ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2023 January 26; 11(3): 487-718

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 11 Number 3 January 26, 2023

MINIREVIEWS

487 Protective effects of combined treatment with ciprofol and mild therapeutic hypothermia during cerebral ischemia-reperfusion injury

Wang YC, Wu MJ, Zhou SL, Li ZH

493 Non-pulmonary involvement in COVID-19: A systemic disease rather than a pure respiratory infection

El-Kassas M, Alboraie M, Elbadry M, El Sheemy R, Abdellah M, Afify S, Madkour A, Zaghloul M, Awad A, Wifi MN, Al Balakosy A, Eltabbakh M

506 Progress and expectation of stem cell therapy for diabetic wound healing

Xu ZH, Ma MH, Li YQ, Li LL, Liu GH

514 Prevention, diagnostic evaluation, management and prognostic implications of liver disease in critically ill patients with COVID-19

Valsamaki A, Xanthoudaki M, Oikonomou KG, Vlachostergios PJ, Papadogoulas A, Katsiafylloudis P, Voulgaridi I, Skoura AL, Komnos A, Papamichalis P

528 Exosomal miRNA in early-stage hepatocellular carcinoma

Wu ZQ, Zhu YX, Jin Y, Zhan YC

534 Impact of multidrug resistance on the management of bacterial infections in cirrhosis

Terra C, de Mattos ÂZ, Chagas MS, Torres A, Wiltgen D, Souza BM, Perez RM

545 Could there be an interplay between periodontal changes and pancreatic malignancies?

Ungureanu BS, Gheorghe DN, Nicolae FM, Râmboiu S, Radu PA, Şurlin VM, Strâmbu VDE, Gheonea DI, Roman A, Şurlin P

ORIGINAL ARTICLE

Retrospective Study

556 Qixue Shuangbu decoction and acupuncture combined with Western medicine in acute severe stroke patients

Gou LK, Li C

566 Successful treatment of patients with refractory idiopathic membranous nephropathy with low-dose Rituximab: A single-center experience

Wang YW, Wang XH, Wang HX, Yu RH

576 Bowel inflammatory presentations on computed tomography in adult patients with severe aplastic anemia during flared inflammatory episodes

Zhao XC, Xue CJ, Song H, Gao BH, Han FS, Xiao SX

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 3 January 26, 2023

Contents

598 Clinical outcomes of AngioJet pharmacomechanical thrombectomy *versus* catheter-directed thrombolysis for the treatment of filter-related caval thrombosis

Li JY, Liu JL, Tian X, Jia W, Jiang P, Cheng ZY, Zhang YX, Liu X, Zhou M

Clinical Trials Study

610 Efficacy and safety of propofol target-controlled infusion combined with butorphanol for sedated colonoscopy

Guo F, Sun DF, Feng Y, Yang L, Li JL, Sun ZL

Observational Study

621 Application of a hospital–community–family trinity rehabilitation nursing model combined with motor imagery therapy in patients with cerebral infarction

Li WW, Li M, Guo XJ, Liu FD

CASE REPORT

629 Congenital biliary atresia caused by *GPC1* gene mutation in Chinese siblings: A case report

Kong YM, Yuan K, Wang CL

635 Rescuing "hopeless" avulsed teeth using autologous platelet-rich fibrin following delayed reimplantation: Two case reports

Yang Y, Liu YL, Jia LN, Wang JJ, Zhang M

645 Acute diffuse peritonitis secondary to a seminal vesicle abscess: A case report

Li K, Liu NB, Liu JX, Chen QN, Shi BM

655 Young thoracic vertebra diffuse idiopathic skeletal hyperostosis with Scheuermann disease: A case report

Liu WZ, Chang ZQ, Bao ZM

662 Relapsed primary extraskeletal osteosarcoma of liver: A case report and review of literature

Di QY, Long XD, Ning J, Chen ZH, Mao ZQ

669 Heterotopic pregnancy after assisted reproductive techniques with favorable outcome of the intrauterine pregnancy: A case report

Wang YN, Zheng LW, Fu LL, Xu Y, Zhang XY

677 Periprosthetic knee joint infection caused by *Brucella melitensis* which was first -osteoarticular brucellosis or osteoarthrosis: A case report

Stumpner T, Kuhn R, Hochreiter J, Ortmaier R

684 Recurrent intramuscular lipoma at extensor pollicis brevis: A case report

Byeon JY, Hwang YS, Lee JH, Choi HJ

692 Imaging features of retinal hemangioblastoma: A case report

Tang X, Ji HM, Li WW, Ding ZX, Ye SL

700 Clinical and genetic diagnosis of autosomal dominant osteopetrosis type II in a Chinese family: A case report

Gong HP, Ren Y, Zha PP, Zhang WY, Zhang J, Zhang ZW, Wang C

709 Soft tissue tuberculosis detected by next-generation sequencing: A case report and review of literature

He YG, Huang YH, Yi XL, Qian KL, Wang Y, Cheng H, Hu J, Liu Y

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 3 January 26, 2023

Contents

ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJCC* as 1.534; IF without journal self cites: 1.491; 5-year IF: 1.599; Journal Citation Indicator: 0.28; Ranking: 135 among 172 journals in medicine, general and internal; and Quartile category: Q4. The *WJCC*'s CiteScore for 2021 is 1.2 and Scopus CiteScore rank 2021: General Medicine is 443/826.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

PUBLICATION DATE
January 26, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 January 26; 11(3): 506-513

DOI: 10.12998/wjcc.v11.i3.506

ISSN 2307-8960 (online)

MINIREVIEWS

Progress and expectation of stem cell therapy for diabetic wound healing

Zhen-Han Xu, Meng-Hui Ma, Yan-Qing Li, Li-Lin Li, Gui-Hua Liu

Specialty type: Endocrinology and metabolism

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): E

P-Reviewer: Jabbarpour Z, Iran; Khan I, Pakistan; Trébol J, Spain; Zhang Q, China

Received: August 31, 2022
Peer-review started: August 31, 2022
First decision: September 26, 2022
Revised: November 8, 2022
Accepted: January 9, 2023
Article in press: January 9, 2023
Published online: January 26, 2023

Zhen-Han Xu, Meng-Hui Ma, Yan-Qing Li, Li-Lin Li, Gui-Hua Liu, Reproductive Medicine Center, The Sixth Affiliated Hospital, Sun Yat-Sen University, Guangzhou 510610, Guangdong Province, China

Corresponding author: Gui-Hua Liu, MD, PhD, Associate Chief Physician, Associate Research Scientist, Reproductive Medicine Center, The Sixth Affiliated Hospital, Sun Yat-Sen University, Yuancuner Road, Tianhe District, Guangzhou 510610, Guangdong Province, China. liuguihua@mail.sysu.edu.cn

Abstract

Impaired wound healing presents great health risks to diabetics. Encouragingly, the current clinical successfully found out meaningful method to repair wound tissue, and stem cell therapy could be an effective method for diabetic wound healing with its ability to accelerate wound closure and avoid amputation. This minireview aims at introducing stem cell therapy for facilitating tissue repair in diabetic wounds, discussing the possible therapeutic mechanism and clinical application status and problems.

Key Words: Stem cell; Diabetic wound; Wound healing; Immunoregulation

Core Tip: Diabetic wound is a common complication of diabetes and stem cell therapy is an effective treatment for diabetic wounds. It helps improve wounds mainly by regulating inflammation and blood circulation. At present, many kinds of stem cells have been used and studied, and good results have been achieved. However, there are still problems that need to be solved. Here we discuss the current role and progress of stem cells in the treatment of diabetic wounds.

Citation: Xu ZH, Ma MH, Li YQ, Li LL, Liu GH. Progress and expectation of stem cell therapy for diabetic wound healing. *World J Clin Cases* 2023; 11(3): 506-513
URL: https://www.wjgnet.com/2307-8960/full/v11/i3/506.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i3.506

INTRODUCTION

Diabetes with neurological abnormalities as well as peripheral artery disease of the lower extremities[1] can lead to diabetic wounds, particularly diabetic foot ulcers, which are considered one of the most serious complications. The international diabetes federation (IDF) reported that in 2021, there were nearly 536.6 million people living with diabetes[2], and the global diabetic foot ulcer prevalence was 6.3%[3]. Due to some risk factors, including poor glycemic control, peripheral neuropathy, peripheral vascular disease and immunosuppression[4], the progression of diabetic wounds can be accelerated, often resulting in complications demanding an amputation. At present, the treatment for diabetic wounds includes improving vascularization, debridement with pharmacological therapy, negative pressure wound therapy or using growth factors and skin substitutes, aiming at epithelial growth across the ulcer bed[4-7].

Stem cell therapies for wounds have vast prospects by using autologous or allogeneic stem cell transplantation for wound closure. It has been shown to help at all stages of wound healing and plays an important role in inflammation regulation, increasing both epithelialization and angiogenesis[8-11]. This minireview concentrates on the progress of stem cell therapy for facilitating tissue repair in diabetic wounds.

POSSIBLE MECHANISM OF STEM CELL THERAPY

Diabetes patients often suffer hyperglycemia, chronic inflammation, microvascular and macrovascular dysfunction, autonomic and sensory neuropathy, hypoxia and impaired neuropeptide signaling[12]. Necroptosis and apoptosis can be inreased by reactive oxygen species (ROS), advanced glycation end products and methylglyoxal, leading to diabetes complications[13]. Long term hyperglycemia leads to metabolic disorders because of the activation of additional polyol glucose metabolic pathway and the accumulation of toxic sorbitol in nerve tissue cells increases, leading to vascular damage[14,15]. With diabetic peripheral neuropathy as well as peripheral artery disease playing a central role, diabetes patients frequently suffer diabetic foot ulcer[16]. At present, stem cell therapies have been reported to contribute to diabetic wound healing in the following ways.

POSSESSING THE FUNCTION OF ANGIOGENESIS

First, stem cells help secrete vascular endothelial growth factor (VEGF), which promotes angiogenesis and the differentiation of endothelial progenitor cells into endothelial cells[17] and the extracellular matrix through the PI3K/threonine kinase (AKT) signaling pathway[18,19]. And they increase epithelialization, granulation tissue formation and capillary formation[20]. In a high glucose environment, stem cell-secreted exosomes contribute to angiopoiesis in endothelial progenitor cells, and overexpression of the transcription factor nuclear factor-E2-related factor 2 synergizes as a protective factor[21]. Moreover, including angiopoietin-1 (Ang-1), stromal cell-derived factor 1, inducible nitric oxide synthase (iNOS), epidermal growth factor (EGF), keratinocyte growth factor 2, erythropoietin, insulin-like growth factor 1 (IGF-1), basic fibroblast growth factor and placental growth factor, there are still many paracrine cytokines helping angiopoiesis, improving microcirculation in diabetic foot ulcer[22-24].

MODULATING INFLAMMATION

Stem cells are able to switch classically activated macrophages, which are called M1 macrophages and have proinflammatory effects, into optionally activated macrophages, which are called M2 macrophages and have anti-inflammatory effects[8,25-27]. In addition, it has been shown that together with exosomes, stem cells can decrease oxidative stress injuries of endothelial cells, providing immunomodulatory effects[28], and the level of Tregs is also upregulated at the same time[29,30]. Cytokines also play an important role in inflammation, and stem cells have the ability to lower the levels of proinflammatory cytokines, including interleukin-1 (IL-1), IL-6, IFN-β and TNF-α, while increasing the levels of anti-inflammatory cytokines, such as IL-10 and IL-4[31,32]. In a recent study mesenchymal stromal cells (MSCs) expressing IL-6, signaled by activating STAT-3 transcription factor, inhibited ROS by protecting neutrophils from apoptosis, preserving the excessive or inappropriate activation of the oxidative metabolism[33].

IMPROVING THE REMODELING PHASE

By cell differentiation, stem cells can translate into keratinocytes as well as endotheliocytes[34]. It has been reported that microvesicles from stem cells help to reprogram injured cells, thus achieving differentiation[35]. Recent studies have shown that stem cells might offer an important early signal to dermal fibroblast responses for their proliferation and migration[9,18]. Additionally, they lower the levels of matrix metalloproteinase-9 (MMP-9) to decrease proteolysis[36]. By reducing expression of phosphorylated focal adhesion kinase and increase the levels of MMP-2, EGF and IGF-1, MSCs improve the function of keratinocytes[37].

REGULATION OF MICRORNAS

MicroRNAs (miRNAs) have been discovered regulators of gene expression in the regulation of inflammation[38]. Generally, miRNAs promote wound healing by activating multiple pathways directly or indirectly. For example, after MSC treatment it is found that the increased levels of miR-146a result in attenuating expression of proinflammatory and inflammatory genes, including IL-1 receptor-associated kinase 1 (IRAK1), TNF receptor-associated factor 6 (TRAF6), and nuclear factor-κB (NF-κB)[39]. MSCs also enhance diabetic wound healing by improving collagen I content through increasing miR-29b expression[36]. A research has revealed that miR-21-5p promoted angiogenesis through upregulations of vascular endothelial growth factor receptor, activations of serine/ AKT and mitogen-activated protein kinase[40]. In addition, miR-126-3p from MSCs contributes to wound healing by increasing the formation of granulation tissue and angiogenesis[41]. MiRNA mediates the cell microenvironment, regulates the biological activity and phenotype of specific target cells, induces changes in the function of target cells, and leads to a series of biological reactions to play a variety of biological functions[42,43].

In conclusion, stem cells accelerate diabetic wound healing in many ways. Nevertheless, more connections between stem cells and diabetic wounds are under exploration.

STEM CELL THERAPIES FOR DIABETIC WOUNDS IN CLINICAL WORK

Over the past few years, it has been revealed that different types of stem cell therapies have been used in clinical work[44], as shown in Table 1. Although clinical data drew the conclusion that using stem cells benefits diabetic wounds, various types of stem cells with diversified methods still need to be identified. Attention should be given to adverse effects that have appeared in some research. For example, increased exudation from diabetic wounds may be associated with stem cells[45]. However, some clinical studies and analyses support its safety[46-48]. There are several types of cells used in clinical work. For example, adipose-derived mesenchymal stromal cells (ADMSCs) have been proven to be able to accelerate the time to wound closure[49] and the level of wound healing[50]. By intravascular and intralesional injection, umbilical cord mesenchymal stromal cells (UCMSCs) can not only improve the completion of wound closure[51] but also increase the number of vessels[52]. One case in which bone marrow mesenchymal stem cells (BMMSCs) were used for diabetic wound healing showed a good result in the next 10 years[53]. In addition, it has been revealed that BMMSC therapy might be better tolerated and more effective than bone marrow-derived mononuclear cells (BMMNCs) for increasing lower limb perfusion and promoting foot ulcer healing in diabetic patients with critical limb ischemia [54]. By treating with different doses of granulocyte colony stimulating factor (G-CSF), peripheral blood stem cells can be gained to promote the establishment of collateral circulation[55].

Although stem cell therapy has been shown to be a relatively safe treatment for diabetic wounds, unavoidable transplantation complications have appeared in diabetics, including febrile neutropenia, alopecia and gastrointestinal reaction[56]. A clinical trial reported one diabetes patient died of pseudomonas sepsis in the course of neutropenia after autologous hematopoietic stem cell transplantation[57]. Thus, complications as well as adverse events still can't be ignored while the safety of stem cell transplantation has been reported in some studies[58].

CONCLUSION

Stem Cell therapy could be an effective treatment for diabetic wounds[59,60], which contains endless medical value together with a wide scientific perspective accelerating diabetic wound healing. Stem cells have also demonstrated their therapeutic potential in the field even if infection is present[61]. However, there are still problems that need to be solved.

First, the mechanisms of stem cell therapy are still considered as a vital part of the theoretical basis of clinical study. Although animal experiments and clinical trials provide us with great results, studies based on the molecular level should be carried out to gain more molecular mechanisms.

Table 1 Recent clinical trials regarding stem cell therapies for diabetic wounds

Ref.	Type of stem cells	Number of cases	Mean age (year)	Methods of treatment	Possible mechanism	Outcome	Adverse events	Conciusion
Uzun *et al* [49], 2021	ADMSCs	10	57.5	Intralesional injection	The release of angiogenic cytokines, increasing epithelialization, granulation tissue formation, anti-inflammatory, and anti-apoptotic effects	Time to wound closure (d): ADMSCs group (n = 10): 31.0 ± 10.7; Control group (n = 10): 54.8 ± 15.0; P = 0.002	No found	Allogeneic ADMSCs injection is a safe and effective method with a positive contribution to wound-healing time in the treatment of chronic diabetic foot ulcers
Suzdaltseva *et al*[51], 2020	UCMSCs	31	58.5	Intralesional injection	The release of angiogenic cytokines, cell differentiation, and immunomodulation	Complete wound closure or significant improvement (% in group)[a]: UCMSCs group (n = 59): 22%; Placebo group (n = 49): 8.2%; P < 0.05	No found	Locally delivered allogeneic UCMSCs can contribute to chronic wound repair and provide an additional support toward new therapeutic strategies
Moon *et al* [50], 2019	ADMSCs	30	59.9	Topical	Synthesizing higher amounts of collagen, fibroblast growth factor, and vascular endothelial growth factor in vitro	Complete wound closure at Week 12 (% in group): ADMSCs group (n = 30): 82%; Control group (n = 29): 53%; P < 0.05	No found	Allogeneic ADMSCs might be effective and safe to treat diabetic foot ulcers
Chen *et al* [53], 2018	BMMSCs	1	64	Intramuscular injection	The release of angiogenic cytokines, differentiation and angiogen	No recurrence in the next 10-yr follow-up span	No found	Autologous BMMSC transplantation therapy may be an effective measure for recurrent bullosis diabeticorum
Qin *et al* [52], 2016	UCMSCs	28	75	Intravascular and intralesional injection	The release of signalling or growth factors, and differentiation of injected precursor cells into functional tissue	Increased number of vessels: Experimental group (n = 28): 9.3 ± 2.7; Control group (n = 25): 5.9 ± 3.3; P < 0.05	No found	UCMSC transplantation after angioplasty is a safe and effective clinical therapy for severe diabetic foot
Xu *et al*[55], 2016	Peripheral blood stem cells	63	69	Intralesional injection	Angiogenesis and vascularization	CTA score[b]: Pre-transplantation (n = 63): 1.22 ± 0.15; Post-transplantation (n = 63): 2.35 ± 0.784; P < 0.01	No found	Autologous peripheral blood stem cell transplantation can promote the establishment of collateral circulation in patients with diabetic foot
Lu *et al*[54], 2011	BMMSCs	18	63	Intramuscular injection	The release of angiogenic cytokines, differentiation and angiogenesis	Angiographic score of MRA in limbs at 24 wk[b]: BMMSCs (n = 18): 1.9 ± 0.5; BMMNCs (n = 19): 1.5 ± 0.6; P = 0.018	No found	BMMSCs therapy may be better tolerated and more effective than BMMNCs for increasing lower limb perfusion and promoting foot ulcer healing in diabetic patients with critical limb ischemia

[a]108 patients, including 31 patients (28.7%) suffering from diabetic foot, were randomized to the umbilical cord mesenchymal stromal cell group and placebo group.

[b]0 points, no new collateral vessels; 1 point, little new collateral circulation; 2 points, moderate new collateral circulation; 3 points, abundant new collateral circulation.

ADMSCs: Adipose-derived mesenchymal stromal cells; UCMSCs: Umbilical cord mesenchymal stromal cells; BMMSCs: Bone marrow mesenchymal stem cells; CTA: Computed tomography angiography; MRA: Magnetic resonance angiography; BMMNCs: Bone marrow-derived mononuclear cells.

Second, the safety of treatment cannot be ignored, although only a few adverse events have been reported, which urges more clinical trials. At the same time, more specific therapeutic doses and administration routes should be revealed, which accounts for how to reduce side effects and adverse reactions. For example, on account of its differentiative capacity, surgical dressing with stem cells may have the ability to decrease bleeding as well as accelerate operative incision closure, since it has been reported that advanced dressings for the delivery of progenitor cells are at the point in research[62]. Moreover, considering patients with cancer who cannot receive stem cell treatment[63], alternative solutions need to be identified.

Third, it is still important for physicians to simplify the approach of gathering as well as preconditioning stem cells because preconditioning MSCs with pretreatment agents significantly hastened healing in delayed-healing wounds[64]. In addition, evidence has shown that the ability of stem cells in elderly people to proliferate and differentiate diminishes with age[65]. Therefore, the differences between autotransplantation and allotransplantation should be taken into consideration to improve the success rate of transplantation.

Last, the questions of ethics also matter. Promising and effective stem cell therapy has raised serious ethical problems[66]. Not only do social responsibility and moral constraints regularize approaches of treatment, but relevant laws and medical guidelines also need to be improved.

The answers to these questions will lead to better and more appropriate treatments for different patients.

FOOTNOTES

Author contributions: Xu ZH, Ma MH, Li YQ, Li LL and Liu GH designed the research study; Xu ZH, Ma MH, Li YQ and Li LL performed the research; Xu ZH and Ma MH contributed literature search; Xu ZH, Li LL and Liu GH contributed data analysis; Xu ZH and Li YQ wrote the manuscript; All authors have read and approve the final manuscript.

Supported by The National Natural Science Foundation of China, No. 82171604.

Conflict-of-interest statement: All the authors declare that there are no conflicts of interest associated with this manuscript.

Country/Territory of origin: China

ORCID number: Zhen-Han Xu 0000-0002-6445-3557; Meng-Hui Ma 0000-0002-6369-1000; Yan-Qing Li 0000-0003-3222-5610; Li-Lin Li 0000-0003-3298-297X; Gui-Hua Liu 0000-0003-1811-8763.

S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES

1 **Edmonds M**, Manu C, Vas P. The current burden of diabetic foot disease. *J Clin Orthop Trauma* 2021; **17**: 88-93 [PMID: 33680841 DOI: 10.1016/j.jcot.2021.01.017]
2 Global diabetes data report 2000 — 2045. Available from: https://diabetesatlas.org/data/
3 **Zhang P**, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis (†). *Ann Med* 2017; **49**: 106-116 [PMID: 27585063 DOI: 10.1080/07853890.2016.1231932]
4 **Lim JZ**, Ng NS, Thomas C. Prevention and treatment of diabetic foot ulcers. *J R Soc Med* 2017; **110**: 104-109 [PMID: 28116957 DOI: 10.1177/0141076816688346]
5 **Cho H**, Blatchley MR, Duh EJ, Gerecht S. Acellular and cellular approaches to improve diabetic wound healing. *Adv Drug Deliv Rev* 2019; **146**: 267-288 [PMID: 30075168 DOI: 10.1016/j.addr.2018.07.019]
6 **Cavanagh PR**, Lipsky BA, Bradbury AW, Botek G. Treatment for diabetic foot ulcers. *Lancet* 2005; **366**: 1725-1735 [PMID: 16291067 DOI: 10.1016/S0140-6736(05)67699-4]
7 **Maksimova N**, Krasheninnikov M, Zhang Y, Ponomarev E, Pomytkin I, Melnichenko G, Lyundup A. Early passage autologous mesenchymal stromal cells accelerate diabetic wound re-epithelialization: A clinical case study. *Cytotherapy* 2017; **19**: 1548-1550 [PMID: 28986173 DOI: 10.1016/j.jcyt.2017.08.017]
8 **Krasilnikova OA**, Baranovskii DS, Lyundup AV, Shegay PV, Kaprin AD, Klabukov ID. Stem and Somatic Cell Monotherapy for the Treatment of Diabetic Foot Ulcers: Review of Clinical Studies and Mechanisms of Action. *Stem Cell Rev Rep* 2022; **18**: 1974-1985 [PMID: 35476187 DOI: 10.1007/s12015-022-10379-z]
9 **Smith AN**, Willis E, Chan VT, Muffley LA, Isik FF, Gibran NS, Hocking AM. Mesenchymal stem cells induce dermal fibroblast responses to injury. *Exp Cell Res* 2010; **316**: 48-54 [PMID: 19666021 DOI: 10.1016/j.yexcr.2009.08.001]
10 **Javazon EH**, Keswani SG, Badillo AT, Crombleholme TM, Zoltick PW, Radu AP, Kozin ED, Beggs K, Malik AA, Flake AW. Enhanced epithelial gap closure and increased angiogenesis in wounds of diabetic mice treated with adult murine bone marrow stromal progenitor cells. *Wound Repair Regen* 2007; **15**: 350-359 [PMID: 17537122 DOI: 10.1111/j.1524-475X.2007.00237.x]

11 **Yang J**, Chen Z, Pan D, Li H, Shen J. Umbilical Cord-Derived Mesenchymal Stem Cell-Derived Exosomes Combined Pluronic F127 Hydrogel Promote Chronic Diabetic Wound Healing and Complete Skin Regeneration. *Int J Nanomedicine* 2020; **15**: 5911-5926 [PMID: 32848396 DOI: 10.2147/IJN.S249129]

12 **Baltzis D**, Eleftheriadou I, Veves A. Pathogenesis and treatment of impaired wound healing in diabetes mellitus: new insights. *Adv Ther* 2014; **31**: 817-836 [PMID: 25069580 DOI: 10.1007/s12325-014-0140-x]

13 **Volpe CMO**, Villar-Delfino PH, Dos Anjos PMF, Nogueira-Machado JA. Cellular death, reactive oxygen species (ROS) and diabetic complications. *Cell Death Dis* 2018; **9**: 119 [PMID: 29371661 DOI: 10.1038/s41419-017-0135-z]

14 **Brem H**, Tomic-Canic M. Cellular and molecular basis of wound healing in diabetes. *J Clin Invest* 2007; **117**: 1219-1222 [PMID: 17476353 DOI: 10.1172/JCI32169]

15 **Jhamb S**, Vangaveti VN, Malabu UH. Genetic and molecular basis of diabetic foot ulcers: Clinical review. *J Tissue Viability* 2016; **25**: 229-236 [PMID: 27372176 DOI: 10.1016/j.jtv.2016.06.005]

16 **Schaper NC**, Van Netten JJ, Apelqvist J, Lipsky BA, Bakker K; International Working Group on the Diabetic Foot (IWGDF). Prevention and management of foot problems in diabetes: A Summary Guidance for Daily Practice 2015, based on the IWGDF guidance documents. *Diabetes Res Clin Pract* 2017; **124**: 84-92 [PMID: 28119194 DOI: 10.1016/j.diabres.2016.12.007]

17 **Ge Q**, Zhang H, Hou J, Wan L, Cheng W, Wang X, Dong D, Chen C, Xia J, Guo J, Chen X, Wu X. VEGF secreted by mesenchymal stem cells mediates the differentiation of endothelial progenitor cells into endothelial cells *via* paracrine mechanisms. *Mol Med Rep*(e-pub ahead of print 14 November 2017) [DOI: 10.3892/mmr.2017.8059]

18 **Wang J**, Wu H, Peng Y, Zhao Y, Qin Y, Zhang Y, Xiao Z. Hypoxia adipose stem cell-derived exosomes promote high-quality healing of diabetic wound involves activation of PI3K/Akt pathways. *J Nanobiotechnology* 2021; **19**: 202 [PMID: 34233694 DOI: 10.1186/s12951-021-00942-0]

19 **Zhang W**, Bai X, Zhao B, Li Y, Zhang Y, Li Z, Wang X, Luo L, Han F, Zhang J, Han S, Cai W, Su L, Tao K, Shi J, Hu D. Cell-free therapy based on adipose tissue stem cell-derived exosomes promotes wound healing *via* the PI3K/Akt signaling pathway. *Exp Cell Res* 2018; **370**: 333-342 [PMID: 29964051 DOI: 10.1016/j.yexcr.2018.06.035]

20 **Guillamat-Prats R**. The Role of MSC in Wound Healing, Scarring and Regeneration. *Cells* 2021; **10** [PMID: 34359898 DOI: 10.3390/cells10071729]

21 **Li X**, Xie X, Lian W, Shi R, Han S, Zhang H, Lu L, Li M. Exosomes from adipose-derived stem cells overexpressing Nrf2 accelerate cutaneous wound healing by promoting vascularization in a diabetic foot ulcer rat model. *Exp Mol Med* 2018; **50**: 1-14 [PMID: 29651102 DOI: 10.1038/s12276-018-0058-5]

22 **Kinnaird T**, Stabile E, Burnett MS, Shou M, Lee CW, Barr S, Fuchs S, Epstein SE. Local delivery of marrow-derived stromal cells augments collateral perfusion through paracrine mechanisms. *Circulation* 2004; **109**: 1543-1549 [PMID: 15023891 DOI: 10.1161/01.CIR.0000124062.31102.57]

23 **Schlosser S**, Dennler C, Schweizer R, Eberli D, Stein JV, Enzmann V, Giovanoli P, Erni D, Plock JA. Paracrine effects of mesenchymal stem cells enhance vascular regeneration in ischemic murine skin. *Microvasc Res* 2012; **83**: 267-275 [PMID: 22391452 DOI: 10.1016/j.mvr.2012.02.011]

24 **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**: e1886 [PMID: 18382669 DOI: 10.1371/journal.pone.0001886]

25 **Maggini J**, Mirkin G, Bognanni I, Holmberg J, Piazzón IM, Nepomnaschy I, Costa H, Cañones C, Raiden S, Vermeulen M, Geffner JR. Mouse bone marrow-derived mesenchymal stromal cells turn activated macrophages into a regulatory-like profile. *PLoS One* 2010; **5**: e9252 [PMID: 20169081 DOI: 10.1371/journal.pone.0009252]

26 **Liu W**, Yu M, Xie D, Wang L, Ye C, Zhu Q, Liu F, Yang L. Melatonin-stimulated MSC-derived exosomes improve diabetic wound healing through regulating macrophage M1 and M2 polarization by targeting the PTEN/AKT pathway. *Stem Cell Res Ther* 2020; **11**: 259 [PMID: 32600435 DOI: 10.1186/s13287-020-01756-x]

27 **Louiselle AE**, Niemiec SM, Zgheib C, Liechty KW. Macrophage polarization and diabetic wound healing. *Transl Res* 2021; **236**: 109-116 [PMID: 34089902 DOI: 10.1016/j.trsl.2021.05.006]

28 **Yan C**, Xv Y, Lin Z, Endo Y, Xue H, Hu Y, Hu L, Chen L, Cao F, Zhou W, Zhang P, Liu G. Human Umbilical Cord Mesenchymal Stem Cell-Derived Exosomes Accelerate Diabetic Wound Healing *via* Ameliorating Oxidative Stress and Promoting Angiogenesis. *Front Bioeng Biotechnol* 2022; **10**: 829868 [PMID: 35174145 DOI: 10.3389/fbioe.2022.829868]

29 **Xiong J**, Hu H, Guo R, Wang H, Jiang H. Mesenchymal Stem Cell Exosomes as a New Strategy for the Treatment of Diabetes Complications. *Front Endocrinol (Lausanne)* 2021; **12**: 646233 [PMID: 33995278 DOI: 10.3389/fendo.2021.646233]

30 **Nojehdehi S**, Soudi S, Hesampour A, Rasouli S, Soleimani M, Hashemi SM. Immunomodulatory effects of mesenchymal stem cell-derived exosomes on experimental type-1 autoimmune diabetes. *J Cell Biochem* 2018; **119**: 9433-9443 [PMID: 30074271 DOI: 10.1002/jcb.27260]

31 **Liu L**, Yu Y, Hou Y, Chai J, Duan H, Chu W, Zhang H, Hu Q, Du J. Human umbilical cord mesenchymal stem cells transplantation promotes cutaneous wound healing of severe burned rats. *PLoS One* 2014; **9**: e88348 [PMID: 24586314 DOI: 10.1371/journal.pone.0088348]

32 **Aggarwal S**, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. *Blood* 2005; **105**: 1815-1822 [PMID: 15494428 DOI: 10.1182/blood-2004-04-1559]

33 **Raffaghello L**, Bianchi G, Bertolotto M, Montecucco F, Busca A, Dallegri F, Ottonello L, Pistoia V. Human mesenchymal stem cells inhibit neutrophil apoptosis: a model for neutrophil preservation in the bone marrow niche. *Stem Cells* 2008; **26**: 151-162 [PMID: 17932421 DOI: 10.1634/stemcells.2007-0416]

34 **Isakson M**, de Blacam C, Whelan D, McArdle A, Clover AJ. Mesenchymal Stem Cells and Cutaneous Wound Healing: Current Evidence and Future Potential. *Stem Cells Int* 2015; **2015**: 831095 [PMID: 26106431 DOI: 10.1155/2015/831095]

35 **Camussi G**, Deregibus MC, Cantaluppi V. Role of stem-cell-derived microvesicles in the paracrine action of stem cells. *Biochem Soc Trans* 2013; **41**: 283-287 [PMID: 23356298 DOI: 10.1042/BST20120192]

36 **Xu J**, Zgheib C, Hodges MM, Caskey RC, Hu J, Liechty KW. Mesenchymal stem cells correct impaired diabetic wound

healing by decreasing ECM proteolysis. *Physiol Genomics* 2017; **49**: 541-548 [PMID: 28842435 DOI: 10.1152/physiolgenomics.00090.2016]

37 **Kato J**, Kamiya H, Himeno T, Shibata T, Kondo M, Okawa T, Fujiya A, Fukami A, Uenishi E, Seino Y, Tsunekawa S, Hamada Y, Naruse K, Oiso Y, Nakamura J. Mesenchymal stem cells ameliorate impaired wound healing through enhancing keratinocyte functions in diabetic foot ulcerations on the plantar skin of rats. *J Diabetes Complications* 2014; **28**: 588-595 [PMID: 25027388 DOI: 10.1016/j.jdiacomp.2014.05.003]

38 **Sheedy FJ**, O'Neill LA. Adding fuel to fire: microRNAs as a new class of mediators of inflammation. *Ann Rheum Dis* 2008; **67** Suppl 3: iii50-iii55 [PMID: 19022814 DOI: 10.1136/ard.2008.100289]

39 **Xu J**, Wu W, Zhang L, Dorset-Martin W, Morris MW, Mitchell ME, Liechty KW. The role of microRNA-146a in the pathogenesis of the diabetic wound-healing impairment: correction with mesenchymal stem cell treatment. *Diabetes* 2012; **61**: 2906-2912 [PMID: 22851573 DOI: 10.2337/db12-0145]

40 **Huang C**, Luo W, Wang Q, Ye Y, Fan J, Lin L, Shi C, Wei W, Chen H, Wu Y, Tang Y. Human mesenchymal stem cells promote ischemic repairment and angiogenesis of diabetic foot through exosome miRNA-21-5p. *Stem Cell Res* 2021; **52**: 102235 [PMID: 33601096 DOI: 10.1016/j.scr.2021.102235]

41 **Tao SC**, Guo SC, Li M, Ke QF, Guo YP, Zhang CQ. Chitosan Wound Dressings Incorporating Exosomes Derived from MicroRNA-126-Overexpressing Synovium Mesenchymal Stem Cells Provide Sustained Release of Exosomes and Heal Full-Thickness Skin Defects in a Diabetic Rat Model. *Stem Cells Transl Med* 2017; **6**: 736-747 [PMID: 28297576 DOI: 10.5966/sctm.2016-0275]

42 **Ferguson SW**, Wang J, Lee CJ, Liu M, Neelamegham S, Canty JM, Nguyen J. The microRNA regulatory landscape of MSC-derived exosomes: a systems view. *Sci Rep* 2018; **8**: 1419 [PMID: 29362496 DOI: 10.1038/s41598-018-19581-x]

43 **Phinney DG**, Di Giuseppe M, Njah J, Sala E, Shiva S, St Croix CM, Stolz DB, Watkins SC, Di YP, Leikauf GD, Kolls J, Riches DW, Deiuliis G, Kaminski N, Boregowda SV, McKenna DH, Ortiz LA. Mesenchymal stem cells use extracellular vesicles to outsource mitophagy and shuttle microRNAs. *Nat Commun* 2015; **6**: 8472 [PMID: 26442449 DOI: 10.1038/ncomms9472]

44 **Kosaric N**, Kiwanuka H, Gurtner GC. Stem cell therapies for wound healing. *Expert Opin Biol Ther* 2019; **19**: 575-585 [PMID: 30900481 DOI: 10.1080/14712598.2019.1596257]

45 **Askø Andersen J**, Rasmussen A, Frimodt-Møller M, Engberg S, Steeneveld E, Kirketerp-Møller K, O'Brien T, Rossing P. Novel topical allogeneic bone-marrow-derived mesenchymal stem cell treatment of hard-to-heal diabetic foot ulcers: a proof of concept study. *Stem Cell Res Ther* 2022; **13**: 280 [PMID: 35765085 DOI: 10.1186/s13287-022-02951-8]

46 **Dubský M**, Jirkovská A, Bem R, Fejfarová V, Pagacová L, Nemcová A, Sixta B, Chlupac J, Peregrin JH, Syková E, Jude EB. Comparison of the effect of stem cell therapy and percutaneous transluminal angioplasty on diabetic foot disease in patients with critical limb ischemia. *Cytotherapy* 2014; **16**: 1733-1738 [PMID: 25304666 DOI: 10.1016/j.jcyt.2014.08.010]

47 **Marino G**, Moraci M, Armenia E, Orabona C, Sergio R, De Sena G, Capuozzo V, Barbarisi M, Rosso F, Giordano G, Iovino F, Barbarisi A. Therapy with autologous adipose-derived regenerative cells for the care of chronic ulcer of lower limbs in patients with peripheral arterial disease. *J Surg Res* 2013; **185**: 36-44 [PMID: 23773718 DOI: 10.1016/j.jss.2013.05.024]

48 **Carstens MH**, Quintana FJ, Calderwood ST, Sevilla JP, Ríos AB, Rivera CM, Calero DW, Zelaya ML, Garcia N, Bertram KA, Rigdon J, Dos-Anjos S, Correa D. Treatment of chronic diabetic foot ulcers with adipose-derived stromal vascular fraction cell injections: Safety and evidence of efficacy at 1 year. *Stem Cells Transl Med* 2021; **10**: 1138-1147 [PMID: 33826245 DOI: 10.1002/sctm.20-0497]

49 **Uzun E**, Güney A, Gönen ZB, Özkul Y, Kafadar İH, Günay M, Mutlu M. Intralesional allogeneic adipose-derived stem cells application in chronic diabetic foot ulcer: Phase I/2 safety study. *Foot Ankle Surg* 2021; **27**: 636-642 [PMID: 32826167 DOI: 10.1016/j.fas.2020.08.002]

50 **Moon KC**, Suh HS, Kim KB, Han SK, Young KW, Lee JW, Kim MH. Potential of Allogeneic Adipose-Derived Stem Cell-Hydrogel Complex for Treating Diabetic Foot Ulcers. *Diabetes* 2019; **68**: 837-846 [PMID: 30679183 DOI: 10.2337/db18-0699]

51 **Suzdaltseva Y**, Zhidkih S, Kiselev SL, Stupin V. Locally Delivered Umbilical Cord Mesenchymal Stromal Cells Reduce Chronic Inflammation in Long-Term Nonhealing Wounds: A Randomized Study. *Stem Cells Int* 2020; **2020**: 5308609 [PMID: 32148521 DOI: 10.1155/2020/5308609]

52 **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**: 497-503 [PMID: 27219884 DOI: 10.1055/s-0042-103684]

53 **Chen Y**, Ma Y, Li N, Wang H, Chen B, Liang Z, Ren R, Lu D, Boey J, Armstrong DG, Deng W. Efficacy and long-term longitudinal follow-up of bone marrow mesenchymal cell transplantation therapy in a diabetic patient with recurrent lower limb bullosis diabeticorum. *Stem Cell Res Ther* 2018; **9**: 99 [PMID: 29631615 DOI: 10.1186/s13287-018-0854-9]

54 **Lu D**, Chen B, Liang Z, Deng W, Jiang Y, Li S, Xu J, Wu Q, Zhang Z, Xie B, Chen S. 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**: 26-36 [PMID: 21216483 DOI: 10.1016/j.diabres.2010.12.010]

55 **Xu SM**, Liang T. Clinical observation of the application of autologous peripheral blood stem cell transplantation for the treatment of diabetic foot gangrene. *Exp Ther Med* 2016; **11**: 283-288 [PMID: 26889255 DOI: 10.3892/etm.2015.2888]

56 **Gu B**, Miao H, Zhang J, Hu J, Zhou W, Gu W, Wang W, Ning G. Clinical benefits of autologous haematopoietic stem cell transplantation in type 1 diabetes patients. *Diabetes Metab* 2018; **44**: 341-345 [PMID: 29331269 DOI: 10.1016/j.diabet.2017.12.006]

57 **Snarski E**, Milczarczyk A, Hałaburda K, Torosian T, Paluszewska M, Urbanowska E, Król M, Boguradzki P, Jedynasty K, Franek E, Wiktor-Jedrzejczak W. Immunoablation and autologous hematopoietic stem cell transplantation in the treatment of new-onset type 1 diabetes mellitus: long-term observations. *Bone Marrow Transplant* 2016; **51**: 398-402 [PMID: 26642342 DOI: 10.1038/bmt.2015.294]

58 **Jin L**, Wang X, Qiao Z, Deng Y. The safety and efficacy of mesenchymal stem cell therapy in diabetic lower extremity

vascular disease: a meta-analysis and systematic review. *Cytotherapy* 2022; **24**: 225-234 [PMID: 34656420 DOI: 10.1016/j.jcyt.2021.08.001]

59 **Gadelkarim M**, Abushouk AI, Ghanem E, Hamaad AM, Saad AM, Abdel-Daim MM. Adipose-derived stem cells: Effectiveness and advances in delivery in diabetic wound healing. *Biomed Pharmacother* 2018; **107**: 625-633 [PMID: 30118878 DOI: 10.1016/j.biopha.2018.08.013]

60 **El Hage R**, Knippschild U, Arnold T, Hinterseher I. Stem Cell-Based Therapy: A Promising Treatment for Diabetic Foot Ulcer. *Biomedicines* 2022; **10** [PMID: 35884812 DOI: 10.3390/biomedicines10071507]

61 **Amini A**, Chien S, Bayat M. Potential of stem cells for treating infected Diabetic Foot Wounds and Ulcers: a systematic review. *Mol Biol Rep* 2022; **49**: 10925-10934 [PMID: 36008608 DOI: 10.1007/s11033-022-07721-6]

62 **Kirby GT**, Mills SJ, Vandenpoel L, Pinxteren J, Ting A, Short RD, Cowin AJ, Michelmore A, Smith LE. Development of Advanced Dressings for the Delivery of Progenitor Cells. *ACS Appl Mater Interfaces* 2017; **9**: 3445-3454 [PMID: 28068055 DOI: 10.1021/acsami.6b14725]

63 **Mohr A**, Zwacka R. The future of mesenchymal stem cell-based therapeutic approaches for cancer - From cells to ghosts. *Cancer Lett* 2018; **414**: 239-249 [PMID: 29175461 DOI: 10.1016/j.canlet.2017.11.025]

64 **Amini A**, Chien S, Bayat M. Effectiveness of preconditioned adipose-derived mesenchymal stem cells with photobiomodulation for the treatment of diabetic foot ulcers: a systematic review. *Lasers Med Sci* 2022; **37**: 1415-1425 [PMID: 34697696 DOI: 10.1007/s10103-021-03451-6]

65 **You D**, Jang MJ, Lee J, Jeong IG, Kim HS, Moon KH, Suh N, Kim CS. Periprostatic implantation of human bone marrow-derived mesenchymal stem cells potentiates recovery of erectile function by intracavernosal injection in a rat model of cavernous nerve injury. *Urology* 2013; **81**: 104-110 [PMID: 23122545 DOI: 10.1016/j.urology.2012.08.046]

66 **de Miguel-Beriain I**. The ethics of stem cells revisited. *Adv Drug Deliv Rev* 2015; **82-83**: 176-180 [PMID: 25446134 DOI: 10.1016/j.addr.2014.11.011]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com