Efficacy of Cellular Therapy for Diabetic Foot Ulcer: A Meta-Analysis of Randomized Controlled Clinical Trials

Ye Zhang¹, Hong Deng¹, and Zhouping Tang¹

Abstract
Diabetes mellitus is a widely spread chronic disease with growing incidence worldwide, and diabetic foot ulcer is one of the most serious complications of diabetes. Cellular therapy has shown promise in the management of diabetic foot ulcer in many preclinical experiments and clinical researches. Here, we performed a meta-analysis to evaluate the efficacy and safety of cellular therapy in the management of diabetic foot ulcer. We systematically searched PubMed, MEDLINE, EMBASE, and Cochrane Library databases from inception to May 2017 for randomized controlled trials assessing the efficacy of cellular therapy in diabetic foot ulcer, and a meta-analysis was conducted. A total of 6 randomized controlled clinical trials involving 241 individuals were included in this meta-analysis. The results suggested that cellular therapy could help accelerating the healing of diabetic foot ulcer, presented as higher ankle-brachial index (mean difference = 0.17, 95% confidence interval [CI] = 0.11 to 0.23), higher transcutaneous oxygen pressure (standardized mean difference [SMD] = 1.43; 95% CI, 1.09– to 1.78), higher ulcer healing rate (relative risk [RR] = 1.78; 95% CI, 1.41 to 2.25), higher amputation-free survival (RR = 1.25; 95% CI, 1.11 to 1.40), and lower scale of pain (SMD = −1.69; 95% CI, −2.05 to −1.33). Furthermore, cellular therapy seemed to be safe, with no serious complications and low risk of short-term slight complications. Cellular therapy could accelerate the rate of diabetic foot ulcer healing and may be more efficient than standard therapy for diabetic foot treatment.

Keywords
diabetic foot, cell transplantation, meta-analysis, diabetes mellitus

Introduction
The prevalence of diabetes mellitus (DM) worldwide is gradually increasing these years and this figure is predicted to continue growing, resulting in more than 360 million patients with DM in 2030.¹ Although it is manageable, diabetic foot ulcer is one of the most common and serious complications secondary to DM. Statistical data have indicated that 2% to 3% of patients with DM were suffering from active foot ulcer and a quarter of DM patients would develop foot ulcer throughout their lifetime.²,³ Diabetic foot ulcer not only affects the physical health of patients, preceding 85% of major lower limb amputations in patients with DM,⁴ but also has a significant effect on their social function and mental health.⁵ Furthermore, the patients and society have to bear the substantial financial burden from treatment and care of diabetic foot ulcer.⁶ The diabetic foot ulcer, in which neuropathy and peripheral vascular disease act as major pathogenic factors, is featured by the typical dysfunctions of wound healing, including coagulation, hemostasis, inflammation, proliferation, and remodeling.⁷ Nowadays, the conventional standard therapy for diabetic foot ulcer consists of glucose-level control, infection management, high pressure remission, and dressings. However, the effectiveness of conventional standard therapy is not satisfying enough. Even with comprehensive treatment programs, the cure rate of diabetic foot ulcer in 12 to 20 wk was only as low as 24% to 30%. More seriously for patients, they are at high risk of serious complications, such as cellulitis, osteomyelitis, amputation, and others.⁸–¹⁰

¹ Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Submitted: July 17, 2017. Revised: August 14, 2017. Accepted: September 3, 2017.

Corresponding Author:
Zhouping Tang, Department of Neurology, Tongji Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology, Jiefang Boulevard, No.1095, Wuhan, Hubei 430030, China.
Email: ddjzp@163.com
Cellular therapy, characterized by using cells from diverse sources, with self-renewing potential and multidifferentiation ability, has shown promise in the management of diabetic foot ulcer. Accumulating evidences from basic science studies and clinical trials have pointed out that cellular therapy could focus on multiple facets during diabetic foot ulcer healing through cell proliferation, vascularization, neurorestoration, inflammation regulation, exosomes synthesis, and others.\(^{11,12}\) Some clinical studies have demonstrated that cellular therapy represents an effective treatment for diabetic foot ulcer. However, reliable evidence on the clinical efficacy remains to be addressed. Therefore, the present study evaluates and synthesizes clinical evidence and aims to critically estimate the therapeutic efficacy of cellular therapy for diabetic foot ulcer compared to standard therapy.

**Research Design and Methods**

**Search Strategy**

An extensive literature search restricted to the English language was carried out up to May 2017 using the PubMed, MEDLINE, EMBASE, and Cochrane Library databases. The search terms we used were (stem cells, mononuclear cells [MNCs], and progenitor cells) and (diabetic foot, diabetic ulcer, and diabetic wound). In addition, we examined the reference list of all relevant articles.

**Selection Criteria**

Publications were screened independently by 2 authors. Studies meeting the following criteria were included: (1) randomized controlled trials comparing cellular therapy with standard therapy conducted in humans, (2) patients with diabetic foot ulcer, (3) full articles reporting the clinical efficacy. Studies that carried out in animals, lacking standard therapy as controls or lacking sufficient data of interest, were excluded. Referring to duplicate publications, the latest or larger one was included in the analysis.

**Data Extraction and Quality Assessment**

Effectiveness outcomes including ankle-brachial index (ABI), amputation-free survival (AFS), transcutaneous oxygen tension pressure (TcPO\(_2\)), ulcer healing rate at 12 to 24 wk posttransplantation, and pain scales and the adverse events representing safety profile occurring during each trial were extracted from all the included studies by 2 authors independently.

The risk of bias of the included clinical trials was assessed in accordance with the modified Jadad rating scales.\(^{13}\) Randomization, blinding, and follow-up were rated as yes, no, and not reported.\(^{13}\)

Discrepancies about literature search, study selection, data extraction, and quality assessment between the 2 authors were settled by discussion and consensus or determined by a senior author.

**Results**

**Literature Search**

The initial literature search yielded a total of 528 articles. After deletion of 379 duplicates, the remaining abstracts were carefully screened. One hundred twenty studies were excluded for various reasons such as reviews, animal experiments, and case reports. Of all the 29 remaining studies, 6 randomized controlled clinical trials meeting all criteria and providing a clear description data were selected.\(^{14-19}\) The screening process of the trials is shown in Fig. 1.

**Fig. 1. Flow chart of study selection.**

**Statistical Analysis**

Extracted data were entered and processed by Stata statistical software, version 12.0 (StataCorp, College Station, TX, USA). In order to estimate the clinical efficacy, mean difference and 95% confidence intervals (CIs) were calculated for quantitative variables and relative risk, and 95% CIs were calculated for dichotomous variables. Two-sided tests and a significant heterogeneity level of \(P < 0.05\) were used in all analyses. Heterogeneity was estimated by the \(I^2\) statistics, with values of 25%, 50%, and 75% being considered low, moderate, and high heterogeneity, respectively. When high heterogeneity was present, weighted mean difference and random effects model were applied to minimize heterogeneity; otherwise, the fixed effects model was used. We also performed Egger’s intercept test and Begg’s rank correlation analysis to estimate publication bias and conducted sensitivity analysis to examine the reliability of outcomes.

**Study Characteristics**

After selection, 6 randomized controlled clinical trials involving 241 patients were included. Considering the cell
type used in each study, 2 studies\textsuperscript{14,19} used mesenchymal stem cells from bone marrow or umbilical cord, 3 studies\textsuperscript{15,17,18} used MNCs from bone marrow or peripheral blood, and 1 study\textsuperscript{16} used bone marrow-derived mesenchymal stem cells (BMMSCs) and bone marrow-derived MNCs (BMMNCs). Details of the study characteristics are listed in Table 1.

### Quality Assessment

As evaluated by modified Jadad rating scales,\textsuperscript{13} 3 included studies were high-quality randomized clinical trials,\textsuperscript{14,16,18} Quality assessment outcomes of all the included studies are presented in Table 2. All the included studies were described as randomized clinical trials, and 3 studies reported adequate sequence generation such as using random number table,\textsuperscript{14} randomization table,\textsuperscript{16} or internet-based system.\textsuperscript{18} Allocation concealment was described only in 1 study.\textsuperscript{14} One study claimed to be double-blinded, but details of blinding were not reported in this study.\textsuperscript{16} All studies described the details of loss to follow-up.

### ABI

The ABI is defined as the ratio of the highest pressure detected by Doppler at the dorsalis pedis and posterior tibial arteries and the highest pressure at the brachial artery. The ABI provides such a great deal of information that it has become a routine measurement in the patients with diabetic foot ulcer. Five of the included studies\textsuperscript{15–19} involving 235 patients reported the ABI. Owing to no heterogeneity between studies ($I^2 = 0.0\%$, $P = 0.751$), fixed effects model was applied in meta-analysis. The outcomes revealed that ABI was significantly raised by cellular therapy (mean difference $= 0.17$, 95\% CI, 0.11 to 0.23; Fig. 2).

### Transcutaneous Oxygen Pressure (TcPO\textsubscript{2})

TcPO\textsubscript{2} is known to be an indicator of the local microcirculation and the degree of ischemia and is valuable to predict healing at various levels of foot ulcer.\textsuperscript{20,21} In the patients treated with cellular therapy, the TcPO\textsubscript{2} values significantly increased (standardized mean difference [SMD] = 1.43; 95\% CI, 1.09 to 1.78) in the analysis of 3 studies\textsuperscript{16,18,19} (Fig. 3).

### Pain Scale

Three trials reported the pain scale of patients with diabetic foot ulcer. Ozturk et al.\textsuperscript{18} used numerical pain rating scale which ranged from 0 to 10, 0 being no pain and 10 being maximum pain.\textsuperscript{22} In the randomized controlled trials conducted by Lu et al.\textsuperscript{16} and Huang et al.,\textsuperscript{15} rest pain scores on rating scales ranged from 0 for the best (completely
resolved) to 4 points for the worst condition (severe pain unresolved with paracetamol or nonsteroidal anti-inflammatory drugs). There was no heterogeneity among these studies ($I^2 = 0.0\%$, $P = 0.973$). The pain scale was significantly decreased (SMD = $-1.69$, 95% CI = $-2.05$ to $-1.33$) in the selected studies in the cellular therapy group (Fig. 4).

**Ulcer Healing Rate**

With regard to the efficacy of cellular therapy in contrast to the standard therapy, the relative risk of 3 trials$^{15,16,18}$ demonstrated a significant increase (relative risk [RR] = $1.78$, 95% CI = $1.41$ to $2.25$) in ulcer healing rate 12 to 24 wk after cellular therapy using a fixed effects model ($I^2 = 0.0\%$, $P = 0.449$; Fig. 5).

**AFS**

The combined end point of AFS was considered to be the best outcome assessment indexes for patients with diabetic foot ulcer.$^{23}$ Four studies$^{15–18}$ provided amputation data. With no heterogeneity ($I^2 = 0.0\%$, $P = 0.400$), calculations under fixed effects model revealed that cellular therapy significantly improved the AFS rate in patients with diabetic foot ulcer (RR = $1.25$, 95% CI = $1.11$ to $1.40$; Fig. 6).

**Adverse Events**

During 1 to 2 y long-time follow-up, no serious complications resulted from cellular therapy, such as rejection, allergic reactions, and tumorigenesis were observed.$^{14–19}$ No
Fig. 4. Forest plots for meta-analysis of pain scale comparing cellular therapy with standard therapy. Area of the symbols for each study (square) is proportional to study weight. The pooled standardized mean difference (fixed effects) and 95% confidence intervals are represented by the rhombus. Heterogeneity test across studies was significant ($I^2 = 0.0\%, \, P = 0.973$). CI, confidence interval; SMD, standardized mean difference.

Fig. 5. Forest plots for meta-analysis of ulcer healing rate comparing cellular therapy with standard therapy. Area of the symbols for each study (square) is proportional to study weight. The pooled relative risk (fixed effects) and 95% confidence intervals are represented by the rhombus. Heterogeneity test across studies was significant ($I^2 = 0.0\%, \, P = 0.449$). CI, confidence interval; RR, relative risk.

Fig. 6. Forest plots for meta-analysis of amputation-free survival comparing cellular therapy with standard therapy. Area of the symbols for each study (square) is proportional to study weight. The pooled relative risk (fixed effects) and 95% confidence intervals are represented by the rhombus. Heterogeneity test across studies was significant ($I^2 = 0.0\%, \, P = 0.400$). CI, confidence interval; RR, relative risk.
complications such as puncture site hematoma, pseudoaneurysm, arterial dissection, or cardiovascular or cerebrovascular events related to the transplantation procedure were detected.\textsuperscript{14–19} No infection, bleeding, or other complications arose from the microbiological condition of the cells were detected.\textsuperscript{14–19} Only 8 of 118 patients suffered from short-term episodes of slight pain after cell transplantation\textsuperscript{15,16} and 3 patients bled at the iliac crest after bone marrow aspiration.\textsuperscript{15,16}

\section*{Sensitivity Analysis}
Sensitivity analysis was performed by reestimating the outcome by removing 1 study in each turn and was indicative of the reliability of the outcomes. Sensitivity analysis did not identify any marked difference in the direction and magnitude of the mean difference and relative risk with respect to ABI, TcPO\textsubscript{2}, pain scale, ulcer healing rate, and AFS, indicating good reliability of the outcomes in this meta-analysis.

\section*{Publication Bias}
We assessed publication bias by Egger’s intercept test and Begg’s rank correlation analysis. The \( P \) values of the Egger’s test and Begg’s test were all greater than 0.05 for ABI (Begg’s test \( P = 1.000 \), Egger’s test \( P = 0.847 \)), TcPO\textsubscript{2} (Begg’s test \( P = 1.000 \), Egger’s test \( P = 0.549 \)), pain scale (Begg’s test \( P = 0.296 \), Egger’s test \( P = 0.309 \)), ulcer healing rate (Begg’s test \( P = 1.000 \), Egger’s test \( P = 0.975 \)), and AFS (Begg’s test \( P = 0.308 \), Egger’s test \( P = 0.302 \)), indicating no significant evidence of publication bias.

\section*{Discussion}
The purpose of the present study was to perform a meta-analysis to assess the efficacy and safety of cellular therapy in treatment of diabetic foot ulcer. Our study included 6 randomized controlled trials involving 241 patients and analyzed 5 end point indexes which were important in the long-term prognosis and quality of life of patients with diabetic foot ulcer. It was shown that cellular therapy was significantly associated with a higher ABI, a higher transcutaneous oxygen pressure, more reduction in pain, a decreased risk of amputation, and a higher proportion of healed ulcers, when compared with standard therapy. The complete ulcer healing rate and AFS in cellular therapy group is 1.78 and 1.25 times compared with standard therapy. The complete ulcer healing rate and AFS in cellular therapy group is 1.78 and 1.25 times compared with standard therapy. The complete ulcer healing rate and AFS in cellular therapy group is 1.78 and 1.25 times compared with standard therapy.

Lots of researches believed that paracrine secretion played a greater role in diabetic wound healing. Numerous studies have proven the high-level secretion of various growth factors and cytokines, such as epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), keratinocyte growth factor (KGF), insulin-like growth factor (IGF-1), transforming growth factor-\( \beta \) (TGF-\( \beta \)), vascular endothelial growth factor (VEGF), smooth muscle cell-derived growth factor-1\( \alpha \), interleukin-8 (IL-8), and angiopoietin-1.\textsuperscript{36–38} These growth factors and cytokines exert diverse therapeutic effects in diabetic wound healing including improving neovascularization, angiogenesis, regeneration, ameliorating inflammation, and interestingly, recruiting endogenous stem cells from the circulation for repair.\textsuperscript{39} Reyes et al. also observed that transplanted mesenchymal stem cells could be differentiated into angioblasts and vascular endothelial cells and then functioned as mature endothelialocytes, contributing to neoangiogenesis in diabetic foot ulcer model.\textsuperscript{40} However, differentiation may be of limited use as there is a low proportion of engraftment and differentiation.\textsuperscript{35,41}

MNCs are a group of cells consisting of several stem/progenitor cell populations and some other cell types. They are so abundant in peripheral blood and bone marrow that they can be collected directly for transplantation with no need for in vitro expansion. MNCs were found to promote local capillary and blood vessel reconstitution in infarcted
limbs in a study by Stamm et al.\textsuperscript{42} Sivan-Loukianova et al. reported accelerated epidermal healing and revascularization after MNC transplantation in a diabetic mouse wound healing model. During a 5 d observation period, an increase in vessel diameter was the main manifestation at early stages. Later, increases in vessel size and number both accounted for increased vascularization.\textsuperscript{43}

Studies also showed that endothelial progenitor cells (EPCs) from bone marrow or peripheral blood could proliferate, migrate, and be mobilized under ischemic stimulation in some pathological conditions.\textsuperscript{44,45} Accumulating evidence has proven their therapeutic ability in diabetic foot ulcer.\textsuperscript{46,47} Wound healing promotion and neovascularization were found by using embryonic stem cell–derived EPCs in Lee’s study.\textsuperscript{48} They found rapid reepithelialization of wounds and reformation of granulation tissue after transplantation in a wound healing model. After further exploration, they put forward the idea that secretion of growth factors and cytokines by EPCs, including EGF, bFGF, VEGF, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF), and platelet-derived growth factor-AA (PDGF-AA), may account for the main therapeutic effect.\textsuperscript{49} EPCs display endothelial-like characteristics, and their neovascularization effect seemed to be particularly suited in improving microcirculation in the management of diabetic foot ulcer. Taking the features of directed migration and vascularization into consideration comprehensively, EPCs not only play a part in tissue repair but also brought reperfusion into ischemic regions.\textsuperscript{48} Asahara et al. reported enhanced capillary density and recovery of blood flow after EPC transplantation in athymic nude mice with hind limb ischemia.\textsuperscript{45}

As far as we know, this study is the first meta-analysis of randomized controlled trials comparing the clinical efficacy of cellular therapy in the management of diabetic foot ulcer. Limitations still existed in this study. First, the number of the included randomized controlled trials was small. Although there has been a growing number of studies reporting cellular therapy in diabetic foot ulcer, only a few studies fully meet our requirements. Second, the sample size and quality of the included studies remained a concern for the strength of the outcomes. Only 1 study contains more than 30 participants in each group. And information of allocation concealment was only reported in 1 study. Third was the variability of measurements and criterion of ulcer healing. Forth, baseline ulcer conditions that would affect the outcomes were not reported in all of the studies.

**Conclusions**

Compared to standard therapy, cellular therapy could help accelerate the healing of diabetic foot ulcer, which presents as higher ABI, TcPO\textsubscript{2}, ulcer healing rate, and lower scale of pain and amputation risk. These results need to be treated with caution, as the number of available randomized controlled studies and the follow-up duration were limited. More large-scale, well-designed randomized controlled studies with long follow-up duration are in urgent need to further examine the clinical value of cellular therapy in the management of diabetic foot ulcer.

**Ethical Approval**

Ethical Approval is not applicable.

**Statement of Human and Animal Rights**

This article does not contain any studies with human or animal subjects.

**Statement of Informed Consent**

There are no human subjects in this article and informed consent is not applicable.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research received funding from National Natural Science Foundation of China (No.81471201).

**References**

1. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract. 2011;94(3):311–321.
2. Boulton AJ. The pathway to foot ulceration in diabetes. Med Clin North Am. 2013;97(5):775–790.
3. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005;293(2):217–228.
4. Frykberg RG, Armstrong DG, Giurini J, Edwards A, Kravette M, Kravitz S, Ross C, Stavosky J, Stuck R, Vanore J. Diabetic foot disorders: a clinical practice guideline. American College of Foot and Ankle Surgeons. J Foot Ankle Surg. 2000;39(5 suppl):S1–S60.
5. Eldor R, Raz I, Ben Yehuda A, Boulton AJ. New and experimental approaches to treatment of diabetic foot ulcers: a comprehensive review of emerging treatment strategies. Diabet Med. 2004;21(11):1161–1173.
6. Brod M, Nikolajsen A, Weatherall J, Pfeiffer KM. The economic burden of post-prandial hyperglycemia (PPH) among people with type 1 and type 2 diabetes in three countries. Diabetess Ther. 2016;7(1):75–90.
7. O’Loughlin A, McIntosh C, Dinneen SF, O’Brien T. Review paper: basic concepts to novel therapies: a review of the diabetic foot. Int J Low Extrem Wounds. 2010;9(2):90–102.
8. Cavanagh PR, Bus SA. Off-loading the diabetic foot for ulcer prevention and healing. Plast Reconstr Surg. 2011;127(suppl 1):248s–256s.
9. Cavanagh PR, Lipsky BA, Bradbury AW, Botek G. Treatment for diabetic foot ulcers. Lancet. 2005;366(9498):1725–1735.
10. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, LeFrock JL, Lew DP, Mader JT, Norden C,
et al. Diagnosis and treatment of diabetic foot infections. Plast Reconstr Surg. 2006;117(7 Suppl):212s–238s.
11. Yang M, Sheng L, Zhang TR, Li Q. Stem cell therapy for lower extremity diabetic ulcers: where do we stand? Biomed Res Int. 2013;2013:462179.
12. Blumberg SN, Berger A, Hwang L, Pastar I, Warren SM, Chen W. The role of stem cells in the treatment of diabetic foot ulcers. Diabetes Res Clin Pract. 2012;96(1):1–9.
13. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1–12.
14. Dash NR, Dash SN, Routray P, Mohapatra S, Mohapatra PC. Targeting nonhealing ulcers of lower extremity in human through autologous bone marrow-derived mesenchymal stem cells. Rejuvenation Res. 2009;12(5):359–366.
15. Huang P, Li S, Han M, Xiao Z, Yang R, Han ZC. Autologous transplantation of granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cells improves critical limb ischemia in diabetes. Diabetes Care. 2005;28(9):2155–2160.
16. Lu D, Chen B, Liang Z, Deng W, Jiang Y, Li S, Xu J, Wu Q, Zhang Z, Xie B, et al. Comparison of bone marrow mesenchymal stem cells with bone marrow-derived mononuclear cells for treatment of diabetic critical limb ischemia and foot ulcer: a double-blind, randomized, controlled trial. Diabetes Res Clin Pract. 2011;92(1):26–36.
17. Mohammadzadeh L, Samedanifard SH, Keshavarzi A, Alimo- mar K, Khayyam-Kia M, et al. Therapeutic outcomes of transplanting autologous granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cells in diabetic patients with critical limb ischaemia. Exp Clin Endocrinol Diabetes. 2013;121(1):48–53.
18. Ozturk A, Kucukardali Y, Tangi F, Erikci A, Uzun G, Bashe-kim C, Sen H, Terekeci H, Narin Y, Ozyurt M, et al. Therapeu- tical potential of autologous peripheral blood mononuclear cell transplantation in patients with type 2 diabetic critical limb ischemia. J Diabetes Complications. 2012;26(1):29–33.
19. Qin HL, Zhu XH, Zhang B, Zhou L, Wang WY. Clinical evaluation of human umbilical cord mesenchymal stem cell transplantation after angioplasty for diabetic foot. Exp Clin Endocrinol Diabetes. 2016;124(8):497–503.
20. Cao P, Eckstein HH, De Rango P, Setacci C, Ricco JB, de Donato G, Becker F, Robert-EBadi H, Diehn N, Schmiddi J, et al. Chapter II: diagnostic methods. Eur J Vase Endovasc Surg. 2011;42(Suppl 2):S13–S32.
21. Poredos P, Rakovec S, Guzic-Salobir B. Determination of amputation level in ischaemic limbs using tcPO2 measurement. Vasa. 2005;34(2):108–112.
22. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005;14(7):798–804.
23. Chung J, Timaran DA, Modrall JG, Ahn C, Timaran CH, Kirkwood ML, Bag MS, Valentine RJ. Optimal medical therapy predicts amputation-free survival in chronic critical limb ischemia. J Vasc Surg. 2013;58(4):972–980.
24. Badiavas EV, Falanga V. Treatment of chronic wounds with bone marrow-derived cells. Arch Dermatol. 2003;139(4):510–516.
25. Humpert PM, Bartsch U, Konrade I, Hammes HP, Morcos M, Kasper M, Bierhaus A, Nawroth PP. Locally applied mononuclear bone marrow cells restore angiogenesis and promote wound healing in a type 2 diabetic patient. Exp Clin Endocrinol Diabetes. 2005;113(9):538–540.
26. Rogers LC, Bevilacqua NJ, Armstrong DG. The use of marrow-derived stem cells to accelerate healing in chronic wounds. Int Wound J. 2008;5(1):20–25.
27. Jiang XY, Lu DB, Chen B. Progress in stem cell therapy for the diabetic foot. Diabetes Res Clin Pract. 2012;97(1):43–50.
28. Lobmann R, Schultz G, Lehnter H. Proteases and the diabetic foot syndrome: mechanisms and therapeutic implications. Diabetes Care. 2005;28(2):461–471.
29. Yager DR, Nwomeh BC. The proteolytic environment of chronic wounds. Wound Repair Regen. 1999;7(6):433–441.
30. Falanga V, Iwamoto S, Chartier M, Yufit T, Butmarc J, Kout-tab N, Shrayer D, Carson P. Autologous bone marrow-derived cultured mesenchymal stem cells delivered in a fibrin spray accelerate healing in murine and human cutaneous wounds. Tissue Eng. 2007;13(6):1299–1312.
31. Gnecczi M, Zhang Z, Ni A, Dzau VJ. Paracrine mechanisms in adult stem cell signaling and therapy. Circ Res. 2008;103(11):1204–1219.
32. Peng C, Chen B, Kao HK, Murphy G, Orgill DP, Guo L. Lack of FGF-7 further delays cutaneous wound healing in diabetic mice. Plast Reconstr Surg. 2011;128(6):673e–684e.
33. Kim SW, Zhang HZ, Guo L, Kim JM, Kim MH. Amniotic mesenchymal stem cells enhance wound healing in diabetic NOD/SCID mice through high angiogenic and engraftment capabilities. PLoS One. 2012;7(7):e41105.
34. Wu Y, Chen L, Scott PG, Tredget EE. Mesenchymal stem cells enhance wound healing through differentiation and angiogenesis. Stem Cells. 2007;25(10):2648–2659.
35. Uysal CA, Ogawa R, Lu F, Hyakusoku H, Mizuno H. Effect of mesenchymal stem cells on skin graft to flap prefabrication: an experimental study. Ann Plast Surg. 2010;65(2):237–244.
36. Usui ML, Mansbridge JN, Carter WG, Fujita M, Olerud JE. Keratinocyte migration, proliferation, and differentiation in chronic ulcers from patients with diabetes and normal wounds. J Histochto Cytochom. 2008;56(7):687–696.
37. Desta T, Li J, Chino T, Graves DT. Altered fibroblast proliferation and apoptosis in diabetic gingival wounds. J Dent Res. 2010;89(6):609–614.
38. Loox MA, Kenter SB, Au FL, van Galen WJ, Middelkoop E, Bos JD, Mekkes JR. Fibroblasts derived from chronic diabetic ulcers differ in their response to stimulation with EGF, IGF-I, bFGF and PDGF-AB compared to controls. Eur J Cell Biol. 2002;81(3):153–160.
39. Chen L, Tredget EE, Wu PY, Wu Y. Paracrine factors of mesenchymal stem cells recruit macrophages and endothelial lineage cells and enhance wound healing. PLoS One. 2008;3(4):e1886.
40. Reyes M, Dudek A, Jahagirdar B, Koodie L, Marker PH, Verfaillie CM. Correction: origin of endothelial progenitors in human postnatal bone marrow. J Clin Invest. 2008;118(11):3813.
41. Lee SH, Jin SY, Song JS, Seo KK, Cho KH. Paracrine effects of adipose-derived stem cells on keratinocytes and dermal fibroblasts. Ann Dermatol. 2012;24(2):136–143.

42. Stamm C, Westphal B, Kleine HD, Petzsch M, Kittner C, Klinge H, Schumichen C, Nienaber CA, Freund M, Steinhoff G. Autologous bone-marrow stem-cell transplantation for myocardial regeneration. Lancet. 2003;361(9351):45–46.

43. Sivan-Loukianova E, Awad OA, Stepanovic V, Bickenbach J, Schatteman GC. CD34+ blood cells accelerate vascularization and healing of diabetic mouse skin wounds. J Vasc Res. 2003;40(4):368–377.

44. Deng X, Szabo S, Chen L, Paunovic B, Khomenko T, Tolstanova G, Tarnawski AS, Jones MK, Sandor Z. New cell therapy using bone marrow-derived stem cells/endothelial progenitor cells to accelerate neovascularization in healing of experimental ulcerative colitis. Curr Pharm Des. 2011;17(16):1643–1651.

45. Asahara T, Masuda H, Takahashi T, Kalka C, Pastore C, Silver M, Kearne M, Magner M, Isner JM. Bone marrow origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization. Circ Res. 1999;85(3):221–228.

46. Lee MJ, Kim J, Lee KI, Shin JM, Chae JI, Chung HM. Enhancement of wound healing by secretory factors of endothelial precursor cells derived from human embryonic stem cells. Cytotherapy. 2011;13(2):165–178.

47. Park S, Tepper OM, Galiano RD, Capla JM, Baharestani S, Kleinman ME, Pelo CR, Levine JP, Gurtner GC. Selective recruitment of endothelial progenitor cells to ischemic tissues with increased neovascularization. Plast Reconstr Surg. 2004;113(1):284–293.

48. Schatteman GC, Dunnwald M, Jiao C. Biology of bone marrow-derived endothelial cell precursors. Am J Physiol Heart Circ Physiol. 2007;292(1):H1–H18.