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A systemic correlation between wound and diabetes: An insight into mechanism of action and diabetic wound treatments

Avijit Mazumdar
Director and Professor, Noida Institute of Engineering & Technology (Pharmacy Institute)
Corresponding author email: avijitmazum@yahoo.com

Sanjana
Master of Pharmacy, Noida Institute of Engineering & Technology (Pharmacy Institute)
Email: sanjanasingh4423@gmail.com

Vikas Gupta
Master of Pharmacy, Noida Institute of Engineering & Technology (Pharmacy Institute)
Email: vksgupta105@gmail.com

***Abstract*---**The current article provides complete information on the association between wounding and diabetes, as well as a brief overview of Wound, Diabetic wounds as well as treatment options. The Diabetic wounds require special attention like a major clinical and societal challenge. The need of research is increased because of the delayed and compromised healing. New treatment techniques, Single growth factors, skin substitutes, interleukin stimulators, interleukin inhibitors, matrix metalloproteinase inhibitors, gene and stem cell therapies, extracellular matrix, and angiogenesis are only a few examples. stimulators, show that research on delayed healing is moving quickly. Despite the fact that multiple studies show that diabetes causes slowed wound healing, more precise mechanistic understanding into the components involved, and their parts are still being played needed. This review focuses on cytokine (with growth factors) and other molecular cascades previously unknown components that cause slowed wound healing, as well as molecular pathways and recent advancements in wound healing and treatment. Clinicians and academics working in relevant fields were given a briefing on new innovative knowledge on possible molecular targets and therapeutic techniques, including clinical trials, in this article.

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Introduction

Wound

A wound is an injury to living tissue produced by an incision, blow, or another impact, most commonly involving the skin. Wounding is a complicated and dynamic procedure that leads to anatomical integrity and performing restored. The most vital feature of wound treatment is that it heals quickly and completely without the spread of infection. Acute wounds usually repair fast and without any complications. The primary source of concern is age regarding changes in normal physiological activities, such as impaired blood circulation, obesity, diseases such as diabetes, and stressful environmental situations. There are two types of wounds and they are characterized based on their abilities to heal: chronic and acute. Long-lasting wounds (Chronic wounds) are tissue damage that does not repair in a logical order and take longer time more than 12 weeks to recover (Mohandas et al., 2015, Anisha et al.,2013).

Normally, the process of healing starts with hemostasis, which prevents loss of blood and microbial invasion of wound. The phase of inflammation follows, in this phase pro-inflammatory cells such as polymorphonuclear (PMN) leukocytes (at first) upregulate, and the processes followed by macrophages, which help in the cleaning up of dead cell, viruses, growth regulators, and other cells and cytokines. The proliferation stage overlaps the phase of inflammation, during which tissue, blood vessels (angiogenesis), and matrix formation are started to complete the wound. The last remodeling step enhances the extracellular matrix's tensile strength while decreasing flow of blood to the injured location (Komarcević et al., 2000; Sharp and Clark, 2011; Singh et al,2011; Singh et al., 2013).

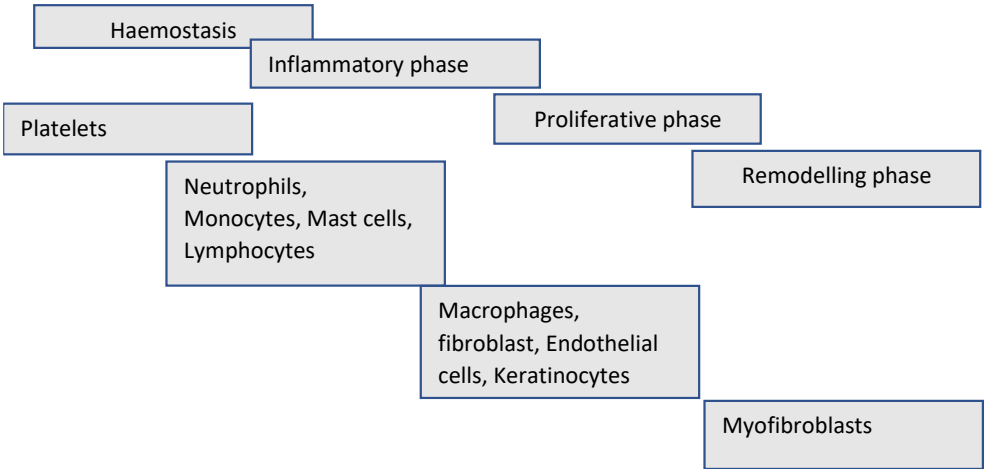

Fig.1 The stages of wound healing

Relation between diabetes and wounding-

Major key issues are wounds caused by diabetes primarily involving leg ulcer as well as diabetic ulcers. Diabetes slows wound recovery by impairing each step of wound recovery, including hemostasis, inflammation, proliferation, and remodeling, and has a long-term deleterious effect on life expectancy, morbidity, and death. A disrupted acute wound or chronic wound with impaired recovery as an outcome delayed, imperfect, or unfinished task healing process characterizes diabetic wounds (DWs). A protracted inflammatory phase is seen in DWs, which is accompanied by a loss in wound tensile strength and a slowdown in the growth of the mature granulation tissue This could be because of ischemia-induced vascular injury. (Galkowska et al., 2006; Kavitha et al.,2014). Each wound is a life-threatening situation that requires immediate attention.

External and internal wounds are the two most prevalent types of injury, cuts, injuries, burns, and bruises are examples of external origin wounds. Because of peripheral neuropathy, these exterior sores may go undiagnosed by diabetic patients. Internal wounds, such as sores on the skin and calluses, destroy the skin and adjacent tissues, as well as risk of bacterial infection rises. The present general thinking is that this method used a group of medical treatments to clean and remove diseased tissue while maintaining moisture and blood supply (Babaji et al., 2013). Recent research focuses on determining the important elements that affect the procedure of recovery. These discoveries could lead to medicines that promote normal tissue regeneration and enhance poor wound healing, despite the fact that much more research is needed.

The aim of this review is to uncover the molecular processes that cause wound recovery to be slowed, and molecular pathways for full healing and current advances in wound care.

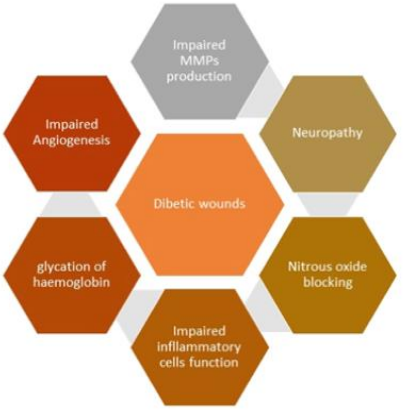

Fig:2. Factors responsible for Diabetic Wounds

The principles of wound healing

When tissue viability is disturbed, wound healing becomes a dynamic, complex process. Hemostasis, inflammation, proliferative, and remodeling stages are four partially overlapping phases of healing

Haemostasis

Platelets are important for hemostasis, which is the first stage in tissue repair. When circulating platelets come into contact with, collagen from the injured tissue, they get activated, aggregate, and stick to the ruptured endothelium (Blayney-Jude, 2006]. When the procedure of clotting is activated, fibrinogen is changed into fibrin, and the thrombus and temporary extracellular matrix are formed (Falanga et al., 2005). Platelets are activated to produce protein that encourage monocytes and neutrophils to migrate and adhere, and many growth factors that promote wound recovery, such as growth factor (platelet-derived) and TGF-b (Dinh et al.,2012).

Inflammation Phase

The procedure of inflammation of wound recovery starts as earlier inflammatory cells inside the wound area just after an injury. The initial cells to infiltrate the wound tissue enterocytes. neutrophils adhere to epithelial tissue once molecules bind together the endothelial surface(vascular) surrounding the activated injured tissue. The enterocytes subsequently penetrate further into the space of tissue (diapedesis) through damaged capillaries or gaps between endothelial cells. (Dinh et al.,2012; Dove et al., 2004). Control of infection and tissue debridement are important functions of neutrophils. They also produce growth factors, which aid in wound healing, that encourage cell proliferation and proteases that break down the extracellular matrix (Koh and DiPietro, 2011).

As circulating monocytes make their way into the tissue area, they rapidly develop into adult macrophages, causing inflammation. Phagocytosis removes germs, foreign substances, apoptotic neutrophils, and damaged tissue components after a wound via activated or pro-inflammatory macrophages (M1 macrophages). They also produce a multitude of cytokines and mediators that are pro-inflammatory (Weller et al., 2006). Resident basophils are also quick to react to tissue wounds and serve an essential part in wound recovery. Basophils degranulate, expelling cytokines that stimulate neutrophil recruitment and proteinases that break down extracellular matrix (Egozi et al.,2003; Brem and Comic-Con, 2007). T-lymphocytes reach the injured area late in the inflammatory stage as well as appear to modulate tissue remodeling.

Proliferative Phase

As the inflammation subsided, the wound begins the proliferative phase, and macrophages transition to an alternate activated or anti-inflammatory phenotype. Anti-inflammatory macrophages (M2 macrophages) produce a large number of anti-inflammatory cytokines, protease inhibitors, as well as growth factor including VEGF and TGF-b, which increase the proliferation of cells as well as

protein synthesis (Weller et al., 2006). Granulation tissue begins to replace the temporary matrix.

Growth factors generated by macrophages activate fibroblasts, they penetrate inside the injury with the help of the temporary matrix as a scaffold, and they begin to multiply and create collagen and constituents of extracellular matrix at this point (fibroplasia). The development of fibroblasts is maintained by the angiogenesis of newer vessels. New blood vessels must be generated from an existing capillary network to provide oxygenated blood to the quick generating cells inside the recovery process. Vasculogenic is the procedure of development of RBC vessels from the ground up using precursor cells from bone marrow (endothelial progenitor cells, EPCs) (Dove et al., 2004).

Adult stem cells can develop inside epithelial cells and encourage endothelial regeneration and neovascularization a reaction to tissue ischemia also called an EPCs. (Fadini et al.,2007; Drela et al., 2012). Angiogenesis is a continuous, a stringently regulated procedure that is primarily dependent on proangiogenic molecules like fibroblast growth factor-2 (FGF-2) and Vascular endothelial growth factor (VEGF), as well as anti-angiogenic factors that operate on endothelial cells.

FGE-2 there looks to be released as an outcome of tissue disturbance all through the first three days of injury repair, whereas VEGF is majorly triggered by loss of oxygen in tissue (hypoxia) beyond those three days (Dove et al., 2004; Lobmann et al., 2005). New capillaries form a microvascular across during the granulation tissue early proliferative phase. The density of vessels of blood decreases as the procedure for recovery progresses. Granulation tissue is a form of connective tissue that has a granular appearance.

it has as an outcome of the abundance of new capillaries. This is made up of fibroblast, endothelial cell, inflammatory cell, extracellular matrix component, and the newly formed blood vessel that grow throughout the procedure for recovery Keratinocyte migrate from the area of the injury or around skin appendages onto the newly formed matrix and start re-epithelializing granulation tissue, is being formed at the very same time. This spans the injury and covers the tissue of granulation (epithelialization). Several variables contribute to growth factors secreted by the damaged epidermis, like FGF-2, keratinocyte growth factor, as well as endothelial growth factor (EGF which increase epithelial proliferation (Dinh et al.,2012).

Remodelling Phase

At about 2-3 weeks following the initial injury, the wound-healing restructuring period starts, as well as granulation tissue forms. gradually converts into mature scar tissue. The number of blood vessels diminishes, as well as collagen is reshaped and organized. During the remodeling phase, new collagen is synthesized and old Collagen is broken down at a constant rate, which is mostly regulated by matrix metalloproteinases (MMPs) activity (Blayney and Jude,2006; Dinh et al.,2012).

Collagen fibers that have been reportedly generated are no more randomly

invented, but rather lay closer collected over tension lines, facilitating cross-linking and therefore continuing to increase the wound's tensile strength. Wound contraction, in which myofibroblasts shrink the wound by pulling the wound's margins together, is another possibility (Mayer et al.,2014).

Mechanistic insight

Diabetes slows down the recovery process, as an outcome, non-healing injuries can result in a various number of consequences, including emotional stress and despair. Functional limits, a complication in walking, and infections like gangrene, abscess, cellulitis, osteomyelitis, and septicemia are among the problems. The connection between pathophysiology and reduced recovery of DWs is well documented, however, the etiology underlying the connection between pathophysiology slowed wound recovery in diabetes is yet unknown.

Collaboration between biological messengers as well as inflammatory cells triggered by numerous causes is essential for the process of recovery. In diabetics, however, changes in cellular and metabolic components and a number of activities have been connected wound recovery failure. Mast cell, T cell, B cell, neutrophils, keratinocytes, monocyte, fibroblast, macrophage and endothelial cells all participate in the recovery of wounds in the procedure of synthesis, cells play an important part and the control of cytokines and growth factor.

In both diabetes and non-diabetic situations, monocytes, which eventually change into macrophages, are the primary producers of cytokines that are pro-inflammatory, like IL-1, TNF-3, IL-64, and VEG-7. Neutrophils, like B as well as T cells, are major producers of TNF-, IL-10, and other cytokine, and fibroblast, keratinocytes, endothelial cells and mast cell. These cells are also participated in the production of IGF-1, TGF and VEGF. Macrophages play an important part in the recovery procedure. Hyperglycemia and oxidative pressure alter the epigenetic coding, as an outcome in polarization and the control of macrophages. Among the most Basic reasons for wound repair delays includes dysregulated macrophage polarization [Mallik et al.,2018; Maruyama et al.,2007).

Other variables that stymie the procedure for recovery in diabetic individual metabolic deficiencies, and altered physiological effects are only a few examples. like hypoxia caused via plasma glycation, RBC (red blood cells) wall changes, as well as blood vessels narrowing. Hypoxia is a situation where the provision of oxygen to wounds is diminished as an outcome of blood vessels constriction. Hemoglobin glycation results in lack of food and oxygen in the tissue, causing a delay in the procedure for recovery even more. Hypoxia/glucose deprivation, and malformed proteins, cause the cell to respond by accumulating proteins in the endoplasmic reticulum that have been unfolded, which is also called as UPR8. Activation of this UPR is associated with the formation of pro-inflammatory mediators and occurs quickly after tissue or skin injury.

In comparison to Diabetic wounds (DWs), DWs showed a prolonged activation of UPR and enhanced production of pro-inflammatory chemokine. (Brem and Tomic-Canic, 2007; Schuurman et al., 2014). Local ischemia caused by diabetes' microvascular problems considerably slowed wound recovery. MiRNAs9 are a kind

of non-protein-coding RNA that has a sequence of 19-24 nucleotides and is engaged in a number of processes in a huge number of physiological functions and plays an important role in a number of difficulties. MicroRNA levels were discovered to be changed in a various way of illnesses, also include slow wound recovery (Moura et al., 2014). MicroR-210, for example, hypoxia is increased in environments and targets E2f3, which suppresses the development of keratinocytes, and growth in the recovery of wounds (Biswas et al.,2010).

By directing globin transcription factor 2 and vascular endothelial growth factor receptor210 (VEGFR210), MicroR-200b inhibits angiogenesis (Chan et al.,2012). Similarly, microRNAs such as microR-130a, microR-21, microR-146a, microR-198, and microR-26a alter epithelization, inflammation, migration of fibroblast, corneocyte migration, re-epithelialization, and formation of blood vessel in DWs. (Bhattacharya et al.,2015; Ili B. C.S. et al.,2016).

Physiological factors like increment in the serum metalloproteinase-9 (Li et al.,2013), accumulation of impaired collagen and ratio variation of collagen types, dysregulation of expression of NPY (neuropeptide) in the skin alongside suppressed response of inflammation (Pradhan et al, 2011), deficiency of TAFI(thrombin-activatable fibrinolysis inhibitor) (Verlie et al.,2010). AGE11 modification of platelet derived growth factor (Nass et al.,2010) & imbalance between the extracellular matrix accumulation components and their remodeling by matrix metalloproteinase are responsible for lower rate of recovery process in diabetic patients.(Gooyit et al.,2014).

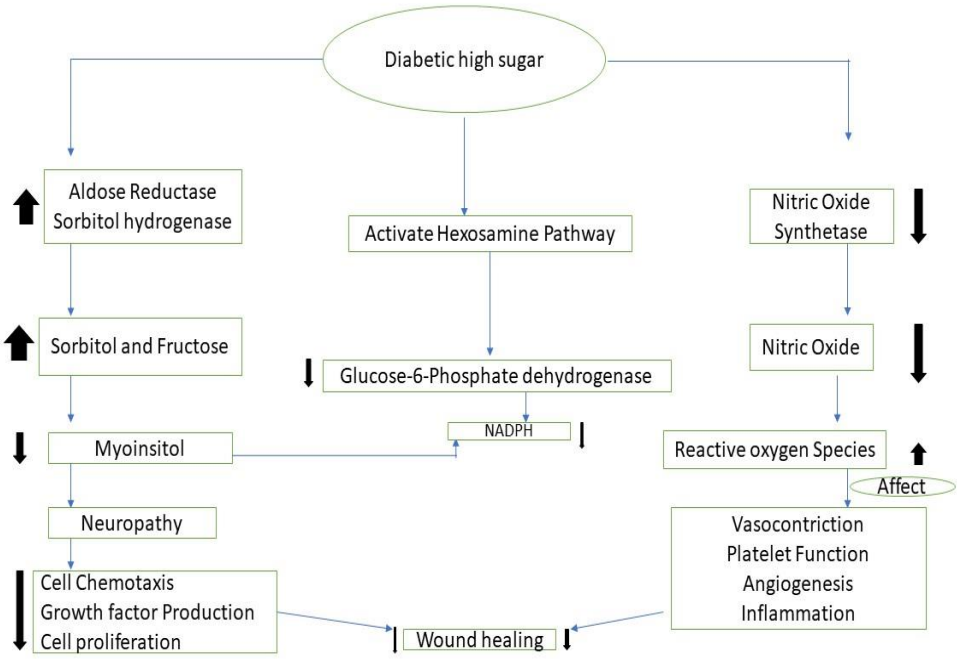

Fig 4. Pathways decreased wound healing in diabetes

Role of the immune system

In wound recovery, the adaptive immune system's proper coordination is crucial. TLRs22 play a major part in the start of the adaptive immune as well as inflammatory responses. TLRs-2 downregulation in wounded tissue hampers or inhibits the immune system and inflammation response in diabetes patients (Peleg et al.,2007; Singh et al., 2015; Singh et al., 2015), as an outcome, diminished chemotactic impact, delaying the recruitment of different inflammatory cells.

Diabetic patients are especially susceptible to infection due to slow wound recovery and immunosuppression (Peleg et al.,2007). The growth of biofilms by bacterial contacts on the injury is significant in the etiology of the diabetic wound. These biofilms protect microorganisms' antimicrobials as well as immune response and also obstruct the healing process. In diabetic wounds, it is the most prevalent reason for amputation of the lower leg. (Smith et al., 2016). Neutrophils, monocytes, mast cells, B cells as well as T cells are examples of inflammatory cells that play a major role in immunity. The dysregulation within these cells could play a major role in the diabetics' host's immune system being suppressed.

In diabetes, pro-inflammatory cytokines in high concentrations like IL-6 as well as TNF- induce an interruption in the inflammatory cascade, leading to hyperinflammation and insulin resistance. The increase of effector T cells could detail the elevated level of TNF-. In DWs patients, Maura et al discovered a decreased number of naïve T cells as well as narrower TCR-V range, the end result is an enhancement of effector T cells (Moura et al., 2016). Increase level AGEs alter immunity by stimulating the growth of cytokines including IL-6 and TNF-.

AGEs also impede collagen formation, cause apoptosis, overactive immunological responses, and negative cell physiology regulation, all of these factors responsible for the slowed recovery (Abiko and Selimovic, 2010). FGF, VEGF, and TGF-1 are all potent angiogenic agents released by mast cells (Nishikori et al., 2014). Mast cells, in collaboration with macrophages, endothelial cells, and fibroblasts, play a major part in the recovery of wounds, according to several studies. It disrupts the equilibrium in wound tissue between anti-angiogenic and pro- angiogenic factors and plays a major part in matrix re-organization (Elechi et al.,2016). Mast cell numbers are declining and malfunctioning, resulting in a number of symptoms, Bevan et colleagues discovered that vascular regression was delayed in the diabetic mice with a hereditary mutation (Bevan et al.,2004).

They arrived at the conclusion that delayed mast-cell increase in diabetes caused an altered proliferation phase in the procedure of repair. Mast cell dysfunction influences angiogenesis at the time of proliferation and vascular regression phases during the remodeling phase (Nishikori et al., 2014). In his study, Elechi et colleagues discovered degranulation of mast cells was increased on the skin surface of both people and mice, resulting in the slowed healing process. Quercetin, luteolin, as well as disodium cromoglycate which block mast cell degranulation, may be effective in improving wound recovery in diabetics (Elechi et al.,2016).

MIF (Macrophage Migration Inhibitory Factor) gene RNA expression declines in diabetics, it is a crucial component in the innate immune system's pro-inflammatory responses. MIF deficiency in DWs has been linked with the decreased generation of endothelial progenitor cells and a delayed recovery process (Grieb et al.,2012; Ebaid et al., 2015). Heat shock proteins (HSPs) aid wound recovery by recruiting dermal fibroblasts, stimulating cell proliferation as well as keratinocyte differentiation, reducing oxidative stress, alleviating actin microfilaments, assisting endothelial cell migration, and stimulating protein homeostasis and pro- collagen synthesis (Luong et al., 2012). HSPs such as (HSP90, HSP70, HSP47, and HSP27) levels fall in diabetes, as do their downstream components TLR4 and p38-MAPK (Park et al., 2018). It could be to blame for slowed recovery.

Role of Growth factors in impaired wound healing

Growth factors such as cytokines, fibroblasts, MMPs (matrix metalloproteinase), inflammatory cells, endothelial cells, and keratinocytes all play a role in normal wound healing. Biologically active polypeptides growth factors which, play a role in the recovery process at every stage (Barrientos et al., 2008). During the granulation phase of tissue development, they enhance the initial inflammatory phase. Due to changes in their expression, decreased production, decreased release, trapping, and excess degradation, compromised wounds usually display deficiencies in the kind and amount of growth factor (Martinelli et al., 2004). ECM synthesis with optimal healing is identified by a balance between matrix creation and matrix degradation.

VEGF (Frank et al.,1995), IGF-I, IGF-II (Brown et al., 1994), TGF-23 (Biter et al., 1996), KGF24 (Werner et al., 1994), PDGF25 (Beer et al.,1997), EGF26 (Burstein et al.,1987), FGF27 (Hosokawa et al., 2000; Parkar et al., 2001), TNF-, and IL-6 are all factors that regulate ECM development in diabetes patients. Growth factors are necessary in kicking off and maintaining the various procedure in wound recovery. In diabetics, any change, such as growth factor receptors being downregulated, as well as growth factors being rapidly degraded, causes wound healing to be slowed.

Platelets emit PDGF, a significant serum mitogen that stimulates fibroblast proliferation, matrix formation, and connective tissue progression (Greenhalgh et al.,1990). Macrophage, which is a prominent cell in the last stages of the inflammatory process, produce PDGF on a continual basis in the injury environment. For fibroblasts and inflammatory cells, PDGF work as a chemoattractant. Glycosaminoglycan, proteoglycan, and collagen synthesis are all aided by it.

During the healing process, this is a critical mediator in migration of fibroblast and proliferation, the granulation tissue protein synthesis and provisional ECM, and angiogenesis (Doxey et al.,1995). In diabetic wounds, the PDGF expression and its receptors is reduced, indicating that it plays a role in recovery process (Li et al.,2008). VEGF promotes blood perfusion and metabolism in wounded tissue by increasing capillary density in DWs.

The restoration of blood flow to wounded tissues allows for the supply of oxygen and nutrients to support the development and function of reparative cells, promoting wound recovery. It is the regulator of wound revascularization and permeability, and a player in the creation of granulation tissue. The activation of VEGF receptors regulates its functions; the first receptor, VEGF receptor-1, causes inflammation, while the second receptor, VEGF receptor-2, causes angiogenesis (Angelo and Kurzrock, 2007). Diabetes, which cause impaired wound recovery, is to blame for the comparatively low amount of VEGF in local wounds.

According to studies, aberrant VEGF receptor patterns reduced the amounts of VEGF mRNA, raised the level of VEGFR-1, and reduced levels of VEGFR-2 are the major cause reasons of wounds non-recovery (Zhou et al.,2015). After attaching to the EGF receptor, platelets release EGF, which enhances epidermal cell motility, cellular migration, mesenchymal regeneration, angiogenesis, and cell proliferation (Hardwicke et al., 2011). Insulin-like growth factor-1 and IGF-2 are peptides that combine to generate a complex Insulin-like growth factor (IGF).

IGF-1 aids wound recovery by promoting cell granulation and re-epithelization, as well as boosting endothelial cell chemotaxis and keratinocyte and fibroblast proliferation. However, in diabetic patients, IGF-1 expression is reduced, which could be the cause of cell granulation defects (Brown et al., 1997; Bruhn-Olszewska et al., 2012). Reduced IGF-1 and TGF-levels in injured tissue have been documented in animal and humans with diabetes, as an outcome delay in wound recovery (Bhora et al., 1995).

TGF- attracts and activates inflammatory cells such as neutrophils, macrophages, lymphocytes, keratinocytes, and fibroblasts, and growth factor synthesis. This speed up vascularization, angiogenesis, and ECM creation while delaying ECM breakdown (Roberts et al.,1995). Several discoveries shown that the promoter region of MMP-encoding genes contains a TGF-1-dependent inhibitory element that suppresses the gene's production.

Excessive degradation of growth factors caused due to low levels of TGF and high expression of MMPs (Stefanovic et al., 2000). Transcription factors like SMAD-2, SMAD-3, and SMAD-4 activate and deactivate TGF-target genes and MMP-encoding genes. TGF-1 stimulates the collagen synthesis by activating Smad-2 and 3 (Hossein et al., 2015). In DWs, decrease in TGF-1 levels resulted in enhancement in the recruitment of activated inflammatory cells, producing a delay in the shifting from the inflammatory to proliferative phase of the recovery process. TGF-3 deficiency was assumed to be the cause of low TGF-1 levels in diabetics (Jude et al., 2002), which resulted in enhancement of macrophages response and reduced synthesis of collagen.

High glucose levels macrophage activity increases, resulting in the more reactive oxygen species as well as prolonged inflammatory phase (Heinlein et al., 2015). Diabetes causes poor and protracted wound recovery due to decreased levels as well as expression of these growth hormones.

Role of MMPs in impaired wound healing

Matrix metalloproteinase (MMPs) is a set of 26 zinc-dependent endopeptidases that are engaged in wound closure and angiogenesis, epithelialization and extracellular matrix remodeling. (Armstrong and Jude, 2002). MMPs degrade all matrix proteins, including collagens, basement membrane collagens, collagens, proteoglycans, elastin, and fibronectin. The gelatinases (MMP-2 and MMP-9) are two proteinases that predominantly deconstruct type 4 collagen from the underlying matrix. These are inert zymogens that must be activated by removing the prod main.

MMP activity is limited by TIMPs29 complexation, which prevents interfere with the active site. According to a number of sources, a healthy balance of TIMPs and MMPs is essential for optimal wound healing (Lohmann et al., 2006). MMPs are engaged in numerous wound healing steps, including cell migration via ECM proteolysis, re-epithelialization via junctional protein degradation, leukocyte invasion via a chemotaxis gradient, and inflammation via inhibition or the formation of different cytokines (McLennan et al., 2008).

MMP-1 is crucial for wound re-epithelialization, MMP-2 is essential for angiogenesis and extended matrix remodeling, and MMP-3 is crucial for the proper contraction of the injury and the basement membrane remodeling. While the role of MMP-9 during recovery is unclear, it may be participated in detaching keratinocytes from basement membranes prior to migration and in assisting neutrophils degraded matrix and macrophages during the phase of damaged tissue removal (Wall et al., 2002).

According to studies, diabetic wounds have huge number of metalloproteases, and MMP levels in a long-term wound fluid are nearly 60 times greater compared to acute wounds This enhanced protease activity promotes tissue death while inhibiting normal tissue healing (Sib bald and Woo, 2008).

Molecular targets

In the past few years, wound research has expanded due to better knowledge of diabetes and its impact on defective wound healing at the molecular level. This research discovered that wound recovery in diabetics is hampered by abnormal cellular activity of all involved cells, and instability of the expression of cytokines, growth hormones, and other molecular components essential for wound recovery that is normal coordination. As a result, non-healing wounds that have not been recovered from a very long time are unable to advance in lockstep and are primarily checked- in an inflammatory phase.

Over the years, various molecular factors/targets for the treatment of DWs discovered. These management strategies are classified on the basis of cellular targets that influence their action directly or indirectly. Growth factors like (PDGF, TGF, FGF, KGF, VEGF, EGF), autologous fibroblasts or autologous keratinocytes and stem cells are among the targets that interact directly. These aims' importance and role were focused in earlier sections.

Depending on the circumstances, target, several drugs may indirectly alter the up- regulation of molecular targets or down-regulating manifestation of growth factors, pro-and anti-inflammatory cytokines, MMP, nitrous oxide level, collagen synthesis/degradation, and factors supporting angiogenesis. These wound treatment methods are classified on the basis of therapeutic agents used, such as drugs, growth factors, other approaches, stem cells as well as highlights in the current status of clinical for the management of DWs are given in table1. The molecular targets used in therapeutic methods by forms, either directly or indirectly are also shown Table no-1.

Natural product-based treatment

Turmeric (curcumin), Castor leaves (Ricinus commune), Neem bark (bitter bark), Ginseng, and other natural sources have traditionally been of paramount role in the recovery of wounds. According to reports, 70% of commercialized treatments have plant-based active components, 20% contain mineral-based active ingredients, and 10% contain animal-based active compounds, with over 13,000 developed specifically to speed wound healing. Glycosides, steroids, saponins, resins, mucilage, and flavonoids are few of the plant actives are participate in the recovery process of wounds. Table 2 covers the majority of medicinally active plants that have been demonstrated to have in diabetic wounds, healing activities, while Table 3 shows the commercially available products used in the treatment of DWs.

Clinical trials

Several clinical trials were underway to find a unique treatment approach for this global health problem. In a clinical investigation using photodynamic therapy, the probability of amputation in the photodynamic therapy group was 0.029 times that of the comparison group, according to Tardive et al., 2014. (Correa et al., 2014). In phase 3 multicenter, double blind, randomized, placebo- controlled study, Park et al.

(2018) assessed the effectiveness and security of spray-applied growth factor therapy integrating recombinant human epidermal growth factor (reef) for the care of DWs. Patients in the reef-treated group healed significantly faster than those in the placebo group (73.2 percent vs 50.6 percent, respectively; p = 0.001). In addition, despite HbA1c levels, the rate of recovery was observed to be quicker in the reef-treated group (p = 0.029).

When matched to the placebo group, the reef-treated group exhibited a faster median time to a 50% decrease in ulcer size and a faster than average time it takes for an ulcer to heal completely (Park et al., 2018) Azadi et al., 2017 used a cathodal direct current of low intensity in a randomized, single-blind, placebo-controlled experiment. According to the findings of this study, by enhancing the production of HIF-1 and VEGF in the injury site, electric stimulation has therapeutic effects and promotes healing in ischemic ulcers. (Azadi et al., 2017). Soleimani et al., 2017 used flaxseed oil omega-3 fatty acids in a randomized, double-blind, placebo-controlled experiment. This study concluded that 12 weeks of omega-3 fatty acid supplementation had a favorable impact on ulcer size,

insulin metabolism markers, plasma TAC, serum has-CRP, as well as GSH levels in DWs patients (Huang et al., 2005).

Future therapeutic strategies

Diabetic wounds can be affected by a combination of factors like peripheral neuropathy, peripheral vascular disease, and foot problems. Despite advancements in technologies such as bioengineered skin cells and the widespread use of standard care in DWs, recovery of wounds has been observed to be less than 50 percent of the time. New therapeutic approaches, like cytokine inhibitors, single growth factor, skin substitute, dual growth factor, cytokine stimulators, matrix metalloproteinase inhibitors, stem cell therapy and gene extracellular matrix, and angiogenesis stimulators, show that research on diabetic wounds is moving quickly.

Recombinant growth factors, sphingosine1-phosphate, stem cell therapy, shock wave therapy, platelet- rich plasma, MMP inhibitors, substance P, laser therapy, and natural product-based therapies are now being studied for the management of the diabetic wound. These methods are critical for a better practical, secure, and effective DWs treatment (Tables 1 and 2). The bulk of these methods are being heavily investigated, and their application has been limited to clinical trials.

Stem Cell Therapies

The application of stem cells to diabetic lesions has been examined in several clinical studies with promising results. Injectable autologous injections activated macrophages (PBMNCs), bone marrow mesenchymal stem cells (BM-MSC), or bone marrow- derived mononuclear cells (BM-MNC) into the ischemia lower limb of patients with diabetes and critical limb ischemia significantly improved blood flow as well as resulted in complete wound recovery, with no major side effects. (Dusky et al.,2013; Humpert et al.,2005).

Local administration of bone marrow cells of adult stem cells improved tissue vascularization as well as wound recovery in a diabetic patient with chronic venous and neuro ischemic wounds without systemic side effects. (Humpert et al.,2005), the individuals having chronic ulcers, topical application of BM-MSCs using a fibrin polymer aerosol system resulted in improved wound healing (Falanga et al.,2007).

Gene Therapies

Gene delivery of wound-healing growth factors like the utilization of PDGF as well as VEGF as possible care for wounds that are resistant to conventional treatments has been advocated. The most well-established technique for gene delivery is viral vectors, and replication-defective adenoviruses carrying PDGF or VEGF have been employed in human and animal research with promising wound recovery results. In patients with diabetes and neuropathic ulcers, topical treatment of a bovine collagen gel containing a replication- defective adenovirus expressing PDGF resulted in rapid wound reduction and complete ulcer healing, with no major safety issues (Mulder et al.,2009).

Cytokine Inhibition

The activation or recruitment of anti-inflammatory macrophages (M2 macrophages) to the wounded tissue, which would increase cell proliferation and angiogenesis, is one therapy technique that could improve wound recovery. Activated macrophages (M1 macrophages) produce a number of pro-inflammatory cytokines, including IL-1, which appear to be important in maintaining a pro-inflammatory macrophage phenotype in DWs. In diabetic mice, inhibiting the IL-1b pathway increases the switch from a pro-inflammatory to an anti-inflammatory or reparative macrophage phenotype, which enhances growth factor production and hence wound healing (Mirza et al.,2013).

Table 1. Therapeutic strategies explored the management of wounds in diabetics

Therapeutic agent	Delivery System and Route	Mechanism of therapeutic agent	References
Growth factors PDGF/TGF-α	Topically/ Gel	Enhancing keratinocyte and fibroblasts nitrogen promotes healing.	(Brown et al.,1994)
basic fibroblast growth factor	PELA Nanofibers/ Topically	Proliferation, migration, fibroblast adhesion, re-epithelization, angiogenesis, ECM restoration, and remodelling are all increased in this study.	(Yang et al.,2011)
Human epidermal growth factor	Cream/ PLGA Microspheres	Reduces the healing time. Enhanced recovery through increasing proliferating cell nuclear antigen in the epidermis and stimulating fibroblast proliferation.	(Tsang et al., 2003)
Recombinant epidermal growth factor	collagen/gelatine sponge	Improve healing.	(Dong et al.,2008)
basic fibroblast growth factor	Gel	Enhanced c-foes protein expression and ERK phosphorylation D improves re-epithelialization, granulation tissue thickness, capillary density, and healing.	(Morimoto et al.,2012)
Recombinant PDGF	Collagen Domain	Maintains VEGF activity via increasing vascularisation.	(Cheng et al.,2007)
Fusion protein (CBD-VEGF)	Poly-epsilon-caprolactone and poly ethylene glycol Nanofibers	Increased epithelization, which reduced wound size.	(Yan et al.,2010)
Recombinant epidermal growth factor	Hyaluronic acid sponge /Collagen-gelatine sponge	Angiogenesis and ECM formation should be accelerated. Healing is improved by promoting reepithelialisation and tissue granulation.	(Matsumoto et al.,2010)
Arginine and Epidermal growth factor beg			

Synthetic drug Pravastatin	Subcutaneous sponges	Up-regulation of Enos and NO activity improves wound breakdown strength and hydroxyproline build-up.	(Koria et al., 2011) (Laing et al.,2010)
Palonidipine	Solution/Orally	Healing is accelerated by increasing NO generation and improving histologic processes.	(Bagheri et al.,2011)
Atorvastatin gel	Carbopol Hydrogel	Within 7 days, the wound was closed and epithelized, resulting in faster healing.	(Aly et al.,2012)
Pentoxifylline	Cream	Reduces MMP expression and increases TIMP-1 expression, which speeds up healing.	(Babaji et al.,2013)
Propranolol	Solution Orally	Inflammatory cell and MMP-9 levels are reduced, whereas cell proliferation and mast cell numbers are increased.	(Romana-Souza et al.,2009)
Other approaches			
Sphingosine 1-phosphate	Subcutaneous	Increased vascular development inside the granulation tissue speeds up healing.	(Kawakami et al.,2007) (Gooyit et al.,2014)
Broad-spectrum MMP inhibitor	Sepharose resin, Topically	Accelerate wound healing, re-epithelialization, and MMP-9 activity inhibition.	
HoxD3 plasmid DNA	Methylcellulose Film	Increased mRNA expression of HoxD3, Col1A1, and 3-integrin leads to increased angiogenesis and collagen deposition, resulting in faster wound contraction.	(Hansen et al.,2003)
Stem Cell			
Adipose tissue-derived Mesenchymal stem cells	Intra-dermally	Anti-inflammatory and anti-apoptotic properties aid healing.	(Macaroni et al.,.2001) (Kazemi-Darabadi.,2014)
Allogenous skin fibroblasts	Cell suspension		
Topical embryonic stem cells	Topical injection	Enhance re-epithelialization, fibroblasts, and angiogenesis to aid healing.	
BM-derived SPC	Topical	Increased EGF, VEGF, and fibronectin stimulate epidermal development, granulation tissue development, and angiogenesis, resulting in faster healing.	(Lee et al.,2011) (Javazon et al.,2007)
Human umbilical cord	Transplantatio	Improves healing by enhancing	

blood-derived mesenchymal stromal cells	n	angiogenesis through indirect methods. Increased collagen synthesis and angiogenesis, which improved healing.	

Table:2. Natural product-based treatment for diabetic wounds

Natural Products	An outcome with possible mechanism	References
Angelica sinensis (Olive.) Diels	. Reduce neutrophil infiltration and macrophage accumulation, improve angiogenesis, and boost collagen deposition to improve healing.	(Zhang et al.,2016)
Aloe vera (L.) Bumf.	Enhanced healing	(Inpanya etal.,2012]
Rosmarinus officinalis L	Debridement, enhanced contraction, epidermal restoration, and organization all help to reduce inflammation.	(Abu-Al-Basal et al.,2010)
Nicotine	Angiogenesis and faster healing	
Allium sativum L.	Accelerate diabetes healing	(Merrell et al.,2009]
Camel milk Peptide	Restores redox balance, activates the inflammatory cascade, and promotes healing.	(Jacobi et al.,2002]
Astragalus membranous (Fisch.)	Improved tissue regeneration, promotion of angiogenesis, and inhibition of inflammation all contribute to improved recovery.	(Zuber et al.,2013]
Annona squamosa L.	Epithelialization rate, tissue regeneration, and collagen production are all improved.	(Tam et al.,2011]
	Reduction of FoxO1, ins activity, and oxidative stress improves healing and angiogenesis.	(Ponrasu et al.,2012)

Table:3. Marketed products available for wound healing

S.no.	Company name	Product	Composed of
1.	Sharell, USA	Derma graft	Cryopreserved human fibroblasts-derived dermal substitute
2.	Endocrinology and Metabolism Research	Angi pars	Melilotus officinalis
3.	Institute, Iran		Bovine collagen and living fibroblasts and keratinocytes
	Novartis, Switzerland	Altigraph	
4.			Platelet-Derived Growth Factor-BB
5.	Smith & Nephew, Inc., USA	Becalming	Biotic Pharmakon's soluble yeast beta-glucan (SBG)
	Biotic Pharmakon, Norway	Wolgan® bagel	

Conclusion

Wound healing is a multi-step biological mechanism involving numerous cell types, growth factors, and cytokines. Diabetes mellitus can impede by interaction with one or more biological systems, wound healing can be slowed. Delayed

wound healing as a result of diabetes is a common problem with potentially catastrophic consequences for diabetics. According to several studies, a number of factors have a part in diabetes-related delayed healing. In the management of wound healing in diabetes, notable progress has been achieved on a number of new therapeutic techniques and devices. Growth factors, dual growth factors, different cytokines modulators, anti-inflammatory medicines, MMP inhibitors, angiogenesis stimulators, ECM stimulators, stem cells, and a number of natural-based items have all been tested with mixed results. Recent research using a combinational technique has outperformed the traditional method.

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