCs could be retained at wound sites during the healing process and subsequently promote wound healing through angiogenesis [59]. Autologous BMSCs have shown efficacy in the treatment of the non-healing diabetic ulcer [52]. Autologous biografts composed of skin fibroblasts seeded on biodegradable collagen membranes in combination with autologous BMSCs were successfully used to close and heal diabetic foot ulcers [60]. These data suggest that cell therapy based on BMSCs has the potential to promote healing in diabetic ulcers.

To compare the safety, feasibility and efficacy between BMSCs and BM-MNCs in the treatment of diabetic CLI and foot ulcers, our team carried out a double-blind, randomized and controlled trial [61] which not only confirmed our earlier work showing that both BMSCs expand ex vivo and that BM-MNCs are relatively safe and efficient in the treatment of diabetic CLI and foot ulcers, but also showed that autologous transplantation of BMSCs may be more effective in increasing lower limb perfusion and promoting foot ulcer healing in diabetic CLI. Our first case report was a fifty-six year old man with CLI for thirteen years. Following conventional treatment, including glucose control, blood pressure control, anti-infection, anti-coagulation, nerve nourishing and blood vessel distension, bone marrow (about 300 ml) was aspirated from the patient's iliac crest under epidural anesthesia and collected into plastic bags containing heparin. The bone marrow aspirate was processed by density gradient centrifugation, and the resulting fraction of BM-MNCs was suspended in normal saline and then injected intramuscularly. After transplantation, symptoms ameliorated, avoiding amputation. There were also no adverse events during the 24 week follow-up period. The treatment appears to work better in younger patients, and those with tighter control of risk factors, such as hyperglycemia, hypertension, hyperlipemia and smoking, tend to have a more satisfactory outcome. Nevertheless, the effects seen in

patients receiving autologous stem cells transplantation more than once are superior to those seen in patients receiving only one transplantation. This also raised a new question: since transplantation uses at least 300 ml of bone marrow, further work was required to reduce the amount of bone marrow. In 2006, we began a new clinical trial amplifying BMSCs in vitro prior to autologous transplantation. In this study, the mount of bone marrow was reduced to only 30 ml, making the procedure more acceptable to patients. Based on our findings, we believe that stem and progenitor cells derived from bone marrow can be used to repair DF. The clinical outcomes appear encouraging, but much work remains to be done. The mechanisms by which autologous stem cells induce angiogenesis are unclear and the long term safety and efficacy has not been adequately explored.

The limited availability of BMSCs has hindered the progress and development of tissue engineering. Recently, adipose tissue stem cells (ASCs) and their secretory factors have been investigated as a substitute for BMSCs and appear to offer a potential solution to diabetic ulcers. ASCs can be derived from human adipose tissue, which can be harvested by direct excision or, more commonly, from lipoaspirate operation. Research over the past decade has shown that these cells have extensive proliferative capacity and are able to undergo differentiation along both mesenchymal lineages (adipogenesis, chondrogenesis, osteogenesis) [62–64] and non-mesenchymal lineages (endothelial, smooth muscle and neurogenic) [65,66], confirming the transdifferentiation ability of ASCs. The ability of ASCs to differentiate down different mesenchymal lineages has led to interest in their clinical use. Currently, several studies have evaluated the potential therapeutic effects of ASCs on vascular ischemia and wound healing. Kim et al. compared the therapeutic potential by transplantation of equal numbers of ASCs or BMSCs in a nude mouse model of hindlimb ischemia. They found that ASCs showed better biological effects of increased blood flow, although both ASC and BMSC injections significantly increased blood flow in the ischemic leg. These results suggest that ASC transplantation is more potent in therapeutic angiogenesis than BMSC transplantation [67]. In addition, local implantation of ASCs has been found to be effective in supporting epidermal healing in a porcine full-thickness wound model [68], as well as in rats, in which the survival area of ischemic skin flaps was significantly increased by local injection of autologous ASCs [69]. Furthermore, the potential for ASCs to enhance wound repair has also been demonstrated in diabetic animal models [70–72] but the exact mechanisms of wound healing in diabetic animal with skin ulcers remain unclear. There is some evidence to show that ASCs improve the healing rate of diabetic mice by secreting growth factors and cytokines, enhancing granulation tissue formation, capillary formation, and epithelialization in healing-impaired wounds [70]. In another study, ASCs improved wound healing rate in non-diabetic mice by increasing angiogenesis and collagen accumulation in the wound tissue [73]. Moreover, Kim et al. showed that ASCs enhanced secretion of type 1 collagen by human dermal fibroblasts by regulating mRNA levels of extracellular matrix proteins [74]. Surprisingly, another study describing a new stereological method showed that ASCs can promote skin wound healing, but not by increasing the volume of collagen fibers or the length of the vessels in the wound tissue in diabetic rats [72]. This controversial conclusion may be due to differences between the methods used to evaluate angiogenesis and collagen accumulation in the wound tissue.

It is important to recognize that there is no animal model that perfectly mimics the clinical, non-healing nature of human DFUs. There is much positive experimental data, accumulated from the studies outlined above in experimental models, but clinical studies are needed. The first study into human peripheral vascular disease described multiple intramuscular injections of cultured autologous ASCs in six patients with Buerger's disease [75]. Endpoints of this study included maximal and pain-free walking distance, toe-brachial and ankle-brachial pressure indices, laser Doppler cutaneous flow, and ulcer healing. After 24 weeks treatment there was improved clinical performance and less resting pain in these patients. Intramuscular injection of ASCs has also recently shown clinical efficacy in patients with diabetic foot; rest pain score, peak walking time, and vascular collateral networks by 6 months after ASC injections [75].

From a practical point of view, the role of ASCs in increasing revascularization and improving wound healing in DF has been decisive; however, there is still a need for further clinical trials to confirm both the safety and efficiency of ASCs.

The human umbilical cord blood (UCB) is a rich source of hemopoietic stem cells and can serve as another source of MSCs for use in wound healing. Many laboratory and clinical data have proved the validity of UCBs for transplantation. One study showed that local administration of UCB-derived MSCs promoted cutaneous wound healing in an immunodeficient Balb/C SCID mouse model [76]. Moreover, Tark et al. used the diabetic mouse as a model of delayed wound healing to observe the effects of human UCB-derived MSCs on wound healing, with no differences seen when administered either via direct local injection or indirect systemic injection [77]. The same encouraging results were also seen in two preliminary case studies using cord blood cells along with fibrin platelet glue for wound repair [78]. However, potential immunological rejection should be considered in clinical application due to the allogenic source of UCB-derived MSCs.

In brief, adult stem cell therapy is a relatively safe and effective method for repair of both vascular disease and wound healing; however, we also realize the current limitations for MSCs therapy in DF. There is ambiguity concerning the repair of neuropathy and tissue defects of the diabetic foot [79]. Moreover, much of the available information suggests that proliferation, paracrine, anti-apoptotic properties, and myogenic differentiation of both BMSCs and ASCs derived from diabetic animal models are significantly impaired [80,81]. Furthermore, although MSCs are present throughout life, their total number is inversely correlated to the age of the patient and also depends upon the site of extraction and systemic disease state. Because isolated primary MSCs are low in number, in vitro expansion is necessary. However, the expansion potential is limited. After 2–3 months, the proliferation rate of MSCs declines until they ultimately reach a senescent state and this is accompanied by an enlarged morphology, reduced expression of surface markers, and decreased differentiation potential [82]. It is suggested that long-term culture has a major impact on the composition of MSC preparations.

3. Safety and efficiency considerations

In order to obtain the required cell numbers for therapeutic applications, there is an occasional need for G-CSF for mobilization or in vitro cell amplification because of the low reproductive activity of the stem cells. Cell amplification is a more primitive, simple operation and with lower-cost, which may overcome the aforementioned shortcomings. During this period, the developmental process of cellular aging is in line with replicative senescence. One purpose of cellular aging might be to protect the organism from tumor formation. Therefore, adult stem cells, such as autologous peripheral blood stem cells and autologous bone marrow stem cell transplantation, are the preferred method of therapy for DF at present. As few stem cells are actually isolated from either peripheral blood or bone marrow, Meng et al. found a combination of G-CSF stimulation and autologous transplantation of BM-MNCs improved blood flow in ischemic limb in diabetic rabbits [83]. There was an increase in the quality and quantity of the therapeutic stem cells, and further improvement in therapeutic effect with autologous bone marrow stem cell transplantation. Currently, techniques for the isolation and in vitro expansion of BMSCs range from aspiration and density-gradient centrifugation, to simple, direct plating methods, to size sieving [84,85]. The preferred method of separation, purification and amplification of autologous stem cells is expected to improve the quality and quantity of the therapeutic stem cells and their therapeutic effect, and also decrease trauma and simplify the operation procedures. In addition, in vitro culture optimizes stem cell growth and contributes to greater clinical response [86].

4. Conclusion

DF is characterized by a chronic advanced stage of hyperglycemia and treatment includes improving foot blood circulation, controlling infection and hyperglycemia associated with endothelial progenitor cell dysfunction and reducing neovascularization in response to tissue ischemia. Stem cell transplantation to treat the diabetic foot is a new treatment for DF, and is becoming more widely applied. Some patients have benefited from this technology. There are no serious complications or side effects. Although the therapeutic effect and safety of stem cell therapy for the diabetic foot has been initially confirmed, its therapeutic mechanisms, effects, and standard generalization still require further research.

Conflict of interest

There are no conflicts of interest.

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