Review Article

Treatment of Wounds in Diabetic Patients

Seema Singh, Richa Srivastava*
Amity Institute of Pharmacy, Amity University, Lucknow Campus, Lucknow-226028, Uttar Pradesh, India.
***Corresponding author's E-mail:** rsrivastava1@lko.amity.edu

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ABSTRACT

Our body system is very well programmed to repair and heal the wounds are present on our skin in day to day life. The wound healing process is very well defined in body. The mechanisms of body work too well to set the system rolling to heal and repair our tissues automatically. This review reflects about the wound healing stages and the issues that occur in healing of the diabetic cuts and wounds. The increased glucose levels cause impairment of the healing system, hence causing delayed healing in the devitalized tissues.

Keywords: Impairment, wound, tissue, treatment.

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INTRODUCTION

A wound may be depicted as an interruption of the physical system of cells on the skin and trouble in its purpose in attaching and caring the underlying tissue and organisms. It is primarily due to accidental cuts, tears, pressure, scratches, high temperature, chemicals or subordinate operating invention or disease (ulcer diabetes)[1]. The wound ranges from apparent (disturbing the skin) to fractional width (disturbing both epidermis and portion of dermis) and complete width (including subcutaneous fat and bones) wound[2]. Wound curing is a physical method the repair of the damage muscle to human body. This will restore the integrity of the body and will control the work of injured parts. The primary task is to close the wound or the wound may be closed with subordinate intention, and in together ways the treatment response may occur through a sequence of overlying events, and can be determine by internal and external factors[3].

Acute wound heals in a restricted amount of period, no complications are frequently seen. Wounded tissue recovers in a probable manner[4]. These wounds will either surgical or painful[5].

Chronic wound these are wounds those who are not well within the time period. Those factors distort the stability between the bio-burden of the wound and patient resistant system[6].

The wound curing method can be regulated by several developmental factors and by the release of cytokines at the wound site. Alteration tissue that inhibits the curing process at a controlled time will only expand tissue and prolonged healing [16].

The inflammatory stage has elaborated vascular response and it has categorized by blood clotting and hemostasis along with cellular procedures, as well as permeation of leukocytes with various purposes in antimicrobial and cytokine free. That will initiate a proliferative response to repair the wound. Some writers divide it into four parts. The presence of the first stage is important for the hemostasis vascular response. A proliferative phase is formed to protection the wound surface with connected development of granular tissue to seal the wound area.The proliferation or spread of fibroblasts, the disposition of collagen and other extravascular matrix and the develop of new blood vessels also include the formation of granular tissue. Once a new tissue created inside the wound to restore the structural integrity and functional volume of the tissue, the remodeling phase is initiated[17].

Diabetes mellitus is a long-lasting metabolic syndrome due to an absence of deficiency in or resistance to insulin[7,8].

Diabetic mellitus has been the most vital public health difficulties due to a high frequency, widespread social and financial significances[9]. Delayed cutaneous lesion curing has become a long-lasting difficulty in diabetic patients manly due to hyperglycemia continued inflammatory phases defected angiogenesis, reduced appearance of cytokines, oxidative stress, vascular deficiency, and bacterial infection, and many other complications related to diabetes such as neuropathy, nephropathy, atherosclerosis, and foot deformity donate to the security of the disease and the growth of long-lasting lesion in patients with diabetes, which is complicated for ulcers, necrosis and elimination[10,12,13].

Diabetes mellitus is severe and has become the third major destroyer of persons after cancer and heart disease with the use of some current synthetic drug for effective treatment possibilities[14]. Healing impairment of patients with diabetes has still become a important clinical difficulty for surgeons, worldwide due to indistinct etiology[15].

Impaired immunity and wound contamination that may result in exposure or poor hygiene are the most frequently encountered and clinically significant barriers to wound curing. Injured skin is vulnerable to all type of invasive microbial infection and subsequent development of wound sepsis until complete epithelium is repaired. Bacteria invade wounds directly, causing inflammation and fluid excretion that can interfere with the healing process. Tissue damage and delayed fibroplasia due to bacterial toxins as well as collagen synthesis, topical antimicrobial treatment may be among the most significant method of wound care. The goal of topical antimicrobial treatment in wound care will be to controller microbial colonization and subsequent spread by which wounds can be cured.

PHASES OF THE WOUND HEALING

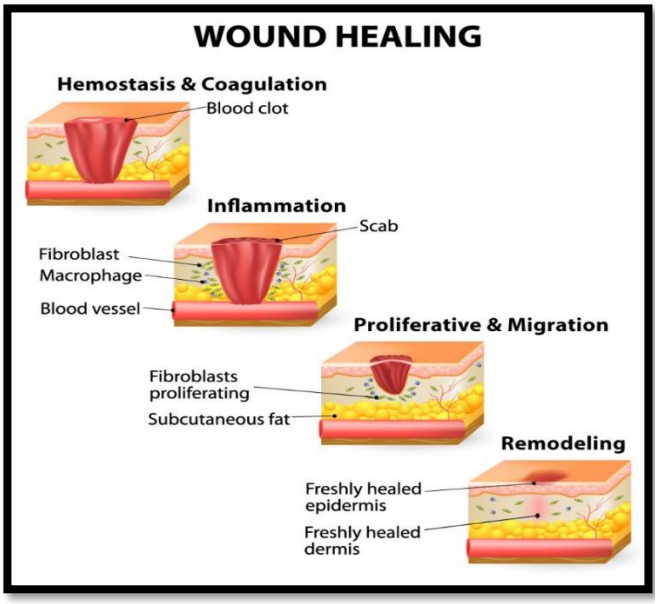

Figure 1: Stages of Wound Healing[40]

1. Inflammatory phase

The effective component of the initiate by the highly inflammation and injury is the preliminary response of the human body. Injury normally results in the restoration of tissue repair purpose. The inflammatory reaction will be divided into vascular and cellular response.

Primary wounding is a method of limited validation, plasma and liquid extravasation into the extravascular capacity and obstructive of lymphatic drainage is make basic symbols of swelling with redness, inflammation and high temperature.

This acute inflammation reaction is frequently 24 to 48 hrs and some cases is persisting upto 2 weeks. The tissue damage may be causes blood vessels distraction and blood loss.

Platelets may be adhering, collective and free various intermediaries to ease clotting. The blood coagulation is the main purpose of the hemostasis and the subordinate but similarly significant role of platelets will be initiating the curing force through release of chemo attractants and growing aspects at the similar time the clot will be given a medium support for the re-equipment of cells to a wounded range in responding to these significant intermediaries will be leukocytes, with neutrophils and macrophages permeate the injured range and support in cleaning and eliminating injured tissue fragments and external elements[18].

2. Proliferative Phase

Early inflammatory responses that may provide to injury the needed outline for manufacture after an innovative functional barricade. The cellular activity will prevail at this stage of treatment. Major events during this phase will create an absorbency barricade (i.e. epithelialization), establishment the suitable body fluid source (i.e., angiogenesis), and purification of the injured subcutaneous muscle (i.e. fibroplasias).

3. Reepithelization phase

Reepithelization after skin injury is a process by which the epidermis can be repaired. In which involved many types of process causing the wound to have epidermal keratinocytes. The proliferation of keratinocytes further extending the epithelial tongue would be used to complement the epithelium to differentiate epithelium into a stratified skin then restore a folded epidermis and underlying dermis[19].

4. Remodeling phase

Remodeling phase is a consist of matrix and subsequent changes over the period. During the process entire wound is repair because primary inflammatory phase in present fibrin clots is exchanged by granulation tissue. Type three collagen and enriches plasma vessels during the proliferative stage. And later the collagenous scar was mainly replaced by the type one collagen with very fewer of matured blood vessels[20]. A feature of wound transformation is the variation in extracellular matrix arrangement. Collagen fibers comprise about 80% of the dehydrated weight of usual human dermis and major proteins which provides strength and hardness of dermal tissue category one collagen to about 80% collagen in healthy adults and constitutes 10% collagen in type three collagen dermis[21]. Type three collagen granulation tissue is the major collagen produced by fibroblasts. Type tree collagen primary appear later (48 to 72 hours) Maximum secretion between five to seven days. Total volume of collagen during repair quickly increased, Reaches an extreme of two to three weeks later injury[22].

WOUND HEALING IN DIABETES

The method of treatment in diabetes is primarily considered by inflammatory conditions, disordered angiogenesis processes, reduction of endothelial progenitor cells and imbalance in the extracellular matrix. As seen in the curing of the wounds in the body, still in diabetes, neutrophils and macrophages were instantly present in the area of infiltrating, a region of wound focused by chemotactic chemokines that was mainly elevated in diabetes[23]. In diabetes the production of some growth factors involved in initiating and maintaining the curing process in diabetes may be compromised.

For example- Low level of insulin such as growth factor-1 (IGF-1) and distorted growth factor-β (TGF-β) have been reported in wound tissue in both diabetic animals and humans. IGF-1 was concerned in cell-granulation and wound repithelialization[24], whereas TGFβ human resources immune cells, keratinocytes, fibroblasts, and vascular cells and is involved in angiogenesis and development of ECM[25]. However, the balance between diabetes, the development of new vessels, and promoting their maturation had deteriorated.

Angiogenesis causes senescence in endothelial cells, having high glucose level and capillary thickness in the wound area are insufficient. Hyperglycaemia affects HIF-1α stability and activation and as a result is underlying HIF-1α target genes such as VEGF[26]. Additionally, in diabetic animal models, macrophages, which were the main source of VEGF, exhibited impaired phagocytic action and altered phenotypes, resulting in breakdown of tissue repair[27]. Therefore in db/db mice VEGF-A mRNA and protein levels were extensively reduced compared to manage mice and treatment with VEGF-A caused accelerated wound closing, though this was characterized by early leaky and malformed vasculature and a big local edema very clear until VEGF-A treatment was ceased[28].

In this situation, distorted production of both proangiogenic and vascular maturation factors seen in diabetes leads to a reduced residents of endothelial progenitor cells in the bone marrow[29], thus leading to an abnormal modifications, in angiogenic sprouts and, in conclusion an aberrant vascular architecture in diabetic lesions[30].

Furthermore, the maturation phase of wound healing appeared to be impaired in diabetes. The production of factors caused by the vascular mature phenotype (including angiopoietin (ANG) 1 and 2, PDGF) was compromised[31] and current application of ANG1 and PDGF increased wound healing in a mouse model of diabetes induced by streptozotocin or in db/db mice respectively[31,32].

Finally, pathology in the regulation of ECM, whose build-up was modified by metalloproteinase (MMPs) and tissue inhibitor of metalloproteinase (TIMPs), was observed in diabetes. High MMPs levels were reported in wound, due to high glucose that could directly induce MMPs production and TIMPs insufficiency, thus contributing to disturbing the healing process[33].

MMPs was involved in different stages of wound healing such as cell migration through degraded ECM, leukocyte invasion, processing of various cytokines and growth factors involved in the curing process. A equilibrium between MMPs and TIMPs was necessary to avoid disruption of the scaffolding structures necessary for wound healing[34].

Factors affecting the wound healing

Many factors are affected to the wound healing.

a) Age

Many treatments related to changes that are related to age. Studies have shown that wound curing is delaying in people over the age of 60 due to changes that occur with age[35, 36].

b) Infection

Fungus and microorganisms are entering the skin due to wound. When infection is present in the surface of wound so these wounds are shaped, this requires antimicrobial drug to cure the wound[38].

c) Poor nutrition

Poor diet can be a resource to cure wound in the body. Because infections increase a person Protein and calories need in addition, the wound come out of huge amount of protein daily. When calories become unsatisfactory, the body can breakdown proteins for energy. This will decrease the body's capacity to heal[37].

d) Lack of hydration

Lacks of wetness on the surface of a wound inhibit cellular migration. This leads to decreased blood oxidation and delayed wound healing. Dehydration due to the lack of sodium or water will delay all aspects of healing progression.

e) Systemic cause

Common systematic ailments will contain diabetes mellitus and immunodeficiency. Diabetes mellitus plays a huge role in the healing method of wound. It can predict lesion due to reduced excitation and poor arterial flow in patients. It is necessary to manage blood sugar in a diabetic patient to encourage wound healing[39].

f) Obesity

Obesity is also at risk for many disease and health related conditions. These include coronary heart disease, type 2 diabetes, cancer, hypertension, respiratory problems, stroke, and impaired wound healing[40].

Abnormal wound healing

Though a complete conversation of the various situations connected with abnormal wound healing is outside the possibility of this analysis, more than a few examples will explain the multifactorial quality of these situations. Diabetic ulcers are a brilliant example of how many physiologic and biochemical faults can central to reduced healing. They generally occur in patients who are incapable to sense and relieve cutaneous pressure because of neuropathy[41].

Needs of antimicrobial wound healing

The main requirement for antimicrobial wound healing is medication resistant to bacteria[42]**.** Most chronic wounds for example older patients and diabetic patients with leg and foot ulcers may suffer from complication of unfortunate movement on the lesser boundaries. In addition to tropical dressing can be helpful in avoiding the adverse effects of high dose antibiotic administration (oral and IV). Which may include allergic reaction, insomnia, vomiting, diarrhea, nausea, headache, etc. infectious concentration may be required at the site of infected bone[43].

Wound healing through antimicrobial

Antibiotic dressings are non-toxic in nature, and effort successfully on goal site lacking harming the multitude muscles perfect antimicrobial healing must consume spectrum movement in opposition to all major microbes, host cells must be non-allergic and nontoxic. These should also be the ability to eliminate and exhaust and maintain the moist environment of a wound[44]. Medication should be rapidly release uninterruptedly must reduce the risk and cost should be reduced[45].

1. *Polymer based antimicrobial wound healing*

Mostly natural and synthetic polymers are used for acute and chronic wound curing due to biodegradable, biocompatible and wound exudate healing capacity. Polymer and antimicrobial drugs will provide effective dressing to progress wound curing[46]**.** For wound healing new insights into ancient challenge led to the evaluation of hydrogel dressing based on a synthetic polymer that revealed biocompatible and antimicrobial action[47]**.**

And another study the synthetic polymer alcohol was miscellaneous with calcium alginate and formed Nanofiber matrix by electro spinning methods. According to in-vitro antibacterial test the rate of embarrassment of *S. aureus* depend on the quantity of calcium alginate chitosan is a polymer[48]. Whose positive charges interact with the microbial cell film together with the negative charges definitely in distraction and excitement Carboxymethyl chitosan was described as wide-ranging spectrum antibiofilm agent[49], which will avoid biofilm creation *E. coli* and *S. aureus* by 81.6 and 74.6 percent correspondingly[50]**.**

2. *Antioxidants*

In wound healing, wound sites were attracted by biologically active mediators in the inflammatory phase of neutrophils, leukocytes, and monocytes, and through phagocytosis, microorganisms and foreign debris were attacked, which also lead to the manufacture of ROS[51]. The antioxidant system in the cell was developed to play a vital role in redox homeostasis or scouring these free radicals to maintain a balance between free radical and antioxidant[52]**.** ROS, including superoxide (O2-), hydrogenperoxide (H2O2), hydroxylhydricle and other reactive oxygen derivatives, were very lethal, which have also caused extensive damage to proteins, DNA, and lipids, there by affecting usual cellular performance[53]. ROS were produced as an unavoidable by-product of oxidative phosphorylation in the cell[54]**.** ROS were constantly generated at basal levels. However, they were not capable to cause harm, as they were being scavenged by the antioxidant mechanism[55]. High levels of ROS could break cells by oxidizing lipids and proteins, with levels strongly controlled by the presence of ROS scavenging enzymes and small molecule antioxidants[56]. Altered redox signalling (non-balance between free radicals and antioxidants) that leads to oxidative stress was broadly accepted as a provider to the development of diabetes complications, including cardiac disease, nephropathy, and retinopathy[57,58]. The build up of ROS lead to the damage of the canteen of endogenous stem cells, growth factors, and nucleic acids in the wound tissue, thus significantly harming their regenerative ability, thereby delaying wound healing[59].

3. *Phenytoin*

Gingival fibrous overgrowth is caused by Phenytoin. Phenytoin is use as an anticonvulsant drug found in about 50% of treated patients[60].

The Phenytoin drug increased the proliferation of fibroblast proliferation during the release of cytokines of keratinocytes, not other cell types in- vitro [61,62].

Phenytoin stimulates the development of granulation tissue, reduce collagen, and promote collagen invention and deposition, growing the strength of the injured area[63].

Phenytoin also showed the ability to increase VGF and FGF at the wound site, resulting in the stimulation of new vessel formation[64].

Accordingly, biopsies of lesion tissue treated with phenytoin exhibited increased collagenisation, signs of neovascularisation and reduced the infiltration of circulating inflammatory cells.

A topical formulation of phenytoin was then formulated and proved to be efficacious in accelerating wound healing in trophic leprosy[65] ulcers and in melanocytic navi surgery. Following several other studies, either placebo or other comparators, random or not, but most of them shared a poor description of the study details. A systematic reconsider had underscored this restriction, importance the poor working quality of the available studies, though,

a large range of concentration used without signal seemed to point out topical phenytoin of a specific effect in wound healing[60].

4. *Metformin*

Biguanide metformin is known worldwide as a drug for the treatment of type II DM[66].

Metformin is exposed to also modulate other pathway of inflammation such as nuclear factor kappa B (NF-kB) and mitogen-activated protein kinase (MAPK)/c-Jun NH2-terminal kinase (JNK). All this confirmed that immune modulators and anti-inflammatory properties may support the possible of metformin for the treatment of wound healing. Activation of AMPK though inhibition of mTOR and NOD-like receptor protein 3 (NLRP3) inflammasome was in fact able to modulate polarization of macrophages near the M2 phenotype, all effects that come together towards the resolution of wound closure[67].

Accordingly, topically applied metformin in a pluronic gel formulation accelerated healing of excisional wounds in rat skin with a parallel increased polarization of M2 macrophages through activation of AMPK and ensuing downregulation of the mTOR/NLRP3 inflammasome signaling pathway[68].

Quicker wound healing and improved angiogenesis have been observed in db/db diabetic rats following systemic administration of metformin for 14 days[69]. These effects have been simultaneous with increased function of endothelial precursor cells and nitric oxide (NO) levels as well as antioxidant activity. Metformin is also able to repair basal levels of thrombospondin 1, an endogenous antiangiogenic mediator known to be involved in vascular complications in diabetes[69].

The clinical response observed have been attributed to increased manufacture of TGFβ in the wounded area, a growth factor known to affect angiogenesis, inflammatory reaction, granulation tissue development, ECM deposition, re-epithelization and remodeling, thus promoting the healing process[70].

More recently, metformin was also tested in combination with non-pharmacological approaches such as photobiomodulation for the effect on wound healing in DM type 2 rats. Interestingly, systemic organization of metformin and photobiomodulation showed a synergistic impact on skin restore by increasing fibroblasts, with improved formation of granulation tissue, by inducing new blood vessels and by modulate the inflammation and proliferation steps of wound healing[71].

CONCLUSION

Wound healing can be successfully achieved by several phenomena that go on simultaneously in body. The timely, optimal co-working of many diverse structural and cellular elements leads to recovery of tissues. The reparative process is a big process and takes lot of energy and synchronization. The diabetic patients need to take care of the management of their glucose levels for easy and rapid recovery of the wounds. This will also help in easy recovery and acute wounds can be treated well before they are converted to chronic wounds.

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