CODEN [USA]: IAJPBB **ISSN: 2349-7750**

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
http://doi.org/10.5281/zenodo.3250292

Available online at: http://www.iajps.com ***Research Article***

PATHOPHYSIOLOGY AND MANAGEMENT OF WOUND IN DIABETIC PATIENTS

[1]Dr. Muhammad Rehman Waheed, [2]Dr. Junaid Amjad, [3]Dr. Javaria Ahmad
[1]MBBS; King Edward Medical University Lahore, Pakistan, [2]MD; Latin American School of Medicine, Havana, Cuba, [3]WMO, DHQ Hospital Kasur.

Abstract:
Wound healing is a challenge among diabetic population. Wound complications like infection, chronicity, dehiscence is more commonly associated with diabetes than non-diabetics. The management of the wound in diabetics will be discussed in this paper. The measures to manage wound in diabetics include optimal glycemic control, debridement, wise use of antibiotics according to culture results, regular and careful antiseptic or wound wash measures, adequate moisturizing and reducing the wound pressure. The novel management options like using autologous skin transplants for those wounds which are difficult to heal by standard therapy will be discussed in this paper.

Corresponding author:
Dr. Muhammad Rehman Waheed,
MBBS; King Edward Medical University, Lahore, Pakistan.

QR code

Please cite this article in press Muhammad Rehman Waheed et al., ***Pathophysiology And Management Of Wound In Diabetic Patients.,*** *Indo Am. J. P. Sci, 2019; 06[06].*

INTRODUCTION:

Diabetic foot is a complication observed in approximately 25% of diabetic patients [1]. The complications associated with management of wound impair quality of life, compromises living status, increase outdoor treatment and in hospital management cost. Neurovascular complications and high serum glycemic levels both affect the wound healing in diabetics [2]. Most diabetic wounds convert into chronic wounds and special attention and treatment protocols are required to manage these. The basic management rules being applied are removing causative infectious agent, extensive debridement in order to enhance the effect of topically applied antibiotics [3]. Cases showing ineffective response to routine management protocols need special attention and alternative treatment options like skin implants either autologous implants or bioengineered. This would help in reducing the amputation rate.

Physiological process of wound healing: The healing physiology follows four steps, hemostasis, inflammation, proliferation, maturation or remodeling. Humoral and cellular factors are involved in these steps of healing [4]. Hemostasis begins within hours, cytokines, growth factors and platelets are involved. The inflammation follows 7 days and usually involves neutrophils and granulocytes. Monocytes participate in healing process in chemotactic manner and late differentiate to form macrophages. Certain growth factors are released to remove cell debris, in addition angiogenesis and fibroplasia also occur [5]. This provides basis for extracellular matrix formation. Proliferation phase starts within 2 days and lasts till 20 days. It involves granulation tissue and angiogenesis formation. Angiotensin, PDGF and macrophage angiogenesis factors are involved. Concomitant epitheliazation is also started. Tissue remodeling takes one week to 6 months after injury [6]. After than wound matrix is replaced by proteoglycans and collagen which continue to deposit and increase wound strength.

Pathophysiology of wound healing in diabetes: Extrinsic and intrinsic factors responsible for delayed wound healing in diabetic patients include repeated trauma due to loss to pain sensations as a result of neuronal impairment, micro and macro-vascular changes lead to ischemia and delayed healing[7,8]. Arterial basement membrane thickening is the reason behind delayed wound healing and ulcer formation [9]. High serum glucose level leads to formation of advanced glycemic end-products which leads to inflammatory molecules production, TNF-α, IL-1 and hampers collagen synthesis [10]. Alteration in cell morphology is associated with high serum glucose level. It also causes decreased cell proliferation, abnormal keratinocytes differentiation. HbA1c level if reduced, lowers wound healing time in legs and foot. Diabetic patients have altered immune system. Decreased phagocytosis, chemotaxis and bacterial killing also hampers healing process [11]. Early leukocyte infiltration and wound fluid IL-6 characterize late inflammation [12]. Altered cytokine pattern lead to delayed wound healing. Altered growth factors and cytokines bioavailability lead to chronic wound formation. Cell proliferation, differentiation, migration and metabolism is controlled by these signaling molecules. Diabetic foot ulcers depict abnormal signaling molecules [13]. Trapping of growth factors and growth factors by macromolecules by albumin, fibrinogen and beta 2 macroglobulin may disrupt healing process [14]. Growth factors increased degradation lead to delayed healing. There is increased activity of insulin degradation enzymes (IDE) activity in patients with diabetic foot ulcers. This degradation activity had positive correlation with HbA1C level[15], normal wound healing require balance between collagenous and noncollagenous extracellular matrix and tissue inhibitors of metalloproteinases(TIPS)[16]. MMPs are important both for initial healing and strengthening of wound[17]. Many studies have reported raised MMP and reduced TIMPS level [18, 19]. Local tissue morphology is also changed leading to reduced proliferative capacity [20].

Standard treatment methods for diabetic wound healing: Assessing the vascular status and optimize glycemic control as well as extensive debridement, infection control by antibiotic therapy on the basis of wound cultures, the use of moisture dressings, and offloading high pressure from the wound bed are used for wound management. Vascular assessment is done by palpation of all peripheral pulses, such as femoral, popliteal, posterior tibial, and dorsalis pedis. Ankle branchial pressure index (ABPI), is used to assess lower extremity vessel insufficiency, the results of which can be validated through Doppler waveform and pulse oximetry. In case of significant peripheral arterial disease, therapeutic revascularisation should be done, as sufficient vascular supply is needed to heal wound. The correlation between normoglycemia and facilitated wound healing in diabetes has been discussed in the previous section. The role of surgical debridement in healing of diabetic foot ulcers is widely acknowledged [21]. The rationale lies in removing necrotic, devitalized wound bed and wound edge tissue that inhibits healing, so that secondary wound healing can be achieved [22]. The determination of

organisms responsible for a diabetic foot infection via culture of appropriately collected tissue specimens enables clinicians to make optimal antibiotic choices based on culture and sensitivity results [23]. A recent meta-analysis of randomized controlled trials (RCTs) comparing the effects of different types of wound dressings in the treatment of diabetic foot ulcers found no significant differences between them so that aspects such as the dressing cost and the wound properties should be considered when making a decision [24]. A strong association between the efficacy to offload the foot and clinical outcome is supported through evidence-based guidelines [25].

ADDITIONAL TREATMENTS:

Skin grafts and flaps: Flaps and grafts are the two principal surgical procedures for skin tissue replacement. A flap is a full-thickness portion of skin sectioned and isolated peripherally and in depth from the surrounding skin, except along one side, called the peduncle. A graft is a section of skin of variable thicknesses and sizes completely detached from its original site and used to cover the zone to be repaired. Particular attention should be paid to mesh grafts which are obtained by passing a whole dermoepidermal explant through a special surgical tool (mesher), thereby increasing the initial surface area of the explanted skin [26]. Skin grafts are traditionally used in the treatment of severe burns. However, a number of studies have recently reported successful managing of large tissue defects in patients with diabetic foot ulcers with microsurgical grafts [27–29]. The process of graft adoption is defined as the adhesion of the graft skin to the recipient wound area and its subsequent vascularization. This process is identical to that of wound healing. Following an initial rejection phase after the skin grafting procedure with massive inflammation, revascularization of the graft starts after 24 to 48 hours. Initially the graft is pale and white but subsequently adopts a pinkish colour which indicates successful adoption in association with firm attachment to the bed. Apart from immune compatibility, basic conditions for graft taking encompass the ability for neoangiogenesis, good adherence of the graft to recipient areas, and hence accurate immobilization of the graft. A graft can only be placed to vital exposed dermis capable of producing granulation tissue. The recipient area must not be infected or excessively exudative. In addition well-functioning haemostasis is required. In fact, any accumulation of exudate or blood underneath the graft jeopardizes its survival as it impedes adherence and penetration of new capillaries. The consequent handling of the transplant is of utter importance. In the first weeks after transplantation, complete removal of pressure is essential. Protective footwear with dully formed inserts can secure adequate offloading of the area of high pressure and protect the transplant.

Bioengineered grafts: In the recent years much attention has been paid to the use of tissue-engineered human skin equivalents in the treatment of diabetic foot ulcers. The first engineered skin substitutes were matrix-based products consisting of cross-linked collagen and glycosaminoglycans. The matrix eventually undergoes degradation, while simultaneously the host's cells invade and proliferate within it. Integra, a product of this category, has shown promising results in deep wounds [30]. The second generation of tissue-engineered skin equivalents consisted of cell-based products, mostly keratinocytes. Marston et al. demonstrated that dermagraft, a cryopreserved human fibroblast-derived dermal substitute, is a safe and effective treatment for diabetic foot ulcers [31]. Veves et al. showed that the application of graft skin (Apligraf)—a human skin equivalent manufactured from cultured living dermis and sequentially cultured epidermis of neonatal foreskins—results in significantly improved healing compared to other available treatments. Moreover, there were no significant side effects [32]. Nevertheless, both products are ultimately rejected, so that their primary task appears to be a transient restoration of the dermis until the patients' keratinocytes can migrate and close the wound.

Stem cells from bone marrow: Another very promising therapeutic option involves the use of bone marrow-derived cells, and recent evidence indicates that bone marrow contains stem cells with the potential for differentiation into a variety of tissues. For example, patients with diabetes are known to have an impaired mobilization of endothelial progenitor cells (EPCs) in the bone marrow and decreased accumulation of these cells in wounds [33, 34]. Bone marrow-derived cells may thus be a valuable and unlimited source of progenitor and/or stem cells [35]. For example, Badiavas and Falanga described that the local application of autologous bone marrow-derived cells resulted in complete wound closure in 3 patients unresponsive to standard therapies including bioengineered skin application and autologous skin grafting [36].

Furthermore, it is assumed that hyperbaric oxygen results in EPC recruitment but does not improve migration of EPC to the wound site. However, in a murine model of diabetes coadministration of stromal cell-derived factor-1-alpha (SDF-1α) resulted in homing of the activated EPCs to the wound site [37].

These data suggest that combining oxygen therapy with SDF-1α may improve wound healing in patients with diabetes.

Another novel interesting approach consists of lineage commitment of stem cells to the keratinocyte lineage. This can be achieved through exposure of the stem cells to a mixture of cytokines, growth factors, and extracellular matrix components in vitro and has been attempted with only moderate success [38, 39]. Another method is through genetic modulation, in particular transfection of stem cells with recombinant DNA encoding for proteins that regulate the commitment to the keratinocyte lineage [40]. Although this method presents with exciting new potential, one cannot overlook the potential detrimental effects and safety concerns of genetic manipulation of stem cells [41].

Growth factors: Of the known growth factors with a proposed role in wound healing, therapeutic efficacy has been demonstrated only for becaplermin (recombinant human platelet-derived growth factor, Regranex) in several randomized controlled clinical trials [42]. Nevertheless, recent data reported an increased cancer risk in patients treated with more than three tubes of becaplermin so that pending lower follow-up data on the potential risk of malignancy in connection with its use this agent should be used with extreme caution in patients with diagnosed malignancy [43].

Dressings: The use of sub-atmospheric pressure dressings such as the commercially available vacuum-assisted closure (VAC) device have been shown to be an effective way in accelerating the healing of various wounds. This technique optimizes blood flow, decreases local tissue edema, and removes excessive fluid from the wound bed. Additionally, the cyclical application of sub-atmospheric pressure alters the cytoskeleton of the cells in the wound bed thereby triggering a cascade of intercellular signals that increases the rate of cell division and formation of granulation tissue. The success rate of skin grafting is significantly increased when VAC is used as bolster covering the freshly skin-grafted wound [44, 45]. A recent review assessing current modalities in the treatment of diabetic foot ulcers [46] concluded that although vacuum compression therapy has been linked to significant reduction in wound area [47] and time to healing [48], this treatment was not shown to be cost effective and should therefore be used only in exceptional circumstances [49,50].

CONCLUSION:

(i) The four phases of physiological wound healing are: haemostasis, inflammation, proliferation, and remodelling.
(ii) Wound healing in diabetes is impaired by factors that are both extrinsic and intrinsic to the biology of wound.
(iii) The standard treatment of diabetic ulcers includes optimization of glycemic control, extensive debridement, infection elimination, use of moisture dressings, and offloading high pressure.
(iv) Current treatment methods in persistent diabetic foot ulcers include autologous skin transplantation, tissue-engineered human skin equivalents, bone marrow derived cells, growth factors, and subatmospheric pressure dressings.

REFERENCES:

1- Tsourdi E, Barthel A, Rietzsch H, Reichel A, Bornstein SR. Current aspects in pathophysiology and treatement of chronic wounds in diabetes mellitus. BioMed Research international 2013.
2- N. Singh, D. G. Armstrong, and B. A. Lipsky, "Preventing foot ulcers in patients with diabetes," Journal of the American Medical Association, vol. 293, no. 2, pp. 217–228, 2005. View at Publisher ·View at Google Scholar · View at Scopus
3- D. J. Margolis, L. Allen-Taylor, O. Hoffstad, and J. A. Berlin, "Diabetic neuropathic foot ulcers and amputation," Wound Repair and Regeneration, vol. 13, no. 3, pp. 230–236, 2005. View at Publisher ·View at Google Scholar · View at Scopus
4- T. K. Hunt, "Basic principles of wound healing," Journal of Trauma, vol. 30, no. 12, supplement 1, pp. S122–S128, 1990. View at Google Scholar · View at Scopus
5- S. Werner and R. Grose, "Regulation of wound healing by growth factors and cytokines," Physiological Reviews, vol. 83, no. 3, pp. 835–870, 2003. View at Google Scholar
6- F. W. LoGerfo and J. D. Coffman, "Vascular and microvascular disease of the foot in diabetes. Implications for foot care," New England Journal of Medicine, vol. 311, no. 25, pp. 1615–1619, 1984.View at Google Scholar · View at Scopus
7- M. D. Flynn and J. E. Tooke, "Aetiology of diabetic foot ulceration: a role for the microcirculation?" Diabetic Medicine, vol. 9, no. 4, pp. 320–329, 1992. View at Google Scholar ·View at Scopus

8- P. J. Hennessey, E. G. Ford, C. T. Black, and R. J. Andrassy, "Wound collagenase activity correlates directly with collagen glycosylation in diabetic rats," Journal of Pediatric Surgery, vol. 25, no. 1, pp. 75–78, 1990. View at Publisher · View at Google Scholar · View at Scopus

9- N. Spravchikov, G. Sizyakov, M. Gartsbein, D. Accili, T. Tennenbaum, and E. Wertheimer, "Glucose effects on skin keratinocytes: implications for diabetes skin complications," Diabetes, vol. 50, no. 7, pp. 1627–1635, 2001. View at Google Scholar · View at Scopus

10- M. Markuson, D. Hanson, J. Anderson et al., "The relationship between hemoglobin A(1c) values and healing time for lower extremity ulcers in individuals with diabetes," Advances in Skin & Wound Care, vol. 22, no. 8, pp. 365–372, 2009. View at Google Scholar · View at Scopus

11- W. Marhoffer, M. Stein, E. Maeser, and K. Federlin, "Impairment of polymorphonuclear leukocyte function and metabolic control of diabetes," Diabetes Care, vol. 15, no. 2, pp. 256–260, 1992. View at Google Scholar · View at Scopus

12- A. L. McMurtry, K. Cho, L. J. T. Young, C. F. Nelson, and D. G. Greenhalgh, "Expression of HSP70 in healing wounds of diabetic and nondiabetic mice," Journal of Surgical Research, vol. 86, no. 1, pp. 36–41, 1999. View at Publisher · View at Google Scholar · View at Scopus

13- T. J. Fahey, A. Sadaty, W. G. Jones, A. Barber, B. Smoller, and G. T. Shires, "Diabetes impairs the late inflammatory response to wound healing," Journal of Surgical Research, vol. 50, no. 4, pp. 308–313, 1991. View at Google Scholar · View at Scopus

14- E. B. Jude, R. Blakytny, J. Bulmer, A. J. M. Boulton, and M. W. J. Ferguson, "Transforming growth factor-beta 1, 2, 3 and receptor type I and II in diabetic foot ulcers," Diabetic Medicine, vol. 19, no. 6, pp. 440–447, 2002. View at Publisher · View at Google Scholar · View at Scopus

15- V. Falanga and W. H. Eaglstein, "The "trap" hypothesis of venous ulceration," The Lancet, vol. 341, no. 8851, pp. 1006–1008, 1993. View at Publisher · View at Google Scholar · View at Scopus

16- W. C. Duckworth, J. Fawcett, S. Reddy, and J. C. Page, "Insulin-degrading activity in wound fluid," Journal of Clinical Endocrinology and Metabolism, vol. 89, no. 2, pp. 847–851, 2004. View at Publisher · View at Google Scholar · View at Scopus

17- M. Vaalamo, T. Leivo, and U. Saarialho-Kere, "Differential expression of tissue inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4) in normal and aberrant wound healing," Human Pathology, vol. 30, no. 7, pp. 795–802, 1999. View at Publisher · View at Google Scholar · View at Scopus

18- V.-M. Kähari and W. K. Saariahlo-Kere, "Matrix metalloproteinases in skin," Experimental Dermatology, vol. 6, no. 5, pp. 199–213, 1997. View at Google Scholar

19- A. B. Wysocki, L. Staiano-Coico, and F. Grinnell, "Wound fluid from chronic leg ulcers contains elevated levels of metalloproteinases MMP-2 and MMP-9," Journal of Investigative Dermatology, vol. 101, no. 1, pp. 64–68, 1993. View at Google Scholar · View at Scopus

20- R. Lobmann, A. Ambrosch, G. Schultz, K. Waldmann, S. Schiweck, and H. Lehnert, "Expression of matrix-metalloproteinases and their inhibitors in the wounds of diabetic and non-diabetic patients," Diabetologia, vol. 45, no. 7, pp. 1011–1016, 2002. View at Publisher · View at Google Scholar · View at Scopus

21- A. Stanley and T. Osler, "Senescence and the healing rates of venous ulcers," Journal of Vascular Surgery, vol. 33, no. 6, pp. 1206–1211, 2001. View at Google Scholar

22- F. L. Game, R. J. Hinchliffe, J. Apelqvist et al., "A systematic review to enhance the healing of chronic ulcers of the foot in diabetes," Diabetes/Metabolism Research and Reviews, vol. 28, supplement 1, pp. 119–141, 2012. View at Google Scholar

23- K. A. Gordon, E. A. Lebrun, M. Tomic-Canic, and R. S. Kirsner, "The role of surgical debridement in healing of diabetic foot ulcers," Skinmed, vol. 10, no. 1, pp. 24–26, 2012. View at Google Scholar

24- B. A. Lipsky, E. J. Peters, E. Senneville et al., "Expert opinion on the management of infections in the diabetic foot," Diabetes/Metabolism Research and Reviews, vol. 28, supplement 1, pp. 163–178, 2012. View at Google Scholar

25- J. C. Dumville, S. Deshpande, S. O'Meara , and K. Speak, "Hydrocolloid dressings for healing diabetic foot ulcers," Cochrane Database of Systematic Reviews, vol. 15, no. 2, 2012. View at Google Scholar

26- S. A. Bus, "Priorities in offloading the diabetic foot," Diabetes/Metabolism Research and Reviews, vol. 28, supplement 1, pp. 54–59, 2012. View at Google Scholar

27- A. Andreassi, R. Bilenchi, M. Biagioli, and C. D'Aniello, "Classification and pathophysiology of skin grafts," Clinics in Dermatology, vol. 23, no. 4, pp. 332–337, 2005. View at Publisher · View at Google Scholar · View at Scopus
28- G. P. Jolly, T. Zgonis, and P. Blume, "Soft tissue reconstruction of the diabetic foot," Clinics in Podiatric Medicine and Surgery, vol. 20, no. 4, pp. 757–781, 2003. View at Publisher · View at Google Scholar · View at Scopus
29- S. M. Mahmoud, A. A. Mohamed, S. E. Mahdi, and M. E. Ahmed, "Split-skin graft in the management of diabetic foot ulcers," Journal of Wound Care, vol. 17, no. 7, pp. 303–306, 2008.View at Google Scholar · View at Scopus
30- T. Zgonis, J. J. Stapleton, and T. S. Roukis, "Advanced plastic surgery techniques for soft tissue coverage of the diabetic foot," Clinics in Podiatric Medicine and Surgery, vol. 24, no. 3, pp. 547–568, 2007. View at Publisher · View at Google Scholar · View at Scopus
31- D. Stiefel, C. Schiestl, and M. Meuli, "Integra Artificial Skin for burn scar revision in adolescents and children," Burns, vol. 36, no. 1, pp. 114–120, 2010. View at Publisher · View at Google Scholar· View at Scopus
32- W. A. Marston, J. Hanft, P. Norwood, and R. Pollak, "The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial," Diabetes Care, vol. 26, no. 6, pp. 1701–1705, 2003. View at Publisher · View at Google Scholar ·View at Scopus
33- A. Veves, V. Falanga, D. G. Armstrong, and M. L. Sabolinski, "Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial," Diabetes Care, vol. 24, no. 2, pp. 290–295, 2001. View at Google Scholar · View at Scopus
34- H. Brem and M. Tomic-Canic, "Cellular and molecular basis of wound healing in diabetes," Journal of Clinical Investigation, vol. 117, no. 5, pp. 1219–1222, 2007. View at Publisher · View at Google Scholar · View at Scopus
35- Z. J. Liu and O. C. Velazquez, "Hyperoxia, endothelial progenitor cell mobilization, and diabetic wound healing," Antioxidants and Redox Signaling, vol. 10, no. 11, pp. 1869–1882, 2008. View at Publisher · View at Google Scholar · View at Scopus
36- P. Fiorina, G. Pietramaggiori, S. S. Scherer et al., "The mobilization and effect of endogenous bone marrow progenitor cells in diabetic wound healing," Cell Transplantation, vol. 19, no. 11, pp. 1369–1381, 2010. View at Google Scholar
37- E. V. Badiavas and V. Falanga, "Treatment of chronic wounds with bone marrow-derived cells," Archives of Dermatology, vol. 139, no. 4, pp. 510–516, 2003. View at Publisher · View at Google Scholar · View at Scopus
38- K. A. Gallagher, Z. J. Liu, M. Xiao et al., "Diabetic impairments in NO-mediated endothelial progenitor cell mobilization and homing are reversed by hyperoxia and SDF-1α," Journal of Clinical Investigation, vol. 117, no. 5, pp. 1249–1259, 2007. View at Publisher · View at Google Scholar · View at Scopus
39- C. Coraux, C. Hilmi, M. Rouleau et al., "Reconstituted skin from murine embryonic stem cells," Current Biology, vol. 13, no. 10, pp. 849–853, 2003. View at Publisher · View at Google Scholar ·View at Scopus
40- C. Bagutti, C. Hutter, R. Chiquet-Ehrismann, R. Fässler, and F. M. Watt, "Dermal fibroblast-derived growth factors restore the ability of β1 integrin-deficient embryonal stem cells to differentiate into keratinocytes," Developmental Biology, vol. 231, no. 2, pp. 321–333, 2001. View at Publisher · View at Google Scholar · View at Scopus
41- C. K. Kaufman, P. Zhou, H. A. Pasolli et al., "GATA-3: an unexpected regulator of cell lineage determination in skin," Genes and Development, vol. 17, no. 17, pp. 2108–2122, 2003. View at Publisher · View at Google Scholar · View at Scopus
42- P. A. Conget and J. J. Minguell, "Adenoviral-mediated gene transfer into ex vivo expanded human bone marrow mesenchymal progenitor cells," Experimental Hematology, vol. 28, no. 4, pp. 382–390, 2000. View at Publisher · View at Google Scholar · View at Scopus
43- T. J. Wieman, J. M. Smiell, and Y. Su, "Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers: a phase III randomized placebo-controlled double-blind study," Diabetes Care, vol. 21, no. 5, pp. 822–827, 1998. View at Publisher · View at Google Scholar · View at Scopus

44- N. Papanas and E. Maltezos, "Benefit-risk assessment of becaplermin in the treatment of diabetic foot ulcers," Drug Safety, vol. 33, no. 6, pp. 455–461, 2010. View at Publisher · View at Google Scholar · View at Scopus

45- M. T. Eginton, K. R. Brown, G. R. Seabrook, J. B. Towne, and R. A. Cambria, "A prospective randomized evaluation of negative-pressure wound dressing for diabetic foot wounds," Annals of Vascular Surgery, vol. 17, no. 6, pp. 645–649, 2003. View at Publisher · View at Google Scholar ·View at Scopus

46- D. G. Armstrong and L. A. Lavery, "Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial," The Lancet, vol. 366, no. 9498, pp. 1704–1710, 2005. View at Publisher · View at Google Scholar · View at Scopus

47- F. Gottrup and J. Apelqvist, "Present and new techniques and devices in the treatment of DFU: a critical review of evidence," Diabetes/Metabolism Research and Reviews, vol. 28, supplement 1, pp. 64–71, 2012. View at Google Scholar

48- A. Akbari, H. Moodi, F. Ghiasi, H. M. Sagheb, and H. Rashidi, "Effects of vacuum-compression therapy on healing of diabetic foot ulcers: randomized controlled trial," Journal of Rehabilitation Research and Development, vol. 44, no. 5, pp. 631–636, 2007. View at Publisher · View at Google Scholar · View at Scopus

49- M. Mars, Y. Desai, and M. A. Gregory, "Compressed air massage hastens healing of the diabetic foot," Diabetes Technology and Therapeutics, vol. 10, no. 1, pp. 39–45, 2008. View at Publisher ·View at Google Scholar · View at Scopus

50- D. T. Ubbink, S. J. Westerbos, D. Evans, L. Land, and H. Vermeulen, "Topical negative pressure for treating chronic wounds," Cochrane Database of Systematic Reviews, no. 3, 2008.