Journal of Lasers in Medical Sciences

J Lasers Med Sci 2024;15:e18

Review Article

http://journals.sbmu.ac.ir/jlms

doi 10.34172/jlms.2024.18

Exploring Photobiomodulation Therapy and Regenerative Medicine for Diabetic Foot Ulcers: Pathogenesis and Multidisciplinary Treatment Approach

Elahe Torabi[1], Samareh Omidvari[2], Zahra Azimzadeh[3], Shahram Darabi[4], Aliasghar Keramatinia[1], Mohammad Ali Asghari[3], Hojjat Allah Abbaszadeh[1,2*], Fariborz Rashnoo[5*]

[1]Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Rayan Stem Cells and Regenerative Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Proteomics Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Cellular and Molecular Research Center, Research Institute for Non-Communicable Diseases, Qazvin University of Medical Sciences, Qazvin, Iran
[5]Department of General Surgery, School of Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

***Correspondence to**
Hojjat Allah Abbaszadeh,
Email: dr.abbaszadeh@sbmu.ac.ir;
Fariborz Rashnoo,
Email: Fariborz.rashnoo@yahoo.com

Received: December 30, 2023
Accepted: March 9, 2024
ePublished: June 29, 2024

Abstract

Introduction: Diabetes is associated with several debilitating complications, including the development of diabetic foot ulcers (DFUs), which can have serious consequences. This study emphasizes a multidisciplinary approach, providing a thorough overview of DFU pathogenesis and available treatments.

Methods: An extensive literature review, covering studies published between 2000 and 2023, was conducted to gather data on DFU pathophysiology and treatments, including wound dressings, photobiomodulation, off-loading devices, adjunct medicines, and stem cell therapy.

Results: DFUs are complicated due to infection, ischemia, and neuropathy. Sufficient wound dressings maintain a moist environment, promoting autolytic debridement and facilitating the healing process. Through cellular mechanisms, photobiomodulation therapy (PBM) was observed to expedite the healing process. Additionally, off-loading devices were invented to reduce ulcer pressure and promote healing. Adjunct therapies such as negative pressure wound therapy and hyperbaric oxygen therapy were identified as valuable tools for enhancing healing outcomes. Furthermore, autologous and allogeneic stem cell treatments exhibited the potential for promoting tissue regeneration and expediting the healing process.

Conclusion: The complex pathophysiology of DFUs necessitates a multimodal treatment approach. Essential components include PBM, wound dressings, off-loading devices, adjunct treatments, and stem cell therapy.

Keywords: Diabetes mellitus; Diabetic foot ulcer; Photobiomodulation.

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by insufficient insulin production and high blood glucose levels. One of the most prevalent illnesses in the world is DM.[1] Type 1 diabetes (T1DM) requires insulin injections due to autoimmune destruction of insulin-producing cells. Type 2 diabetes (T2DM) results from insufficient insulin production and reduced insulin effectiveness (insulin resistance).[2] According to the International Diabetes Federation (IDF), there are more than 415 million diabetic patients in the world. By 2040, this number is expected to rise to 642 million.[3] In 2015, approximately 5.0 million patients died from DM globally.[4] Vascular problems such as cardiovascular disease, diabetic kidney disease, diabetic retinopathy, and peripheral neuropathy are the major causes of morbidity and mortality in diabetic patients.[5] Diabetic foot ulcers (DFUs)are a major complication of diabetes, caused by various factors such as peripheral neuropathy, peripheral vascular disease, foot deformities, arterial insufficiency, trauma, and inadequate resistance to infections.[6] In the UK, the DFU is the most common cause of hospitalization for diabetic patients, posing a significant health burden. It is estimated that between 2%-3% of diabetic patients currently have a foot ulcer, with a lifetime risk of up to 25%.[7,8] DFU treatment constitutes nearly one-third of

Please cite this article as follows: Torabi E, Omidvari S, Azimzadeh Z, Darabi S, Keramatinia A, Asghari MA, et al. Exploring photobiomodulation therapy and regenerative medicine for diabetic foot ulcers: pathogenesis and multidisciplinary treatment approach. *J Lasers Med Sci.* 2024;15:e18. doi:10.34172/jlms.2024.18.

diabetes care costs, totaling $176 billion in 2012. Despite this, 20% of patients' DFUs remain unhealed after a year, with a 40% recurrence rate.[9] The etiology of DFUs is derived from a triad of arterial occlusive disease, neuropathy, and trauma leading to infection.[10] Peripheral neuropathy affects 10.9%–32.7% of individuals with diabetes in the United States,[11,12] with key risk factors including the duration of DM, severe hyperglycemia, dyslipidemia, hypertension, smoking, and age. The pathophysiology involves complex interactions in the case of type 1 DM, insulin deficiency.[13] Hyperglycemia limits endothelial nitric oxide synthase production and activation and induces the protein-sugar reaction called the Maillard reaction linked to vascular change and neuropathy.[14] Motor neuropathy in diabetics affects foot and leg muscles, altering biomechanics, coordination, and proprioception. This leads to abnormal loading, thickened skin, callus formation, and frequent ulcers and hemorrhages.[15,16] Minor foot injuries in diabetic patients, often unnoticed due to sensory deficits, worsen with motor neuropathy, leading to muscle atrophy and various foot deformities such as Charcot arthropathy, claw foot, pes cavus, and hallux valgus. Combined with vascular and immune system issues, diabetic patients are prone to ulceration, delayed healing, and infection.[17,18] Preventive care is a key for diabetic patients to avoid DFUs. Treatments for DFUs include pharmaceutical therapy, wound dressing, debridement, revascularization, growth factors, and skin replacements, alongside glycemic control.[19] To enhance wound healing, a wide range of new therapies are being examined. The goal of this article was to review and discuss the current standard of care and current DFU treatment recommendations. We also examined the latest therapies for DFU.

Methods

An extensive review was conducted by using various databases (MEDLINE, PubMed, EMBASE, Cochrane Library, Web of Science, and Google Scholar) from 2000 to 2023. Specific terms related to therapies for foot ulcers were used, including stem cell, stem cell therapy, stem cell implantation, chorion/amnion, chorion/amnion therapy, human umbilical cord therapy, photobiomodulation therapy (PBM), low-level light therapy, laser therapy, and laser level. Three independent authors reviewed titles and abstracts, excluding irrelevant or duplicated articles, and assessed full texts for eligibility. Non-English articles and those involving non-human subjects were excluded. This study used a comprehensive literature review approach to assess the effectiveness of PBM and regenerative medicine in managing DFUs. It focused on English-language publications involving human participants from 2000 to 2023. Inclusion criteria comprised studies on DFUs in humans, investigating PBM, wound dressings, off-loading devices, adjunct medicines, and stem cell therapy. Exclusion criteria included non-English publications, studies on non-human subjects, and review articles. A systematic search using predefined keywords and Medical Subject Headings (MeSH) terms was followed by the independent screening of titles, abstracts, and full-text articles by two reviewers. Data extraction, quality assessment, and result synthesis were conducted rigorously to ensure a comprehensive and systematic review process (Figure 1).

Results

Types of Treatments for Diabetic foot Ulcers

DFUs put a significant burden on governments. For instance, in the United States, 14% to 20% of diabetic patients undergo amputation operations, totaling over six billion dollars annually. A multidisciplinary approach involving specialties like nursing, endocrinology, plastic surgery, vascular surgery, nutrition, and orthopedics has been shown to reduce the DFU and amputation risk by 50% to 85%, lower costs, and improve patients' quality of life.[20,21]

Photobiomodulation

Photons, emitted as light, carry energy based on their wavelength. It is shown that they can cause a biological effect when they are absorbed by molecules of a tissue, which are called chromophores. Each chromophore reacts at a specific wavelength. For example, the wavelengths that are mostly used for clinical purposes are between 600 to 1064 nm (specifically between 690 nm and 860 nm) because of their penetration ability and effectiveness into human cells.[22] The process is called PBM due to its photobiological and photochemical effects, and it is not thermal as it was called low-level laser therapy (LLLT) in the past.[22,23] PBM is a safe, cost-effective, noninvasive therapy for DFUs. Skin color affects photon absorption. About 30% of light is reflected, with the rest scattered, absorbed, or transmitted based on the wavelength. Treatment efficacy relies on the "optical window" where tissue-light interaction occurs, with 600-700 nm wavelengths preferred for superficial wounds and 780-950 nm for deeper wounds due to their enhanced penetration.[23] A double-blind, randomized, placebo-controlled study demonstrated that combined 660 and 890 nm LED phototherapy significantly enhanced the healing of diabetic ulcers compared to placebo. This indicates the potential for accelerating tissue granulation and healing rates in challenging cases.[24] There are many studies about the use of LLLT for DFUs. Ebad et al[25] studied LLLT with 630 and 819 nm wavelengths for treating diabetic peripheral neuropathy (DPN). They found significant improvement in sensory function in patients receiving LLLT, indicating its potential as a non-invasive treatment for managing DPN symptoms. Also, Kajagar et al[26] conducted a randomized controlled study

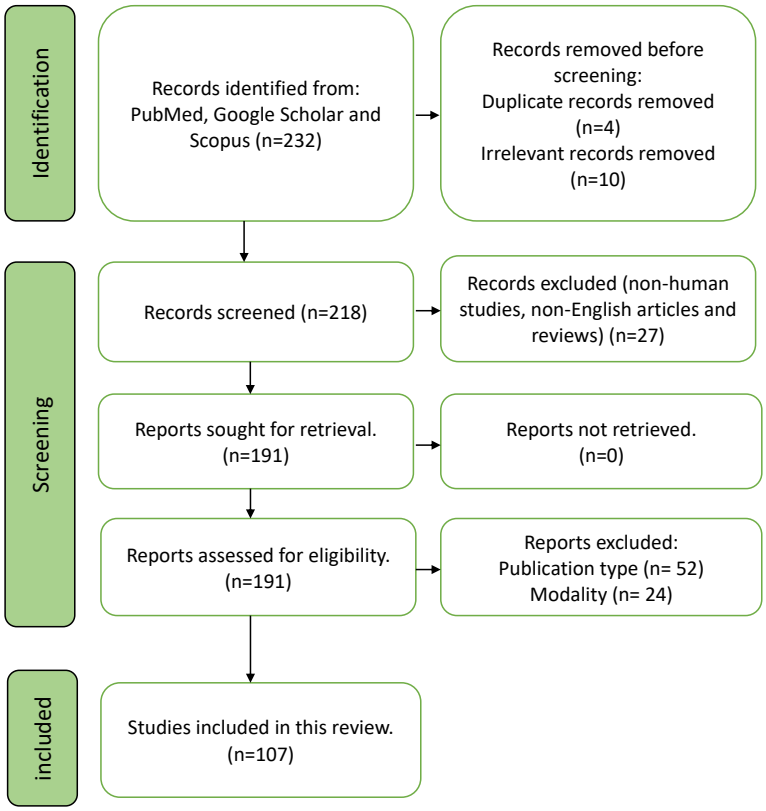

Figure 1. Identification of Studies via Databases and Registers

assessing LLLT as an adjunct to conventional therapy for DFUs. They found a notable difference in wound contraction, with LLLT-treated ulcers showing a mean percentage reduction of 40.24% compared to 11.87% in the control group. In 2011, Kaviani et al conducted a double-blind randomized clinical trial assessing the efficacy of LLLT in chronic DFU healing acceleration. By week four, the LLLT group exhibited significant ulcer size reduction compared to placebo. By week 20, more LLLT patients achieved complete healing, highlighting its potential efficacy.[27] On the other hand, Sandoval Ortíz et al conducted a randomized controlled trial comparing LLLT and HVPC with standard wound care (SWC) for DFUs. Despite adjunct therapies, no significant differences were observed in healing rates, protective sensation, nerve conduction studies, or quality of life. The study highlights the necessity for larger-scale investigations and additional care components to fully assess the potential benefits of biophysical agents in managing diabetic ulcers.[28] Maiya et al[29] examined PBM therapy effects on 17 type 2 diabetic patients with peripheral neuropathy and ischemic DFUs using scanning and a non-contact probe. Healing progress was monitored weekly until complete wound closure, alongside investigating the impact of matrix metalloproteinases (MMPs) on wound healing in diabetic patients. MMPs aid wound healing by extracellular matrix (ECM) removal in the inflammatory phase. PBM restores MMP balance, crucial for optimal healing.[30] In 2020, Raizman and Gavish[31] evaluated the efficacy of a self-applied PBM device at home for treating DFUs in four cases, aiming to determine its effectiveness while considering the benefits of PBM. This approach could reduce the time and cost of clinic visits for laser therapy. All patients experienced wound healing within 1 to 3 weeks without adverse effects and reported pain reduction satisfaction. In 2021, Haze et al conducted research on home PBM laser therapy for treating DFUs in patients with significant co-morbidities. They found that the wound size significantly decreased compared to untreated individuals, with over 90% of wounds healing in diabetic patients with serious co-morbidities using PBM at home.[32]

Wound Dressings

There is no single specific dressing work for all DFUs due to their variations. Dressings should provide a moist environment to promote angiogenesis, autolytic debridement, granulation, and epidermal cell migration. They should also manage excessive wound exudates. An ongoing study discusses numerous dressing varieties for DFU treatment.[9] Various wound dressings, both traditional and modern, exist with unique qualities and underlying theories. They can be categorized as basic, advanced, antimicrobial, and specialist types. However, none has demonstrated clear superiority over others.[33] Researchers have studied the efficacy of natural remedies

like honey and aloe vera for DFUs. Their high osmolarity promotes hygroscopic activity, improving lymphatic and blood circulation, which aids in autolytic debridement by enhancing protease activity.[34]

Forty years ago, animal experiments showed that maintaining moist wounds accelerates healing compared to allowing them to dry and scab. Moist environments aid cell healing and promote autolytic debridement.[33]

Alginate Dressing

Alginate dressing, either sodium or calcium sea alginate, absorbs wound exudate and can be mixed with collagen. Upon contact with the wound, it forms a gel that can be easily removed with the dressing or cleaned with sterile saline. Alginate dressings are used for extremely wet wounds to absorb excess moisture and prevent skin impregnation, owing to their high hydrophilic nature.[35]

Hydrogel Dressing

Hydrogel dressing is made of a crosslinked insoluble polymer containing up to 96% water. It absorbs wound exudate or rehydrates a wound based on moisture levels. It comes in beads, amorphous hydrogel, or flat sheets.[36]

Mepitel Films

Mepitel film is a new wound dressing combining a polyurethane film with a Safetac wound contact layer, supported by a paper frame for easy application. It is designed for burns and skin injuries, providing delicate skin protection. Compatible with gels and ointments, it can be covered with fixation tapes.[37]

Protease-Modulating Matrix Dressings

Chronic wounds result from an imbalance between tissue deposition (induced by growth factors) and tissue breakdown (mediated by proteases), with a bias towards tissue breakdown. PROMOGRAN deactivates key proteases found in fluid from chronic wounds, restoring the balance between tissue production and breakdown by reducing harmful substances.[38]

Honey Dressing

Honey has antibacterial properties against a wide range of bacteria due to its Acidic pH, hyperosmolarity, inhibins, antioxidants, hydrogen peroxide (H2O2), and various enzymes. Studies have shown anti-pseudomonal activity. The healing properties of honey are attributed to improvements in epithelization, neoangiogenesis, and collagen production, mediated by growth factors/chemokines (VGEF, IL-6, IL-12, etc.) and signaling pathways.[34]

Off-Loading Devices

DFUs result mainly from improper footwear, sudden injuries, and neuropathy-induced pressure. Improper shoes elevate foot pressure, reducing tissue perfusion, while neuropathy causes sensory, autonomic, and motor issues, leading to toe deformities and increased foot pressure.[39] The goal is to reduce vertical pressure, which can be achieved through such methods as complete bed rest, wheelchair use, or off-loading devices. Among these methods, the off-loading device is more practical than others are. In the following, we will discuss different types of offloading devices.[40-44]

1. Felted-foam dressing (FFD): It is multilayer felted foam in which the first layer applies at least 1 inch beyond the edges of the ulcer and is fixed to the foot with the second layer.[39]
2. Post-operation shoes: They are lightweight medical shoes and can have a closed or opened toe with a flat and rigid sole.[44] They can protect the foot and pressure relief.[39]
3. Removable long-leg walking boots (RCW): Walking braces, also known as removable knee-high devices, support and immobilize the ankle joint and forefoot for faster healing.[45,46]
4. Non-removable long-leg walking cast: It is a TCC, which is a non-removable knee-high device. It fully contacts the foot and is made of plaster or fiberglass.[45-48]

Comparison of Different Types of Offloading Devices

Post-op shoes and FFDs do not lock the ankle joint during push-off, causing shear stress and pressure on the foot, leading to longer recovery times compared to other offloading devices. Post-op shoes take an average of 85 days to heal, while FFDs take 75 days. In contrast, TCC and walking braces have shorter healing of 42 days 48. Despite limitations, many patients prefer FFDs and post-op shoes for their affordability, comfort, and lower fall risk compared to TCC and walking braces, especially among the elderly.[39] Therefore, FFD and post-op shoes are recommended in the guidelines.

Adjunct Treatment

A major concern in diabetic patients is chronic DFUs, which can lead to upper limb infection and life-threatening consequences. Clinicians often use adjunct treatments alongside main therapy, selecting them based on DFU classifications. Some of the classifications are:

- The Grading of Recommendation Assessment, Development, and Evaluation
- International Working Group on Diabetic Foot
- Classic Wagner
- University of Texas Health Science Center in San Antonio
- Infectious Disease Society of Americans.[49]

Hyperbaric Oxygen Therapy

One of the adjunct treatments commonly used is hyperbaric oxygen therapy (HBOT). In HBOT, the patient is placed in a chamber where 100% oxygen is diffused while the atmospheric pressure is increased.[50]

The latest clinical practice guideline recommends the use of HBOT in specific types of diabetic patients with DFUs:

- For patients with a lower DFU, it is suggested to avoid HBOT.
- For high-risk DFU patients showing no signs of recovery after 30 days, a combination of HBOT and standard treatment is recommended to decrease the risk of major amputation.
- For high-risk DFU patients who have undergone surgical debridement of an infected foot, combining acute postoperative HBOT with standard treatment is suggested to reduce the risk of major amputation and incomplete healing.[49]

The mechanisms of HBOT are unclear, but one theory posits that it enhances healing by increasing oxygen levels in damaged tissue. Normally, oxygen is supplied by microvascular arteries [51-53]. Furthermore, HBOT has bacteriostatic effects.[54]

Negative pressure wound therapy

Many studies support the use of negative pressure wound therapy (NPWT), especially in postoperative diabetic patients. NPWD devices apply varying levels of suction to the wound to reduce local pressure.

NPWT's Mechanism of Action

a. Macro-deformation: The NPWT device applies suction, which can bring the edges of the wound closer, reducing its size.[55]
b. Fluid removal**:** The body comprises intravascular, intracellular, and extracellular fluids. In DFUs, extracellular edema can compress microvasculature, impairing tissue perfusion. NPWT regulates fluid circulation, mitigating fluid overload using the Starling equation.[55,56]
c. Micro-deformation: NPWD causes stretching of the cell wall, triggering the molecular response that leads to neovascularization due to mechanical force and hypoxia.[56-58]

There have been different types of studies investigating the NPWT mechanism at the molecular level, and they are categorized as follows:

1. Human studies[59-65]
2. Animal models[66-72]
3. *In vitro* models[73,74]

These studies have provided some overlapping and contrasting findings. In the following, an attempt has been made to explain the mechanism of NPWT.[58]

Effects of NPWT on Cytokines and Chemokine Expression

- Interleukin 8 (IL-8): The application of NPWT locally increases IL-8 levels. IL-8 is an important chemokine involved in regulating neutrophil function and macrophage migration.[61,75,76]
- Interleukin 10 (IL-10): NPWT application leads to a significant increase in the systemic level of IL-10.[68] This results in a decrease in the number of CD68 positive macrophages.[59] However, a non-randomized, non-blinded trial of 21 human traumatic wounds dressed with Epigard did not demonstrate any expression of IL-10.[64]
- Tumor necrosis factor (TNF): Two different studies using different methods 41 have shown a notable reduction in local TNF levels.[63,64]
- Interleukin 6 (IL-6): Three studies have examined the effect of NPWT on IL-6 expression. Two large studies by Labler et al[64] found no signs of IL-6 expression following NPWT application. In addition, another study using a porcine model did not observe any signs of IL-6 expression.

Effects of NPWT on Growth Factor Expression

- Vascular endothelial growth factor (VEGF): More studies have concentrated on VEGF changes compared to other inflammatory factors. Seven papers, comprising three human studies and four animal studies, reported an elevation in VEGF levels after NPWT application.[61,65,66,70-76]
- Fibroblast growth factor (FGF): FGF2, an angiogenic factor, was studied *in vitro* 74, Rat Wound 67 and Human Models.

FGF2 expression increased in vitro, while in the human model, no difference in the level of FGF2 was observed due to the application of NPWT.[64]

Overall, all of these data suggest NPWT helps wounds through different pathways, including local immune modulation, mechanoreceptor signaling, and hypoxia-mediated signaling.[58] Tissue traumas trigger inflammatory factors, activating resident macrophages, circulating monocytes, and engaging neutrophils.[77] Other inflammatory factors, such as leukocytes, infiltrate the inflammatory site and lead to the synthesis of pro-inflammatory cytokines, especially TNF and IL-6 78. As mentioned earlier in this study, NPWT application affects pro-inflammatory cytokine expression and signaling, shifting towards an anti-inflammatory phenotype. This is achieved by reducing TNF expression, locally engaging macrophages, increasing systemic IL-10, and elevating IL-8 at the wound bed.[78]

The volume of filler material changes as a result of the application of NPWT, and this deformational force leads to cell strain.[79] This mechanical stress induces cell proliferation, which is under stress. Then, Integrin, a transmembrane receptor that aids in cell-cell and cell-extracellular adhesion,[80] triggers mechanoreceptor signaling pathways,

which upregulate the expression of proto-oncogenes like *myc, c-jun, and Bcl-2*. This, in turn, affects cellular meiotic rate and signals for ECM synthesis and remodeling.[81-83] Early growth response (EGR-1), a significant nuclear mechanoreceptor, contributes to wound healing by expressing VEGF, PDGF, TGF-B1, and FGF-2 83. VEGF and TGF-B1 prompt EGR-1 expression. NPWT induces mechanoreceptors, stimulates HIF-1 synthesis under hypoxia, and reduces tissue blood flow.[84] HIF-1 signals genes that lead to collagen deposition and alignment.[85]

This is how hypoxic fibroblasts impact wound healing through the formation of the ECM. The relationship between EGR-1 and HIF-1 remains a question.[58]

Stem Cell Therapy

The standard treatment for DFUs usually involves medical treatment, along with surgical intervention to restore blood flow.[86] Combination treatments are effective for DFUs but ineffective in foot ischemia cases due to reduced distal arterial outflow. Surgical interventions like angioplasty below the knee are challenging due to limited arterial involvement.[86-88] Diabetic patients with cardiovascular or cerebrovascular issues may not qualify for arterial bypass. Stem cell therapy is vital for chronic DFU treatment, offering comprehensive tissue regeneration compared to topical growth factors.[86] Stem cells promote angiogenesis by activating repair cell activities and increasing ECM synthesis.[89,90] Some animal studies have also shown improved blood circulation in ischemic limbs following stem cell implantation.[91-92] In addition, stem cell therapy plays a key role in post-injury and routine homeostasis skin repair, reducing the complications of severe DFUs.[86] Different types of stem cells are used in DFUs, including autologous, allogeneic, and xenotransplantation cells.[93]

Autologous Stem Cell Therapy

Autologous stem cell therapy (ASCT) is an advanced and unique therapy for chronic lower extremity wounds.[89,90,94-96]

The first human trial in 2002 involved bone marrow mononuclear cell implantation, which proved to be effective and safe.[90]

Subsequent studies have shown that the combination of traditional treatment with ASCT is more effective than traditional treatment alone for chronic wound healing.[90,97]

Bone Marrow Derived Stem Cell

Bone marrow is ideal for treating chronic wounds because it contains MSCs, inflammatory cells, and multipotent stem cells, all of these factors contribute to wound healing.[98,99] Additionally, hematopoietic hormones such as granulocytes colony-stimulating factor (G-CSF) promote wound healing and can fill the dermis.[100] Due to their plasticity, they can also produce new skin cells.[101]

In another study, Dash et al[102] reported that the application of autologous bone marrow mesenchymal stem cells (BMMSCs) was safe and simple to use. Wu et al[103] found that combining autologous platelet-rich gel (APG) with BMMSCs aided DFU healing and tissue regeneration. BMNCs and BMMSCs reduced pain and improved perfusion, with BMNCs achieving complete healing four weeks earlier.[104]

Peripheral Blood Stem Cells and G-CSF

Scatena et al[105] compared PBMNC treatment with standard treatment in no-option critical limb ischemia, reporting a lower amputation rate and a higher survival rate in the PBMNC group compared to the control group during a two-year follow-up.

Administered subcutaneously, intramuscularly, intravenously, or rarely topically, G-CSF promotes neutrophil growth and supports immunity.[106,107] Different studies on DFU treatment are shown in Table 1.

Discussion

A DFU presents a healthcare challenge, with high morbidity and costs. In extreme cases, amputation can have a fatal consequence. Due to the intricate nature of this condition, a multidisciplinary treatment reduces the DFU and amputation risk. A number of specific treatment techniques have gained recognition within this comprehensive approach. Comprehensive studies[40,43] highlight the clinical effectiveness of offloading devices, emphasizing the practicality and patient compliance associated with FFD, post-operation shoes, removable long-leg walking boots (RCW), and non-removable long-leg walking casts (total contact cast - TCC). Although FFD and post-op shoes may lengthen healing times, their inclusion in guidelines is justified due to their affordability and comfort, particularly for elderly patients.[39,46] The wide range of offloading options caters to diverse patient needs and preferences. According to the studies, wound dressings play a crucial role in DFU management by creating a moist wound environment that facilitates granulation tissue formation and autolytic debridement. Various options are available, including alginate dressings, hydrogel dressings, Mepitel films, protease-modulating matrix dressings, and honey dressings.[33-35,37,38] While each dressing has unique properties, no single dressing has demonstrated superiority over others. Therefore, selecting a dressing depends on the individual patient's needs and wound characteristics.

PBM, a non-invasive intervention, has shown promise for improving DFU healing. By utilizing LLLT in specific wavelength ranges, PBM triggers beneficial cellular responses like angiogenesis and tissue repair. Its non-thermal nature makes it a favorable option for patients, considering factors like skin color to optimize outcomes.[22,23,29] Compared to other treatments, PBM

Table 1. Diabetic Foot Ulcers treatment and intervention.

Authors	Population	Intervention	Result
Maiya et al[29]	17 participants with T2DM	PBMT with non-contact probe	Wound closure occurred within 26±11 days, preventing future complications.
Raizman and Gavish[31]	4	Self-applied PBM device at home	Patients experienced wound healing in 1-3 weeks with pain reduction.
Haze et al[32]	20 Patients with severe co-morbidities	PBM laser therapy at home	Significant wound closure (>90%) with no adverse effects was observed.
Caravaggi et al[42]	50 DM patients with neuropathic plantar ulcers	2 groups: Shoe group (cloth shoe with rigid sole), Cast group (nonremovable off-bearing fiberglass cast)	Cast group: Faster ulcer area reduction, 50% completely healed after 30 days. Just in the shoe group, new ulcers were seen.
Wu et al[43]	901 DFU treatment centers in 50 states of America	A diabetic foot management survey was sent about off-loading devices	TCC, the gold standard for pressure reduction in DFU, was used in only 1.7% of centers; shoe mods prevalent.
Zimny et al[48]	54 type 1 and 2 diabetic patients with a DFU	Two groups: FFD therapy (24 patients) vs. conventional therapy (30 patients).	FFD therapy is effective for a DFU, particularly in patients with weight-bearing limitations.
Eisenhardt et al[59]	30 patients with skin grafted free muscle transfer for covering defect	First group: flap covered with NPWT. Second group: covered with petroleum gauze dressings.	NPWT reduced inflammation, improved microcirculation, and minimized tissue damage in skin-grafted muscle flaps.
Labler et al[61]	32 patients with traumatic wounds	2 groups: Temporary covering with vacuum-assisted closure (VAC) and Epigard application	VAC therapy can increase local IL-8 and VEGF concentration in the wound place, cause more angiogenesis, and help neovascularization.
Younan, G., et al[69]	20 mice with wound	2 groups: VAC therapy and foam-dressing or occlusive dressing as controls	VAC enhances nerve fiber and neuropeptide production, improving wound healing, especially in denervated wounds like DFUs.
Carstens, M. H., et al[97]	63 type 2 DM with a chronic DFU (all candidate for amputation)	Local injections of autologous adipose-derived SVF cells	After 6 months, 51 patients' wounds were fully closed, 8 nearly 75% closed, with 3 early amputations and 1 death. Therefore, SVF showed excellent wound healing.
Scatena et al[105]	76 No-option critical limb ischemia (NO-CLI)	Standard care given to all; 38 had PBMNCs implants additionally.	PBMNCs reduced amputations (4/38 vs. 15/38) and improved two-year survival (80% vs. 20%) with 87% experiencing healing.
Wu et al[103]	54-year-old DM patients with a DFU that had an infection	Standard care: insulin for glucose, anti-infection treatment, APG+BMMSC.	APG combined with in vitro amplified BMMSCs may enhance DFU healing, yet additional research is warranted to validate its efficacy.
Minatel, D. G. et al[24]	23 diabetic leg ulcers	Two groups: both treated with silver sulfadiazine cream and phototherapy (placebo vs. 3 J/cm^2).	Group two showed superior healing rates on days 15, 30, 45, 60, 75, and 90, with 58.3% fully healed by day 90.
Ebadi et al[25]	60 Diabetic peripheral neuropathy (DPN) patients	The laser group received LLLT (630 and 819 nm)+conventional therapy; the control had no laser.	Patients' sensation of both right and left foot with the monofilament test increased significantly. No side effects were seen.
Kajagar et al[26]	68 type 2 diabetic ulcer patients stayed>4 weeks, culture-free.	2 groups: LLLT group plus conventional therapy and control group with only conventional therapy	According to the size of ulcers after 15 days, it was said that LLLT could be a good adjunct to conventional therapy for DFUs.
Kaviani et al[27]	23 patients with DFUs	2 groups: placebo group only received conventional therapy, Second group (LLLT) with conventional therapy	After 20 weeks, 8 patients in the LLLT group fully healed, compared to 3 in the control group, indicating accelerated healing.
Sandoval Ortíz et al[28]	28 diabetic patients	Three groups: 1) HPVC+SWC, 2) LLLT (685nm)+SWC, 3) SWC only (control group)	Healing rates in the 16th week were 7/9 for LLLT, 8/10 for HVPC, and 6/9 for control groups, with no significant differences.

appears to effectively treat DFUs with fewer side effects. Studies suggest that adjunct treatments like HBOT and NPWT in the management of DFUs have certain uncertainties and limitations. HBOT, involving the administration of oxygen under increased pressure, lacks consistent evidence supporting its effectiveness, and its recommendation varies based on specific DFU cases. NPWT, while demonstrating potential benefits, yields variable responses, including cytokine and growth factor expression, which do not consistently align across different study types (human, animal, and in vitro).[58,68] More research is necessary to grasp the limitations and challenges of adjunct treatments in DFU management. Despite the promise of stem cell therapy, its drawbacks and challenges warrant careful consideration. Autologous stem cell therapies, including bone marrow-derived and peripheral blood stem cells, may be constrained by patient health and age, influencing their effectiveness. Further research is necessary to ascertain their long-term safety and efficacy in DFU management, emphasizing the importance of cautious implementation.[101,105] In managing DFUs, treatment should be individualized, considering patient characteristics, wound specifics, and treatment preferences. The ideal approach often involves a combination of these modalities within a multidisciplinary framework, aiming to mitigate the burden of DFUs, improve outcomes, and reduce amputations. As research progresses, new treatments are expected to emerge, enhancing patient-centered care. Determining the superior treatment for DFUs is a complex task with no one-size-fits-all solution. The effectiveness of treatments depends on several factors, including wound

characteristics, patient health, adherence to treatment, and resource availability. A multidisciplinary approach is often favored for personalized care, considering cost, clinical evidence, and patient preferences. Monitoring treatment responses and healing rates is crucial. There is no universal "best" treatment for DFUs; it requires a comprehensive evaluation of these factors to optimize wound healing and enhance patient quality of life. However, PBM should receive more attention in DFU studies and research due to its lower side effects and cost-effectiveness.

Conclusion

In conclusion, managing DFUs is a complex and personalized endeavor, with treatment choices shaped by wound characteristics, patient health, resources, and preferences. Regular monitoring is vital. PBM offers a promising, cost-effective option with the potential for faster healing and fewer complications. When integrated into a personalized approach, PBM can improve DFU management and enhance patient outcomes.

Acknowledgments

We express our gratitude for the funding support provided by the Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences in Tehran, Iran.

Authors' Contribution

Conceptualization: Hojjat Allah Abbaszadeh, Fariborz Rashnoo.
Data curation: Elahe Torabi, Samareh Omidvari, Zahra Azimzadeh.
Formal analysis: Shahram Darabi, Aliasghar Keramatinia, Mohammad Ali Asghari.
Funding acquisition: Hojjat Allah Abbaszadeh, Fariborz Rashnoo.
Investigation: Elahe Torabi, Samareh Omidvari , Zahra Azimzadeh.
Methodology: Hojjat Allah Abbaszadeh.
Project administration: Hojjat Allah Abbaszadeh, Fariborz Rashnoo.
Resources: Shahram Darabi, Aliasghar Keratitis, Mohammad Ali Asghari.
Software: Shahram Darabi, Aliasghar Keratitis, Mohammad Ali Asghari.
Supervision: Hojjat Allah Abbaszadeh.
Validation: Elahe Torabi, Samareh Omidvar, Zahra Azimzadeh.
Visualization: Elahe Torabi, Samareh Omidvar, Zahra Azimzadeh.
Writing–original draft: Hojjat Allah Abbaszadeh, Elahe Torabi, Samareh Omidvari, Zahra Azimzadeh.
Writing–review editing: Hojjat Allah Abbaszadeh, Fariborz Rashnoo.

Competing Interests

The authors declare that they have no conflict of interest.

Ethical Approval

All protocols were confirmed by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.LASER.REC.1401.003).

Funding

This work was financially supported by Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

References

1. Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. Nat Rev Nephrol. 2020;16(7):377-90. doi: 10.1038/s41581-020-0278-5.
2. Permutt MA, Wasson J, Cox N. Genetic epidemiology of diabetes. J Clin Invest. 2005;115(6):1431-9. doi: 10.1172/jci24758.
3. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017;128:40-50. doi: 10.1016/j.diabres.2017.03.024.
4. García-Chapa EG, Leal-Ugarte E, Peralta-Leal V, Durán-González J, Meza-Espinoza JP. Genetic epidemiology of type 2 diabetes in Mexican mestizos. Biomed Res Int. 2017;2017:3937893. doi: 10.1155/2017/3937893.
5. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia. 2001;44 Suppl 2:S14-21. doi: 10.1007/pl00002934.
6. Noor S, Zubair M, Ahmad J. Diabetic foot ulcer--a review on pathophysiology, classification and microbial etiology. Diabetes Metab Syndr. 2015;9(3):192-9. doi: 10.1016/j.dsx.2015.04.007.
7. Audit C. Registries management service. In: National Diabetes Foot Care Audit Report 2014-2015. NHS England Digital; 2014.
8. Bowling FL, Rashid ST, Boulton AJ. Preventing and treating foot complications associated with diabetes mellitus. Nat Rev Endocrinol. 2015;11(10):606-16. doi: 10.1038/nrendo.2015.130.
9. Everett E, Mathioudakis N. Update on management of diabetic foot ulcers. Ann N Y Acad Sci. 2018;1411(1):153-65. doi: 10.1111/nyas.13569.
10. Bandyk DF. The diabetic foot: pathophysiology, evaluation, and treatment. Semin Vasc Surg. 2018;31(2-4):43-8. doi: 10.1053/j.semvascsurg.2019.02.001.
11. Candrilli SD, Davis KL, Kan HJ, Lucero MA, Rousculp MD. Prevalence and the associated burden of illness of symptoms of diabetic peripheral neuropathy and diabetic retinopathy. J Diabetes Complications. 2007;21(5):306-14. doi: 10.1016/j.jdiacomp.2006.08.002.
12. Gregg EW, Gu Q, Williams D, de Rekeneire N, Cheng YJ, Geiss L, et al. Prevalence of lower extremity diseases associated with normal glucose levels, impaired fasting glucose, and diabetes among U.S. adults aged 40 or older. Diabetes Res Clin Pract. 2007;77(3):485-8. doi: 10.1016/j.diabres.2007.01.005.
13. Papachristou S, Pafili K, Papanas N. Skin AGEs and diabetic neuropathy. BMC Endocr Disord. 2021;21(1):28. doi: 10.1186/s12902-021-00697-7.
14. Alavi A, Sibbald RG, Mayer D, Goodman L, Botros M, Armstrong DG, et al. Diabetic foot ulcers: part I. Pathophysiology and prevention. J Am Acad Dermatol. 2014;70(1):1.e1-1.e18. doi: 10.1016/j.jaad.2013.06.055.
15. Apelqvist J. Diagnostics and treatment of the diabetic foot. Endocrine. 2012;41(3):384-97. doi: 10.1007/s12020-012-9619-x.
16. Boulton AJ. The diabetic foot: grand overview, epidemiology and pathogenesis. Diabetes Metab Res Rev. 2008;24 Suppl 1:S3-6. doi: 10.1002/dmrr.833.
17. Rubitschung K, Sherwood A, Crisologo AP, Bhavan K, Haley RW, Wukich DK, et al. Pathophysiology and molecular imaging of diabetic foot infections. Int J Mol Sci. 2021;22(21):11552. doi: 10.3390/ijms222111552.
18. Ababneh A, Bakri FG, Khader Y, Lazzarini P, Ajlouni K.

Prevalence and associates of foot deformities among patients with diabetes in Jordan. Curr Diabetes Rev. 2020;16(5):471-82. doi: 10.2174/1573399815666191001101910.
19. Lim JZ, Ng NS, Thomas C. Prevention and treatment of diabetic foot ulcers. J R Soc Med. 2017;110(3):104-9. doi: 10.1177/0141076816688346.
20. Perez-Favila A, Martinez-Fierro ML, Rodriguez-Lazalde JG, Cid-Baez MA, de Jesús Zamudio Osuna M, Del Rosario Martinez-Blanco M, et al. Current therapeutic strategies in diabetic foot ulcers. Medicina (Kaunas). 2019;55(11):714. doi: 10.3390/medicina55110714.
21. Wang C, Mai L, Yang C, Liu D, Sun K, Song W, et al. Reducing major lower extremity amputations after the introduction of a multidisciplinary team in patient with diabetes foot ulcer. BMC Endocr Disord. 2016;16(1):38. doi: 10.1186/s12902-016-0111-0.
22. Mohsenifar Z, Fridoni M, Ghatrehsamani M, Abdollahifar MA, Abbaszadeh H, Mostafavinia A, et al. Evaluation of the effects of pulsed wave LLLT on tibial diaphysis in two rat models of experimental osteoporosis, as examined by stereological and real-time PCR gene expression analyses. Lasers Med Sci. 2016;31(4):721-32. doi: 10.1007/s10103-016-1916-9.
23. Dhlamini T, Houreld NN. Clinical effect of photobiomodulation on wound healing of diabetic foot ulcers: does skin color needs to be considered? J Diabetes Res. 2022;2022:3312840. doi: 10.1155/2022/3312840.
24. Minatel DG, Frade MA, França SC, Enwemeka CS. Phototherapy promotes healing of chronic diabetic leg ulcers that failed to respond to other therapies. Lasers Surg Med. 2009;41(6):433-41. doi: 10.1002/lsm.20789.
25. Ebadi SA, Tabeie F, Tavakoli S, Khalili S. Effects of photobiomodulation with two wavelengths of 630 and 810 nm on diabetic neuropathy. J Lasers Med Sci. 2023;14:e22. doi: 10.34172/jlms.2023.22.
26. Kajagar BM, Godhi AS, Pandit A, Khatri S. Efficacy of low level laser therapy on wound healing in patients with chronic diabetic foot ulcers-a randomised control trial. Indian J Surg. 2012;74(5):359-63. doi: 10.1007/s12262-011-0393-4.
27. Kaviani A, Esmaeeli Djavid G, Ataie-Fashtami L, Fateh M, Ghodsi M, Salami M, et al. A randomized clinical trial on the effect of low-level laser therapy on chronic diabetic foot wound healing: a preliminary report. Photomed Laser Surg. 2011;29(2):109-14. doi: 10.1089/pho.2009.2680.
28. Sandoval Ortíz MC, Herrera Villabona E, Camargo Lemos DM, Castellanos R. Effects of low-level laser therapy and high voltage stimulation on diabetic wound healing. Salud UIS. 2014;46(2):107-17.
29. Maiya AG, Kumar AS, Hazari A, Jadhav R, Ramachandra L, Hande HM, et al. Photobiomodulation therapy in neuroischaemic diabetic foot ulcers: a novel method of limb salvage. J Wound Care. 2018;27(12):837-42. doi: 10.12968/jowc.2018.27.12.837.
30. Ayuk SM, Abrahamse H, Houreld NN. The role of matrix metalloproteinases in diabetic wound healing in relation to photobiomodulation. J Diabetes Res. 2016;2016:2897656. doi: 10.1155/2016/2897656.
31. Raizman R, Gavish L. At-home self-applied photobiomodulation device for the treatment of diabetic foot ulcers in adults with type 2 diabetes: report of 4 cases. Can J Diabetes. 2020;44(5):375-8. doi: 10.1016/j.jcjd.2020.01.010.
32. Haze A, Gavish L, Elishoov O, Shorka D, Tsohar T, Gellman YN, et al. Treatment of diabetic foot ulcers in a frail population with severe co-morbidities using at-home photobiomodulation laser therapy: a double-blind, randomized, sham-controlled pilot clinical study. Lasers Med Sci. 2022;37(2):919-28. doi: 10.1007/s10103-021-03335-9.
33. Wu L, Norman G, Dumville JC, O'Meara S, Bell-Syer SE. Dressings for treating foot ulcers in people with diabetes: an overview of systematic reviews. Cochrane Database Syst Rev. 2015;2015(7):CD010471. doi: 10.1002/14651858.CD010471.pub2.
34. Rayate AS, Nagoba BS, Mumbre SS, Mavani HB, Gavkare AM, Deshpande AS. Current scenario of traditional medicines in management of diabetic foot ulcers: A review. World J Diabetes. 2023;14(1):1-16. doi: 10.4239/wjd.v14.i1.1.
35. Zhou DR, Deng HY, Pu LL, Lin SL, Gou R, Wang FL. The effectiveness and safety of recombinant human growth hormone combined with alginate dressing in the treatment of diabetic foot ulcer: a protocol for systematic review and meta-analysis. Medicine (Baltimore). 2021;100(5):e23984. doi: 10.1097/md.0000000000023984.
36. Dumville JC, O'Meara S, Deshpande S, Speak K. Hydrogel dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev. 2013;2013(7):CD009101. doi: 10.1002/14651858.CD009101.pub3.
37. Meuleneire F. A vapour-permeable film dressing used on superficial wounds. Br J Nurs. 2014;23(15):S36-43. doi: 10.12968/bjon.2014.23.Sup15.s36.
38. Cullen B, Smith R, McCulloch E, Silcock D, Morrison L. Mechanism of action of PROMOGRAN, a protease modulating matrix, for the treatment of diabetic foot ulcers. Wound Repair Regen. 2002;10(1):16-25. doi: 10.1046/j.1524-475x.2002.10703.x.
39. Giacalone V. Off-loading the diabetic foot. Podiatry Management. 2006;25(3):253-64.
40. Morona JK, Buckley ES, Jones S, Reddin EA, Merlin TL. Comparison of the clinical effectiveness of different off-loading devices for the treatment of neuropathic foot ulcers in patients with diabetes: a systematic review and meta-analysis. Diabetes Metab Res Rev. 2013;29(3):183-93. doi: 10.1002/dmrr.2386.
41. Levin ME. Preventing amputation in the patient with diabetes. Diabetes Care. 1995;18(10):1383-94. doi: 10.2337/diacare.18.10.1383.
42. Caravaggi C, Faglia E, De Giglio R, Mantero M, Quarantiello A, Sommariva E, et al. Effectiveness and safety of a nonremovable fiberglass off-bearing cast versus a therapeutic shoe in the treatment of neuropathic foot ulcers: a randomized study. Diabetes Care. 2000;23(12):1746-51. doi: 10.2337/diacare.23.12.1746.
43. Wu SC, Jensen JL, Weber AK, Robinson DE, Armstrong DG. Use of pressure offloading devices in diabetic foot ulcers: do we practice what we preach? Diabetes Care. 2008;31(11):2118-9. doi: 10.2337/dc08-0771.
44. Waduge SD. Medically Reviewed by Drugs. com. Last updated on Jul 3, 2020.
45. Bus SA, Armstrong DG, Gooday C, Jarl G, Caravaggi C, Viswanathan V, et al. Guidelines on offloading foot ulcers in persons with diabetes (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36 Suppl 1:e3274. doi: 10.1002/dmrr.3274.
46. Fernando ME, Horsley M, Jones S, Martin B, Nube VL, Charles J, et al. Australian guideline on offloading treatment for foot ulcers: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. J Foot Ankle Res. 2022;15(1):31. doi: 10.1186/s13047-022-00538-3.
47. National Institute for Health and Care Excellence (NICE). Diabetic Foot Problems: Prevention and Management (NICE Guideline NG19). NICE; 2019.
48. Zimny S, Schatz H, Pfohl U. The effects of applied felted foam on wound healing and healing times in the therapy of neuropathic diabetic foot ulcers. Diabet Med. 2003;20(8):622-5. doi: 10.1046/j.1464-5491.2003.01011.x.

49. Huang ET, Mansouri J, Murad MH, Joseph WS, Strauss MB, Tettelbach W, et al. A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers. Undersea Hyperb Med. 2015;42(3):205-47.
50. Braswell C, Crowe DT. Hyperbaric oxygen therapy. Compend Contin Educ Vet. 2012;34(3):E1-6.
51. Tibbles PM, Edelsberg JS. Hyperbaric-oxygen therapy. N Engl J Med. 1996;334(25):1642-8. doi: 10.1056/nejm199606203342506.
52. Hunt TK, Hopf HW. Wound healing and wound infection. What surgeons and anesthesiologists can do. Surg Clin North Am. 1997;77(3):587-606. doi: 10.1016/s0039-6109(05)70570-3.
53. Krogh A. The number and distribution of capillaries in muscles with calculations of the oxygen pressure head necessary for supplying the tissue. J Physiol. 1919;52(6):409-15. doi: 10.1113/jphysiol.1919.sp001839.
54. Thom SR. Hyperbaric oxygen: its mechanisms and efficacy. Plast Reconstr Surg. 2011;127(Suppl 1):131S-41S. doi: 10.1097/PRS.0b013e3181fbe2bf.
55. Huang C, Leavitt T, Bayer LR, Orgill DP. Effect of negative pressure wound therapy on wound healing. Curr Probl Surg. 2014;51(7):301-31. doi: 10.1067/j.cpsurg.2014.04.001.
56. Orgill DP, Manders EK, Sumpio BE, Lee RC, Attinger CE, Gurtner GC, et al. The mechanisms of action of vacuum assisted closure: more to learn. Surgery. 2009;146(1):40-51. doi: 10.1016/j.surg.2009.02.002.
57. Saxena V, Hwang CW, Huang S, Eichbaum Q, Ingber D, Orgill DP. Vacuum-assisted closure: microdeformations of wounds and cell proliferation. Plast Reconstr Surg. 2004;114(5):1086-96. doi: 10.1097/01.prs.0000135330.51408.97.
58. Glass GE, Murphy GF, Esmaeili A, Lai LM, Nanchahal J. Systematic review of molecular mechanism of action of negative-pressure wound therapy. Br J Surg. 2014;101(13):1627-36. doi: 10.1002/bjs.9636.
59. Eisenhardt SU, Schmidt Y, Thiele JR, Iblher N, Penna V, Torio-Padron N, et al. Negative pressure wound therapy reduces the ischaemia/reperfusion-associated inflammatory response in free muscle flaps. J Plast Reconstr Aesthet Surg. 2012;65(5):640-9. doi: 10.1016/j.bjps.2011.11.037.
60. Greene AK, Puder M, Roy R, Arsenault D, Kwei S, Moses MA, et al. Microdeformational wound therapy: effects on angiogenesis and matrix metalloproteinases in chronic wounds of 3 debilitated patients. Ann Plast Surg. 2006;56(4):418-22. doi: 10.1097/01.sap.0000202831.43294.02.
61. Labler L, Rancan M, Mica L, Härter L, Mihic-Probst D, Keel M. Vacuum-assisted closure therapy increases local interleukin-8 and vascular endothelial growth factor levels in traumatic wounds. J Trauma. 2009;66(3):749-57. doi: 10.1097/TA.0b013e318171971a.
62. Shi B, Chen SZ, Zhang P, Li JQ. [Effects of vacuum-assisted closure (VAC) on the expressions of MMP-1, 2, 13 in human granulation wound]. Zhonghua Zheng Xing Wai Ke Za Zhi. 2003;19(4):279-81. [Chinese].
63. Stechmiller JK, Kilpadi DV, Childress B, Schultz GS. Effect of vacuum-assisted closure therapy on the expression of cytokines and proteases in wound fluid of adults with pressure ulcers. Wound Repair Regen. 2006;14(3):371-4. doi: 10.1111/j.1743-6109.2006.00134.x.
64. Labler L, Mica L, Härter L, Trentz O, Keel M. [Influence of VAC-therapy on cytokines and growth factors in traumatic wounds]. Zentralbl Chir. 2006;131 Suppl 1:S62-7. doi: 10.1055/s-2006-921511. [German].
65. Cao DY, Chen SZ, Tang SY, Hu ZH, Song M, Lu XX. Effect of vacuum-assisted closure on angiogenesis of human chronic wound healing. Zhongguo Linchuang Kangfu. 2004;8:264-5.
66. Erba P, Ogawa R, Ackermann M, Adini A, Miele LF, Dastouri P, et al. Angiogenesis in wounds treated by microdeformational wound therapy. Ann Surg. 2011;253(2):402-9. doi: 10.1097/SLA.0b013e31820563a8.
67. Jacobs S, Simhaee DA, Marsano A, Fomovsky GM, Niedt G, Wu JK. Efficacy and mechanisms of vacuum-assisted closure (VAC) therapy in promoting wound healing: a rodent model. J Plast Reconstr Aesthet Surg. 2009;62(10):1331-8. doi: 10.1016/j.bjps.2008.03.024.
68. Kilpadi DV, Bower CE, Reade CC, Robinson PJ, Sun YS, Zeri R, et al. Effect of vacuum-assisted closure therapy on early systemic cytokine levels in a swine model. Wound Repair Regen. 2006;14(2):210-5. doi: 10.1111/j.1743-6109.2006.00112.x.
69. Younan G, Ogawa R, Ramirez M, Helm D, Dastouri P, Orgill DP. Analysis of nerve and neuropeptide patterns in vacuum-assisted closure-treated diabetic murine wounds. Plast Reconstr Surg. 2010;126(1):87-96. doi: 10.1097/PRS.0b013e3181da86d0.
70. Liu Y, Hu DH, Dong ML, Wang YC, Liu JQ, Bai L, et al. [Efficacy of vacuum sealing drainage in mice infected with Pseudomonas aeruginosa and its mechanism]. Zhonghua Shao Shang Za Zhi. 2011;27(4):255-9. [Chinese].
71. Yang F, Hu D, Bai XJ, Zhang K, Li RJ, Xue CC. [The influence of oxygen partial pressure change and vascularization of rabbit wound through negative pressure wound therapy]. Zhonghua Wai Ke Za Zhi. 2012;50(7):650-4. [Chinese].
72. Tang SY, Xu HR, Qi LJ, Guo YL, Ji HR. Effect of vacuum-assisted closure on angiogenesis during denervation of wound healing. Zhongguo Linchuang Kangfu. 2005;46:91-3.
73. McNulty AK, Schmidt M, Feeley T, Villanueva P, Kieswetter K. Effects of negative pressure wound therapy on cellular energetics in fibroblasts grown in a provisional wound (fibrin) matrix. Wound Repair Regen. 2009;17(2):192-9. doi: 10.1111/j.1524-475X.2009.00460.x.
74. Lu F, Ogawa R, Nguyen DT, Chen B, Guo D, Helm DL, et al. Microdeformation of three-dimensional cultured fibroblasts induces gene expression and morphological changes. Ann Plast Surg. 2011;66(3):296-300. doi: 10.1097/SAP.0b013e3181ea1e9b.
75. Koch AE, Polverini PJ, Kunkel SL, Harlow LA, DiPietro LA, Elner VM, et al. Interleukin-8 as a macrophage-derived mediator of angiogenesis. Science. 1992;258(5089):1798-801. doi: 10.1126/science.1281554.
76. Mukaida N, Harada A, Matsushima K. Interleukin-8 (IL-8) and monocyte chemotactic and activating factor (MCAF/MCP-1), chemokines essentially involved in inflammatory and immune reactions. Cytokine Growth Factor Rev. 1998;9(1):9-23. doi: 10.1016/s1359-6101(97)00022-1.
77. Chan JK, Roth J, Oppenheim JJ, Tracey KJ, Vogl T, Feldmann M, et al. Alarmins: awaiting a clinical response. J Clin Invest. 2012;122(8):2711-9. doi: 10.1172/jci62423.
78. Glass GE, Chan JK, Freidin A, Feldmann M, Horwood NJ, Nanchahal J. TNF-alpha promotes fracture repair by augmenting the recruitment and differentiation of muscle-derived stromal cells. Proc Natl Acad Sci U S A. 2011;108(4):1585-90. doi: 10.1073/pnas.1018501108.
79. Wilkes R, Zhao Y, Cunningham K, Kieswetter K, Haridas B. 3D strain measurement in soft tissue: demonstration of a novel inverse finite element model algorithm on MicroCT images of a tissue phantom exposed to negative pressure wound therapy. J Mech Behav Biomed Mater. 2009;2(3):272-87. doi: 10.1016/j.jmbbm.2008.10.006.
80. Hynes RO. Integrins: bidirectional, allosteric signaling machines. Cell. 2002;110(6):673-87. doi: 10.1016/s0092-8674(02)00971-6.

81. Galbraith CG, Sheetz MP. Forces on adhesive contacts affect cell function. Curr Opin Cell Biol. 1998;10(5):566-71. doi: 10.1016/s0955-0674(98)80030-6.
82. Kessler D, Dethlefsen S, Haase I, Plomann M, Hirche F, Krieg T, et al. Fibroblasts in mechanically stressed collagen lattices assume a "synthetic" phenotype. J Biol Chem. 2001;276(39):36575-85. doi: 10.1074/jbc.M101602200.
83. Schwachtgen JL, Houston P, Campbell C, Sukhatme V, Braddock M. Fluid shear stress activation of egr-1 transcription in cultured human endothelial and epithelial cells is mediated via the extracellular signal-related kinase 1/2 mitogen-activated protein kinase pathway. J Clin Invest. 1998;101(11):2540-9. doi: 10.1172/jci1404.
84. Glass GE, Nanchahal J. The methodology of negative pressure wound therapy: separating fact from fiction. J Plast Reconstr Aesthet Surg. 2012;65(8):989-1001. doi: 10.1016/j.bjps.2011.12.012.
85. Gilkes DM, Bajpai S, Chaturvedi P, Wirtz D, Semenza GL. Hypoxia-inducible factor 1 (HIF-1) promotes extracellular matrix remodeling under hypoxic conditions by inducing P4HA1, P4HA2, and PLOD2 expression in fibroblasts. J Biol Chem. 2013;288(15):10819-29. doi: 10.1074/jbc.M112.442939.
86. Yu Q, Qiao GH, Wang M, Yu L, Sun Y, Shi H, et al. Stem cell-based therapy for diabetic foot ulcers. Front Cell Dev Biol. 2022;10:812262. doi: 10.3389/fcell.2022.812262.
87. 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. doi: 10.1055/s-0042-103684.
88. Houlind K. Surgical revascularization and reconstruction procedures in diabetic foot ulceration. Diabetes Metab Res Rev. 2020;36 Suppl 1:e3256. doi: 10.1002/dmrr.3256.
89. Niknazar S, Abbaszadeh HA, Peyvandi H, Rezaei O, Forooghirad H, Khoshsirat S, et al. Protective effect of [Pyr1]-apelin-13 on oxidative stress-induced apoptosis in hair cell-like cells derived from bone marrow mesenchymal stem cells. Eur J Pharmacol. 2019;853:25-32. doi: 10.1016/j.ejphar.2019.03.012.
90. Ziaeipour S, Ahrabi B, Naserzadeh P, Aliaghaei A, Sajadi E, Abbaszadeh HA, et al. Effects of Sertoli cell transplantation on spermatogenesis in azoospermic mice. Cell Physiol Biochem. 2019;52(3):421-34. doi: 10.33594/000000030.
91. Kalka C, Masuda H, Takahashi T, Kalka-Moll WM, Silver M, Kearney M, et al. Transplantation of ex vivo expanded endothelial progenitor cells for therapeutic neovascularization. Proc Natl Acad Sci U S A. 2000;97(7):3422-7. doi: 10.1073/pnas.97.7.3422.
92. Takahashi T, Kalka C, Masuda H, Chen D, Silver M, Kearney M, et al. Ischemia- and cytokine-induced mobilization of bone marrow-derived endothelial progenitor cells for neovascularization. Nat Med. 1999;5(4):434-8. doi: 10.1038/7434.
93. El Hage R, Knippschild U, Arnold T, Hinterseher I. Stem cell-based therapy: a promising treatment for diabetic foot ulcer. Biomedicines. 2022;10(7):1507. doi: 10.3390/biomedicines10071507.
94. 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. doi: 10.1155/2013/462179.
95. Dai J, Jiang C, Chen H, Chai Y. Treatment of diabetic foot with autologous stem cells: a meta-analysis of randomized studies. Stem Cells Int. 2020;2020:6748530. doi: 10.1155/2020/6748530.
96. Rigato M, Monami M, Fadini GP. Autologous cell therapy for peripheral arterial disease: systematic review and meta-analysis of randomized, nonrandomized, and noncontrolled studies. Circ Res. 2017;120(8):1326-40. doi: 10.1161/circresaha.116.309045.
97. Carstens MH, Quintana FJ, Calderwood ST, Sevilla JP, Ríos AB, Rivera CM, et al. 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(8):1138-47. doi: 10.1002/sctm.20-0497.
98. Lingen MW. Role of leukocytes and endothelial cells in the development of angiogenesis in inflammation and wound healing. Arch Pathol Lab Med. 2001;125(1):67-71. doi: 10.5858/2001-125-0067-rolaec.
99. Gillitzer R, Goebeler M. Chemokines in cutaneous wound healing. J Leukoc Biol. 2001;69(4):513-21.
100. 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. doi: 10.1016/j.diabres.2011.10.032.
101. Badiavas EV, Falanga V. Treatment of chronic wounds with bone marrow-derived cells. Arch Dermatol. 2003;139(4):510-6. doi: 10.1001/archderm.139.4.510.
102. 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):359-66. doi: 10.1089/rej.2009.0872.
103. Wu Q, Lei X, Chen L, Zheng Y, Huang H, Qian C, et al. Autologous platelet-rich gel combined with in vitro amplification of bone marrow mesenchymal stem cell transplantation to treat the diabetic foot ulcer: a case report. Ann Transl Med. 2018;6(15):307. doi: 10.21037/atm.2018.07.12.
104. Lu D, Chen B, Liang Z, Deng W, Jiang Y, Li S, 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. doi: 10.1016/j.diabres.2010.12.010.
105. Scatena A, Petruzzi P, Maioli F, Lucaroni F, Ambrosone C, Ventoruzzo G, et al. Autologous peripheral blood mononuclear cells for limb salvage in diabetic foot patients with no-option critical limb ischemia. J Clin Med. 2021;10(10):2213. doi: 10.3390/jcm10102213.
106. Cruciani M, Lipsky BA, Mengoli C, de Lalla F. Granulocyte-colony stimulating factors as adjunctive therapy for diabetic foot infections. Cochrane Database Syst Rev. 2009(3):CD006810. doi: 10.1002/14651858.CD006810.pub2.
107. Hartung T. Granulocyte colony-stimulating factor: its potential role in infectious disease. Aids. 1999;13 Suppl 2:S3-9.