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· Review ·

Update on New Therapies of Diabetic Foot Ulcers: A Systematic Review

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Abstract

Diabetic foot ulcers (DFUs) are as a chronic wound with a serious and rampant complication of diabetes mellitus. Treatment of DFU remains often challenging and time-consuming due to consecutive uncomfortable outcomes. Therefore, this review helps to inform clinicians of the current status of new effective therapies for DFUs.

Key words Diabetic foot ulcers; Diabetes mellitus; Treatment; Clinicians

Introduction

Wound repair or healing is an intricate process that involves severe regulated reactions from determined cells that have secreted local growth factors that play an important role in ulcer healing process[1,2]. To achieve wound regeneration with high quality, healing should be organized with a set of mechanisms and modernization of the cellular and extracellular matrix (ECM) ingredients of the damaged tissue[3-6].

Diabetic foot ulcers (DFUs) are as a chronic wound with a serious and widespread complication of diabetes mellitus[7-10], leading to substantial morbidity and mortality and DFUs related to infection, pain, skin discolouration and occasional hemorrhage in diabetes mellitus patients. Different studies have been reported DFU about 2% of whole diabetes mellitus patients[11,12] as well as mortality rates associated with DFU are estimated at 5% and 42%, in 1 year and 5 years, respectively[13,14].

Treatment of DFU remains often challenging and time-consuming due to repeated uncomfortable outcomes from both surgical and non-surgical procedures[9,15,16]. Therefore, in this review, we discuss the current standard of new therapeutic therapies in DFU management

Debridement

Nowadays, based on studies conducted, various debridement techniques have been proposed on the wound healing, including: surgical, mechanical, enzymatically, maggot, biological, hydrogels, biosurgery and autolytic debridements. Debridement involves the removal of whole superficial debris and peri-wound callus, necrotic or dead, hyperkeratoti and pestiferous tissues and external bodies in DFUs, which ameliorates the wound healing potential of the remaining residual tissues by meliorating the generation of granulation tissue and also, for reducing the hazard of infection and decrease peri-wound pressure an appropriate debridement is essential, which can prevent the contraction of the normal wound and regeneration. Additionally, utilizing the saline and dressing should be applied after debridement[2,17-21]. In parallel, a 10-year review revealed a reduction in amputation rate in DFUs patients via efficient on-time debridement on the standard wound care protocol[22].

Wound off-loading

For the repair of plantar ulcers, wound off-loading of the ulcer region is sorely significant. In diabetic patients, investigations have shown that increased plantar pressures notably contribute to the progression of plantar ulcers. Decreasing the vertical plantar pressure and plantar shear stress from a DFU is a fundamental section of wound care, because it improves regeneration and barricades recurrence. In addition, the nonremovable total-contact cast (TCC) is as the superlative impressive procedure of off-loading, which is introduced to be the gold standard system and it is demonstrated for the efficient off-loading of ulcers determined at the forefoot or midfoot. Furthermore, studies have shown that TCC up to 87% diminish plantar peak pressure in the forefoot as well as there are abundant reports

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showing that TCC is more advantageous than removable off-loading in time terms to regeneration and percentage of DFUs healed[13,23-25].

Antibiotic therapy

Currently, antibiotic therapy should be utilized only to remedy defined infection due to it is related to frequent side effects, considerable financial costs, and resistance promotion. The known sore infection is predictive of poor ulcer repair and amputation. Proper diagnosis of infection and antibiotic therapy in DFUs infections is necessary to ameliorate the yields, because inopportune application of antibiotics can lead to resistance and side effects. Three principle factors, such as 1: particular agents, 2: route of administration and 3: duration of remedy may efficacy on the antibiotic therapy of DFUs infection. Of course, the antibiotic therapy formula is associated with document obtained through reports on bacteriological culture and sensitivity from various centers around the world. However, some practitioners believe that DFUs need to be antibiotic management, but existing studies generally do not support this view. In many clinical trials published, antibiotic treatment did not reclaim the outcome of non-infectious lesions. Therefore, to avoid of drug resistance and adverse effects, convenient cultures should be guided for the use of anti-infections/antibiotics therapies[2,27].

Dressings

In this method, DFUs healing happen rapidly and faster and usually have fewer infections in a wet environment and dressings are defined as an external conservation and obstacle versus exterior forces. Of course, there is an exception that the necrotic zone of the dry gangrene should be dried to prevent infection and transformation to wet gangrene. Appropriate dressing should be permissible of contaminants that mighty to eliminate surplus exudates and poisonous components, impound a web environment at the wound-dressing interface, be impermeable to microorganisms, allow gas swapping, inhibit tissue dessication, imbibe excess fluid, and ultimately should be quickly removed and cost-effective. Stimulation factors improve wound healing through angiogenesis process and proliferation of fibroblast and keratinocyte. There are a diversity of dressing kinds available along with increasingly advanced methods of meliorating wound healing, and multiple studies support their effectiveness for this purpose, including, tulle, alginate, hydrogels, hydrocolloid, foams such as polyurethane foam, silver, calcium alginates, povidone iodine solution, honey-impregnated, absorbent polymers, growth factors, wet to dry dressing or simple saline and skin replacements[13,21,27-30].

Adjuvant therapies

Stem cells therapy

In DFUs, according to studies published, stem cells originated from bone marrow or other sites can persuade the progenitors of blood vessels, the operations of healing cells, ECM cells, releasing growth factors and meliorating angiogenesis in ischemic tissues. Stem cells may be transplanted into the ulcer area to raise the organization of de novo cells in the wound zone. But, more evaluations are indispensable in order to assess the long-term viability and the useful life of stem cells as well as effectiveness of this treatment. In fact, recently, some clinical studies published suggest examine their potential effectiveness and safety of use potential multiple stem cells to improve ulcerative ulcer wounds. Also, in another researches it is expressed that stem cell therapy is secure and remarkably helps DFUs healing, without any increased hazard of remedy - linked detrimental events as well as it have an effective effects on the healing of both large and small wounds and may decrease the size of greater ulcers likewise. In parallel, Skardal *et al*. indicated that stem cells therapy could be a beneficial treatment for size the large ulcers. On the other hand, recent studies has been shown outstandingly elevate wound healing through variety of various types of progenitor cells on DFU healing, including, mesenchymal stem cells, granulocyte-macrophage colony stimulating factor, endothelial progenitor cells, and adipose-derived stem cells[12,31-35].

Hyperbaric oxygen therapy

This treatment method as an adventitious to standard wound care is planned to enhance the local delivery of oxygen to ischemic tissues or wound sites, which may support fight infections and ameliorate ulcer healing in the DFUs and also, it is cost-effective. Therapy with hyperbaric oxygen therapy conducts in a chamber that involves the intermittent administration of 100% oxygen at a pressure higher of sea level. This therapeutic strategy cause to the propagation of cell, synthesis of collagen, re-epithelization, and defense versus bacteria in ulcers areas for having a faster healing process. Moreover, at superior levels in an oxygen-rich environment have shown with potent document the attendance of fibroblasts, endothelial cells, and keratinocytes are iterated and wound site when supplied by oxygen, leukocytes extinguish bacteria agents available in further beneficially. Recently, different studies on effects of hyperbaric oxygen therapy, especially a double-blind randomized trial, have shown recovered wound healing and a decreased rate of amputation that may avoid

amputations together with limited side effects for diabetic foot disorders[19,26,36-40].

Revascularization

Revascularization plays an important role in the therapy of ischemic lower limb ulcers and should be conducted before drainage or debridement and it ameliorating blood flow may also be used to control of infection in an ischemic or diabetic foot. With developments of vascular and orthopedic surgeries, multiple endovascular techniques are now available for revascularization such as percutaneous transluminal angioplasty, balloon-expandable stents, self-expanding stents, and covered stents and the success rate these options after surgery is more than 90% in most studies[2,26,41-44].

Human growth factors

Newer therapies contain utilize the potential effects of human growth factors as cellular and molecular agents for the formation of angiogenesis, enzyme generation, cell migration, proliferation of cell, re-epithelialization and granulation tissue with various components of healing in DFUs have been investigated for adjunct use in the management of DFUs, that including fibroblast growth factor (PGF), extracellular matrix proteins (EMP), and matrix metalloproteinases modulators (MMP), epidermal growth factor (EGF), recombinant human EGF (rhEGF), transforming growth factor alpha (TGF-α), transforming growth factor (TGF)-β, vascular endothelial growth factor (VEGF), granulocyte colony-stimulatingfactor (G-CSF), and platelet-derived growth factors (PDGF-beta, PRP) which can contribute to the complete recovery of DFU wound in patients with this disease[2,6,13,19,46-48].

Human amniotic membrane

A recent progress in wound healing therapy is the application of amniotic membrane's that is considered to be an adjunctive wound treatment. When applied to the ulcer region, it prevents the bacteria from attacking, diminishes pain and damage of fluids and proteins in body, and emancipations growth and regulatory factors and wound regeneration modulators to the wound site and next that, the proper condition is created to recuperate the internal wound for promotion, therefore, all of these affirmative specifications show that amniotic membrane can be an effective coating for accelerating the recovery process of patients with DFU and some earlier studies have already shown the large efficacy of beneficial effects for treating chronic DFUs[49-54].

Conclusions

Based on the overall evidence, whole the above treatments will be helpful in combining a number of new therapies or adjuvant agents to treat DFU complications and therefore successful management of new approaches can play an extremely substantial role. However, due to therapies challenges, management requires a multimedia team of different specialists

Conflicts of interest

None.

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