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Exploring Metformin as the Potential Oral Antidiabetic of Choice for Type II Diabetes Mellitus with Wound Comorbid: A Case-based Literature Review

Almira Talitha Ulima[1], Ahmad Fawzy[2]

[1]Rantau Suli Public Health Center, East Jangkat, Jambi, Indonesia

[2]Department of Surgery, Universitas Jendral Soedirman, Indonesia

ABSTRACT

Diabetes is a metabolic disease characterized by hyperglycemia caused by a disruption in insulin secretion, insulin function, or both. An individual with diabetes have a greater likelihood to develop chronic non-healing wounds, and if untreated, various chronic complications are associated with psychiatric stress and depression. In diabetic wounds, the inflammatory phase becomes persistent and excessive with impaired cell proliferation and greater risk of infection. Several studies have shown that metformin has potential effect for diabetic wound healing. Here, we reported a case of diabetic wound in East Jangkat, a rural area in Indonesia, with premorbid type 2 diabetes mellitus and obesity class II with a deeper discussion about the potential effect of metformin for wound healing in diabetic ulcers.

KEYWORDS: metformin, wound healing, diabetic ulcer, hyperglycemia, diabetes mellitus.

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INTRODUCTION

Diabetes is a metabolic disease characterized by hyperglycemia caused by a disruption in insulin secretion, insulin function, or both. Diabetes can cause severe damage to the heart, blood vessels, eyes, kidneys, and nerves over time. The most common is type 2 diabetes, which occurs in adults and occurs when the body becomes resistant to insulin or does not produce enough insulin.[1,2] Diabetes affects approximately 422 million people worldwide, with the majority living in low and middle-income countries, and diabetes is directly responsible for 1.5 million deaths each year. Type 2 diabetes mellitus has emerged as a global public health concern, particularly in developing countries. In 2021, Indonesia will have 19.5 million diabetics, making it one of the top five highest prevalence countries in the Western Pacific.[3,4] Diabetes was one of the top three causes of death in Indonesia in 2019.[5] Diabetic patients' ability to metabolize glucose decreased, resulting in impaired wound healing and a greater likelihood of developing chronic non-healing wounds. If untreated, various chronic wound complications are associated with psychiatric stress and depression.[6,7]

The wound healing process is orchestrated by inflammatory cells, biochemical mediators, and collaboration with various factors, but individuals with diabetes experience change in all aspects of the healing process, resulting in wound healing failure. Chronic inflammatory conditions characterize the change. The inflammatory response remained in the acute repair phase for a long time, with high levels of inflammatory cytokines such as 1 (IL-1) and tumor necrosis factor (TNF-α) in the injured area, decreased endothelial progenitor cells, decreased levels of several growth factors such as insulin-like growth factor-1 (IGF-1) and transforming growth factor-β (TGF-β), disrupted angiogenic process, imbalance in extracellular matrix regulation, and promoted the unbalance.[8-12]

Metformin is a biguanide that is used as a first-line oral drug therapy. It is an old drug, but it is still widely used around the world due to its high clinical value and low cost for diabetes mellitus. Metformin has been used to treat diabetes by French physician Jean Sterne since 1957. Metformin was derived from extracts of *Galega officinalis* leaves, a traditional herbal medicine found to be high in guanidine in Europe.[13,14] Several studies have shown that metformin can increase the number and function of circulating EPCs, as well as increase angiogenesis, anti-inflammatory, anti-oxidant endothelial cell precursors, collagen deposition, and ECM organization.[15-17]

Here we reported a case of a diabetic wound in East Jangkat, a rural area in Indonesia, with premorbid type 2 diabetes mellitus and obesity class II with a deeper discussion about the potential effect of metformin for wound healing in diabetic ulcers.

CASE PRESENTATION

A 41-year-old female farmer visited primary health care facilities in Jangkat village's rural area (21 January 2023). She complained about a wound that was getting bigger by the day. She claimed that two weeks ago, a green bean-sized lump, pretty much identical to acne, appeared in her right buttock. The lump grew until it was the size of a chicken egg. It had exploded and formed a wound three days before she arrived at primary care. She experienced pain in the unhealed wound, as well as swelling and pus oozing from the wound. She didn't get a fever at all. Other symptoms such as headache, cough, nausea, vomiting, and diarrhea were denied.

She has a three-year history of uncontrolled diabetes mellitus. She received insulin therapy from her internist a year ago, but she discontinued it because she felt healthy and never returned to the internist.

When the lump exploded three days before, she went to primary health care. She received treatment from a midwife in her village in the form of an ointment, but she didn't bring it with her.

The patient was fully conscious and calm during the physical examination. The blood pressure was 110/60, the pulse rate was 84x/m regular, equal, and full, and the respiration rate was 18x/m. With a weight of 76 kg and a height of 154 cm, the patient was classified as obesity class II. The general condition was within normal limits. Local examination revealed a wound in the right gluteus with erythema surrounding it. The wound had an irregular shape, with the longest length being 4 cm and the widest width being 2.8 cm. Slough has covered the wound (fibrinopurulent pus). When the slough is removed, the deepest depth is 0.7 cm with a subcutis fat floor. The wound's border and wall were irregular. A random blood sugar level of 448 mg/dL was measured during a laboratory examination. A diabetic ulcer at regio gluteus sinistra with obesity class II was diagnosed based on anamnesis and physical examination.

Sharp debridement with a blade was performed on the patient to remove the slough. The wound was irrigated as much as possible with NaCl 0.9% in 5 minutes. After irrigating the wound, 10% povidone-iodine and 0.1% Gentamicin cream were applied. The wound was dressed with moist gauze stacked from the deepest space and was held in place with a soft fabric fixation dressing.

The patient was educated to be referred to the hospital for insulin therapy, but the patient refused due to a geographic obstacle. Ciprofloxacin 2 x 500 mg and Metronidazole 3 x 500 mg were given to the patient for 14 days, Metformin 3 x 500 mg dc, Glibenclamide 1 x 5 mg, and Mefenamic Acid 3 x 500 mg were given if she felt pain. The patient was instructed to return every three days for wound care. The last time a patient arrived for treatment was on February 25th, 2023. (day 26 of treatment). Until now, the patient has not been returned to control.

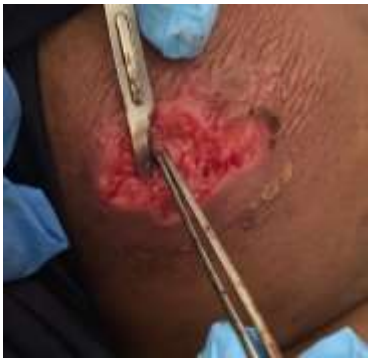


Figure 2. Sharp Debridement

Figure 1. Dressing with gauze pressure

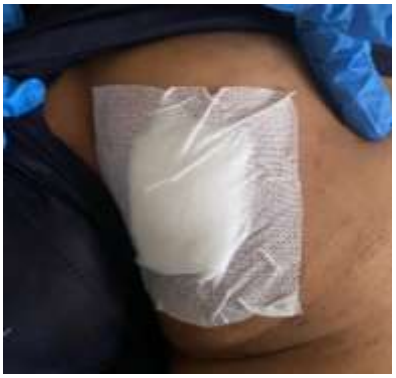
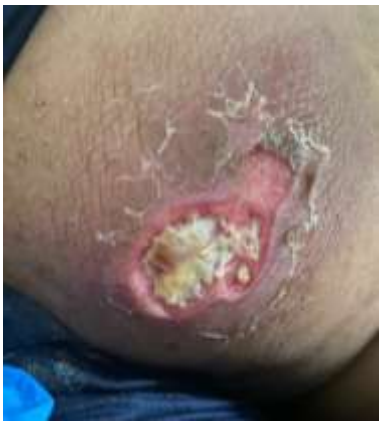
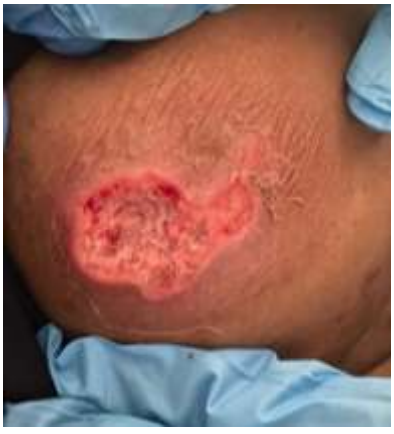


Figure 3. Soft fabric fixation dressing

Wound evolution

21/1/2023





Length 4 cm

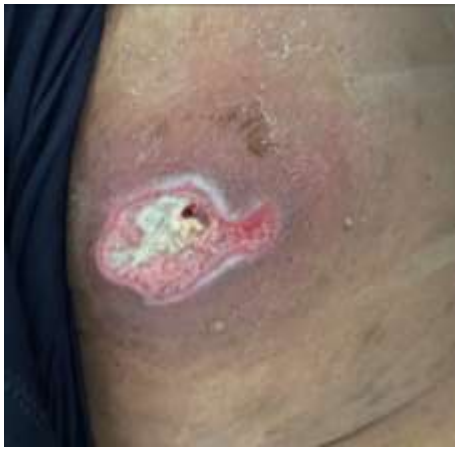
Width 2.8

Depth 0.7 cm

Slough +

Blood Sugar : 448 mg/dL

24/1/2023



Length 3.5 cm

Width 2.6 cm

Depth 0.5 cm

Slough +

Blood sugar : 305 mg/dL

26/1/2023

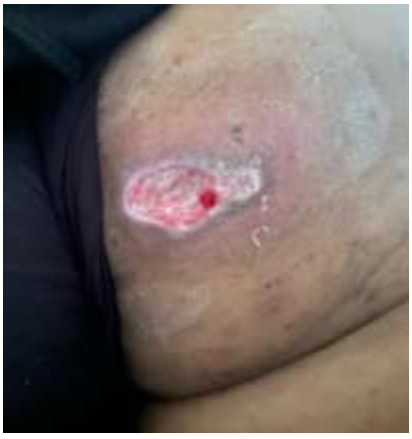
Length 3.3 cm

Width 2.5 cm

Depth 0.5 cm

Blood sugar : 327 mg/dL

30/1/2023



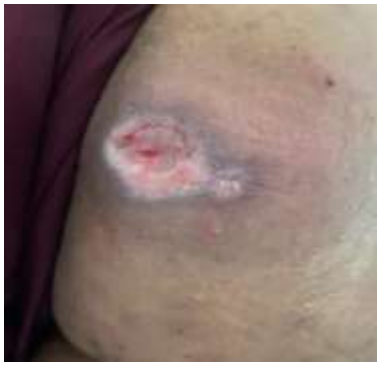
Length 3 cm

Width 2.3 cm

Depth 0.4 cm

Blood sugar : 409 mg/dL

2/2/2023



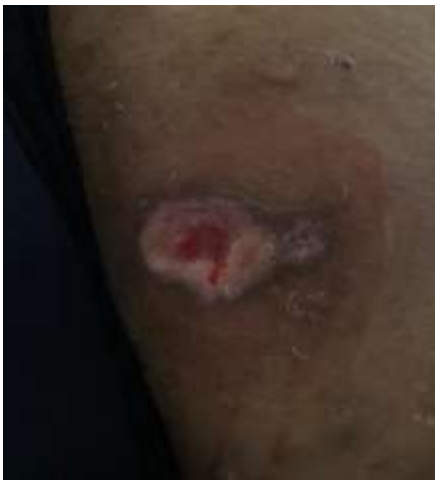
Length 2.5 cm

Width 2 cm

Depth 0.3 cm

Blood sugar 295 mg/dL

4/2/2023



Length 2.5 cm

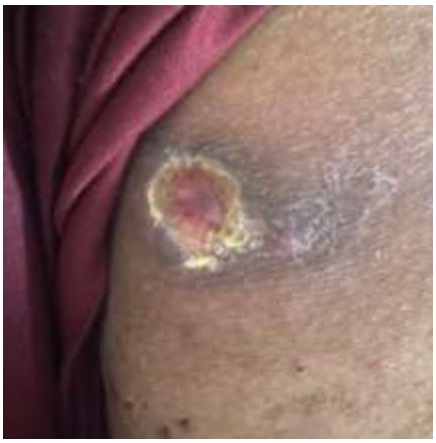
Width 2 cm

Depth 0.3 cm

Blood sugar 365 mg/dL

Because of inceased blood sugar level, diabetes therapy adjusted to Metformin 4 x 500 mg and Glibenclamide 1 x 5 mg

10/2/2023



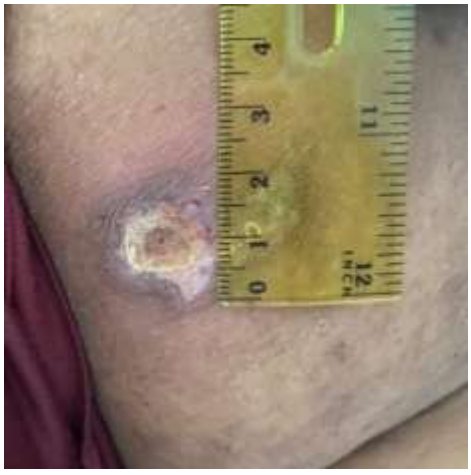
Length 1.6 cm

Width 1.2 cm

Depth 0.2 cm

Blood sugar 185 mg/dL

15/2/2023



Length 1.0 cm

Width 0.7 cm

Depth 0.1 cm

Blood sugar 295 mg/dL

DISCUSSION

Diabetes is a metabolic disease that causes hyperglycemia due to a disruption in insulin secretion, insulin function, or both. Diabetes can lead to serious complications in the heart, blood vessels, eyes, kidneys, and nerves. Hyperglycemia can interfere with many aspects of life and lead to complications such as neuropathy, angiopathy, and infection. Sensory neuropathy causes a loss of protective and proprioceptive sensations, which increases the risk of wound development, especially in body parts that are frequently traumatized. Hyperglycemia damages blood vessels, reduces perfusion, causes ischemia, and makes wounds more likely. Chronic hyperglycemia narrowed blood vessels and disrupted blood circulation. Wounds in hyperglycemic individuals are more likely to develop in areas of the body that are frequently pressured and subject to repeated trauma, such as the foot.

Chronic hyperglycemia also makes patients more susceptible to infection due to decreased blood perfusion to the wound, increasing the possibility of infection and pathogens entering the skin easily, bacteria proliferating and manifesting as cellulitis and or an abscess.[1,8]

A wound heals easily in healthy people, but not in diabetics. Because of disruption in wound healing and infection, a simple wound can progress to non-healing chronic wounds and ulcers. Wound healing is a complex process that is divided into four stages: (1) hemostasis, (2) inflammation, (3) proliferation, and (4) remodeling. Phases of wound healing overlapped and are interconnected with one another. When tissue is injured and capillaries are damaged, a coagulation cascade is initiated by activating fibrinogen, resulting in platelet aggregation and the formation of a fibrin scaffold, which prevents blood loss and allows cells to migrate. Platelets play an important role in wound healing as the primary effector cells during hemostasis. Platelet cytoplasm contains α-granules involving a variety of growth factors and cytokines that promote wound healing by attracting neutrophils, macrophages, and fibroblasts, such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β). Platelets also secrete VEGF and platelet-derived stromal cell-derived factor 1 (SDF-1) which are proangiogenic and antiangiogenic growth factors necessary for wound revascularization. The hemostasis phase and the inflammatory phase overlapped. During the inflammatory phase, which typically lasts 48 hours, the coagulation cascade begins, the complement is activated, and bacteria begin to be cleaned. Chemotactic factors (TGF-β) and complement components (C3a and C5a) attract inflammatory cells to the scaffold. Neutrophils are the first to arrive at the wound and phagocyte foreign debris, followed by monocytes, which differentiate into macrophages and also help to phagocyte the debris. Macrophages bind to ECM integrin receptors, releasing mediators such as tumor necrosis factor (TNF-α), and interleukin-1 (IL-1) and stimulating fibroblast infiltration from the surrounding ECM. Macrophage invasion is important in the inflammatory phase; for example, macrophages are depleted in animals that undergo abnormal healing. The next order of events is the proliferative phase, which overlaps with the inflammatory phase and typically occurs 48 hours to 10 days after tissue injury. Keratinocytes proliferate and migrate to form an epithelial layer to cover the wound, which is stimulated by epidermal growth factors, heparin-binding epidermal growth factor (HB-EGF), and transforming growth factor-alpha (TGF-α), along with fibroblasts, which produce collagen as a scaffold for the vascular network. In this phase, the wound in a hypoxic environment increases protein expression of hypoxia-inducible factor 1 (HIF-1) as a primary stimulus for angiogenesis and induced neovascularization with activated VEGF and SDF-1. Following that, granulation tissue is formed by fibrin mesh that is replaced by fibroblasts and macrophages, and it includes new connective tissue (hyaluronic acid, procollagen, elastin, and proteoglycan) and blood vessels with the appearance of a capillary network. Its formation increases the oxygen supply to the wound surface. Fibroblasts are also differentiated into myofibroblasts, which perform wound contraction to bring wound edges together. The final phase is remodeling, which increases the tensile strength of the ECM while decreasing the blood supply to the wound. It begins two weeks after the wound occurs and can last for years. Apoptosis of wound cells occurs during this phase, leaving collagen and ECM protein. Matrix metalloproteinases (MMPs) convert type III collagen to type I collagen to strengthen and remodel the wound. Even though the wound appears to be healed, it never fully recovers strength, only regaining 80% of the strength of the undamaged skin.[7,8]

Several factors disrupt the healing phase in diabetic wounds, such as hyperglycemia, microvascular abnormalities, hypoxia, and changes in the ECM scaffold, which causes the skin to be unable to complete all four phases of wound healing within the normal timeframe, the inflammatory phase to become persistent and excessive, cell proliferation to become impaired, cell migration to become abnormal, pathogen colonization to become easier, and biofilm to establish.[8]

In this case, the patient developed a tissue infection before developing an abscess. Later on, the abscess burst and became infected, with the slough covering the wound. She has been diagnosed with diabetes mellitus three years ago. Diabetes became a premorbid condition for this ulcer. Diabetes causes wound healing to take longer in the initial inflammation phase and to resist further progression because proinflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor remain elevated in the injured area for an extended period.[8,12] Matrix synthesis and remodeling were halted due to a protein imbalance and their inhibitor. Hyperglycemia increases advanced glycation end-products and decreases ECM solubility, prolongs the inflammatory phase, increases cell apoptosis, and induces MMP to degrade the matrix.[8]

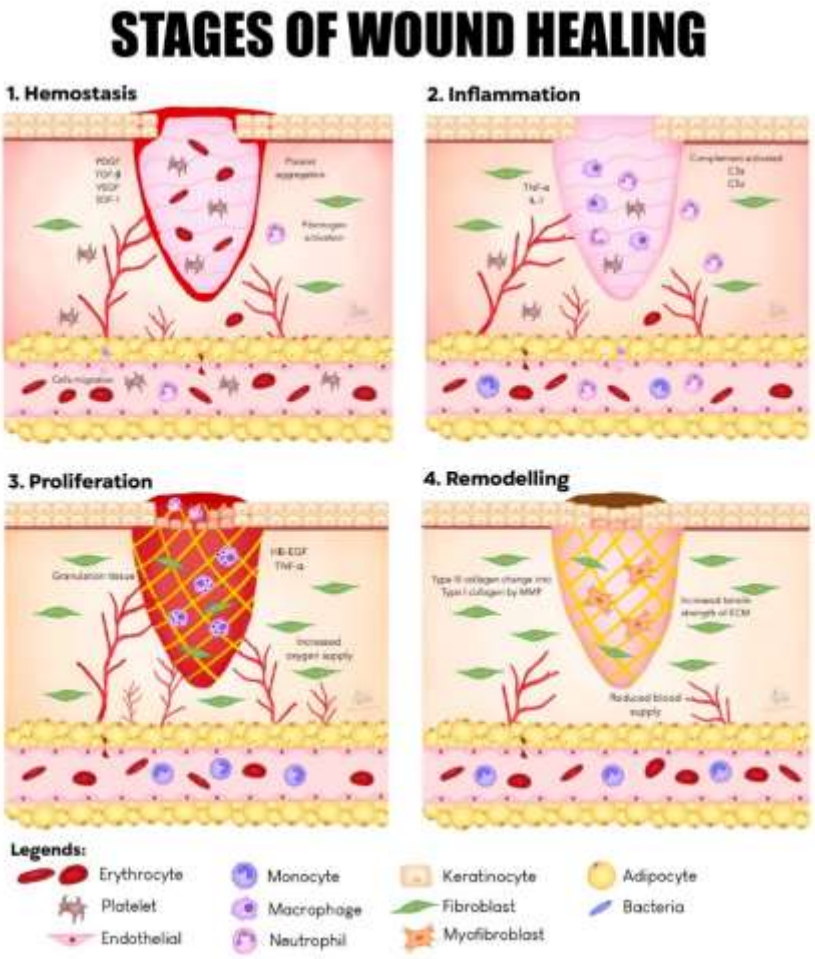


Figure 4. Stages of wound healing

Chronic hyperglycemia also causes tissue to deal with a hypoxic environment by reducing oxygen supply and increasing free radical levels, causing inflammation to last longer and wound healing to be delayed. Glycation of the extracellular matrix (ECM) has been linked to cell apoptosis and disruption of normal wound healing processes such as angiogenesis, cell migration, and proliferation. To break down the matrix, high levels of glucose induce the expression of MMP by fibroblasts, endothelial cells, and macrophages.[8] Hyperglycemia induced imbalances in metalloproteinase (MMPs) and tissue inhibitors of metalloproteinase (TIMPs) play a significant role in extracellular membrane regulation (ECM). Diabetes wounds had higher MMPs levels and lower tissue inhibitors of metalloproteinase (TIMPs), which disrupted wound healing.[17-19]

Several growth factors, including insulin-like growth factor-1 (IGF-1) and transforming growth factor-β (TGF-β), were found to be reduced. IGF-1 promotes cell granulation and wound re-epithelization, whereas TGF-β attracts fibroblasts, keratinocytes, immune cells, and vascular cells, implying that TGF-β plays a role in angiogenesis and the formation of extracellular matrix (ECM).[9,10]

Hyperglycemia causes macrophages, the primary source of VEGF, to have impaired phagocytic activity and an altered phenotype, resulting in tissue repair failure. Target genes such as VEGF, which play a role in wound closure, are also affected. HIF-1a activation and stability are affected by hyperglycemia, and target genes such as VEGF are suppressed. According to Khanna's research in db/db mice, VEGF-a treatment produces better results than control mice and speeds up wound closure.[20,21]

Angiogenesis is important for promoting vessel formation, which provides oxygen and nutrients to regenerating tissue. The promotion of new vessel formation and maturation is unbalanced in diabetes. Because of the high levels of glucose in the wound area, angiogenesis in endothelial cells is insufficient.[11] Reduced oxygen supply also has an impact on wound healing. Chronic hyperglycemia increases free radical levels, which prolongs inflammation and delays wound healing.[8]

The patient also had a premorbid BMI of obesity II, which raised her likelihood of complications such as wound infection, impaired wound healing, pressure injuries, venous ulcers, hematoma formation, and seroma formation. Obesity also contributes to the development of pressure injuries due to hypovascularity, difficulty repositioning, and skin-to-skin friction in skin folds. Obesity causes cell damage as well. Most growth factors (TGF-β, PDGF, and IGF-1) were

reduced, proinflammatory cytokines (TNF-α and IL-1) were reduced, and peripheral immune function was altered. Impaired healing is also associated with collagen turnover dysregulation, increased MMP, and decreased tissue inhibitors of metalloproteinase (TIMP), as well as decreased activity in angiogenesis, granulation tissue formation, and collagen deposition.[8,22-23]

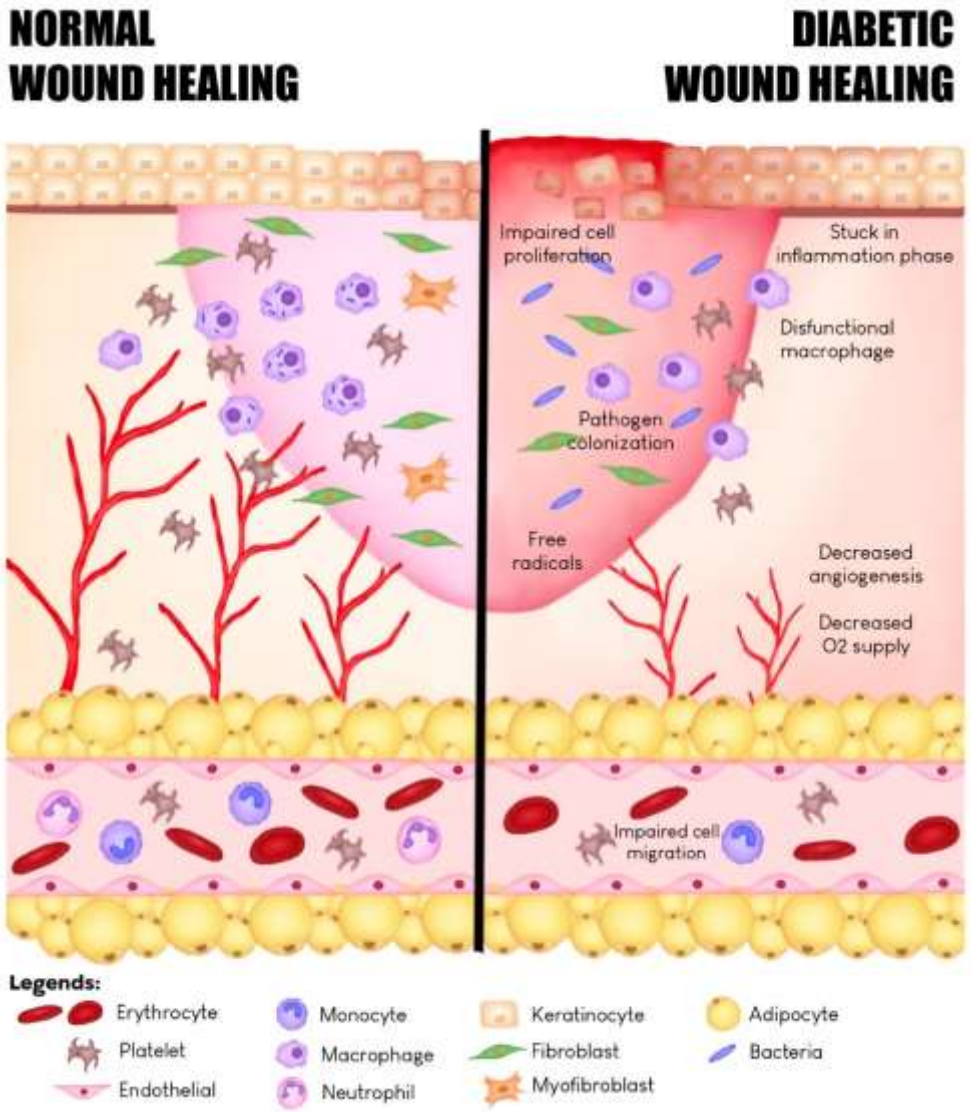


Figure 5. Difference of normal wound healing and diabetic wound healing

Obesity was also linked to oxidative stress. Adiponectin, which protects against oxidative stress and inflammation, was found to be reduced, even though it is secreted by adipocytes. Adiponectin promotes angiogenesis in response to ischaemic stimulation by activating the AMP-activated protein kinase signaling pathway. Adiponectin also plays a role in the re-epithelialization phase by activating the ERK signaling pathway, which promotes keratinocyte proliferation and migration. Adiponectin deficiency harms proper perfusion and re-epithelialization. One of the factors contributing to an increased risk of wound infection is a hypoxic condition in wounded tissue. Leukocytes can ingest but not kill bacteria in a hypoxic environment. Collagen synthesis, which is essential for achieving maximum strength, is also impaired. Although fibroblasts can survive in hypoxic environments, hypoxia impairs their ability to produce collagen. Furthermore, obesity causes type I collagen fibers to become disorganized and increase the expression of immature type III collagen. Without the proper collagen, the collagen matrix cannot be properly rebuilt.[24,25] According to Xie et al, EPC function is linked to cellular oxidative stress. The study found that a decrease in NO levels or excessive superoxide (O2) production can harm EPCs, as evidenced by impaired angiogenesis and tube formation.[26]

The patient was a farmer who lived in a rural area and did not have a high school degree. These factors also play an important role in hygiene, making pathogens more easily infect the skin. Poor hygiene has been linked to a variety of skin diseases. Poor literacy, which was related to socioeconomic status, was associated with an increased risk of ulceration. Knowledge and education for self-care were hampered due to a low educational level. Rural activities,

such as farming, expose the patient to trauma as a result of those activities.[27,28] According to a study conducted in West Bengal, rural populations, jobs that require heavy sweating, poor personal hygiene, poor living conditions, and people with diabetes are more vulnerable to a superficial skin infection (SSI).[29]

Metformin, a biguanide anti-hyperglycemic agent, is the first-line treatment for type 2 diabetes. It works in several ways as an antihyperglycemic agent. Metformin reduces insulin resistance, particularly in the liver and skeletal muscle, suppresses gluconeogenesis in the liver, increases peripheral insulin sensitivity in insulin-sensitive tissues (muscle, adipose tissue), and improves peripheral glucose utilization.[30] Metformin, in moreover to being an antihyperglycemic agent, has beneficial effects such as renal and cardiovascular protection, antioxidant, antifibrotic, and antiproliferative properties, and the ability to increase the number and function of endothelial precursor cells.[17]

Metformin activates AMPK and stimulates catabolic pathways that produce adenosine triphosphate (ATP). AMPK activation increases glucose uptake and lipid oxidation in skeletal muscle. AMPK activation in the liver inhibits gluconeogenesis and lipid synthesis while increasing lipid oxidation. It inhibits lipolysis and lipogenesis in adipose tissue. As a result, AMPK activation in skeletal muscle, liver, and adipose tissue reduced circulating glucose, lipids, and ectopic fat accumulation while increasing insulin sensitivity. Metformin has a half-life of about six hours and is excreted primarily through the kidneys, with 90% eliminated within 24 hours. Metformin is prescribed in doses of 500 mg or 850 mg. It should be started at 500 mg and increased weekly until the maximum tolerated dose is 2 g/day. Metformin must be taken with food to avoid gastrointestinal side effects. Metformin's main side effect is lactic acidosis, which is especially prevalent among individuals with renal and cardiac failure.[30]

Metformin also has a pleiotropic effect that supports wound healing. Metformin has been shown to speed up wound healing by improving the epidermis, hair follicles, and collagen deposition by increasing fibroblasts, improving granulation tissue formation, inducing new blood vessels, and modulating the inflammation and proliferation steps of wound healing.[31] Metformin has also been shown to modulate inflammatory pathways such as nuclear factor kappa B (NF-kB) and mitogen-activated protein kinase (MAPK)/c-Jun NH2-terminal kinase (JNK). Metformin's immunomodulatory and anti-inflammatory properties may support its use in the treatment of wound healing. Notably, metformin was effective in accelerating wound healing by improving epidermis, hair follicles, and collagen deposition when applied topically to young rats undergoing an excision wound, and its efficacy was also confirmed in patients with non-healing lower limb traumatic wounds or ulcers. Interestingly, systemic metformin administration with photobiomodulation had a synergistic effect on skin repair by increasing fibroblasts, improving granulation tissue formation, inducing new blood vessels, and modulating the inflammation and proliferation steps of wound healing.[16,31]

Metformin has immunomodulatory and anti-inflammatory properties via AMPK-dependent and AMPK-independent mechanisms. Metformin inhibits mTOR signaling and modulates inflammatory pathways such as nuclear factor kappa B (NF-kB) and mitogen-activated protein kinase (MAPK)/c-Jun NH2-terminal kinase (JNK). Inhibiting both mTOR and NOD-like receptor protein 3 (NLRP3) activates AMPK, allowing it to modulate macrophage polarization and thus improve wound healing. Han et al show in a study that db/db diabetic rats given systemic metformin administration for 14 days heal faster. It is associated with increased endothelial precursor cell (EPC) function, increased nitric oxide (NO), and antioxidant activity.[13,15,17]

Metformin also decreases the level of thrombospondin-1, an anti-angiogenic adipokine allegedly involved in obesity and responsible for diabetic vascular complications. TSP-1 has been shown to impair EPC function, which correlates with decreased nitric oxide regeneration.[15] Cellular oxidative stress is also linked to EPC. A decrease in NO levels or an excess of superoxide (O2-) causes EPCs to function inadequately, as evidenced by impaired angiogenesis and tube formation. Metformin plays a protective role in improving EPC function by interacting with TSP-1 and cellular oxidative stress.[26]

Metformin treatment improves EPC function and stimulates angiogenesis, which is important for promoting vessel formation to provide oxygen and nutrients to the tissue, with TSP-1 levels inhibited and NO levels increased.[17] TGF production increased in the injured area, promoting angiogenesis, inflammatory response, granulation tissue formation, ECM deposition, re-epithelization, and remodeling, and thus the healing process.[32] A study also combined metformin with non-pharmacological approaches like photobiomodulation. As a result, systemic metformin administration and photobiomodulation in T2DM rats had a synergistic effect on skin repair by increasing fibroblasts, improving granulation tissue formation, inducing new blood vessels, and modulating the inflammation and proliferation steps of wound healing.[33]

This case illustrates how metformin affects wound healing. In three weeks, the patient's wound had reduced in size and healed. To lower blood glucose, the patient has been given Glibenclamide 1x5 mg and Metformin 3x500 mg. Aside from anti-hyperglycemic medication, the patient has also been given the antibiotics Ciprofloxacin 2 x 500 mg and Metronidazole 3 x 500 mg to kill the pathogen bacteria that infected the wound.

The use of metformin to accelerate wound healing is still debatable. In general, metformin was stated to downregulate angiogenesis in the context of tumors, but in

models such as diabetes, it increased VEGF expression and angiogenesis[34], and it was described in several studies that metformin mechanism, inhibit cancer cells proliferation both in vitro and in vivo by inhibition of the AMPK pathway, mTOR inhibition, and CyclinD1 inhibition of the cell type, leading to a decreased incidence of cancer patients.[34,35]

In our case report, metformin treatment did not alter wound healing but appeared to improve wound healing. This is consistent with studies showing that metformin significantly increased the number of circulating EPCs while maintaining endothelial cell function in T2DM patients.[16] Han et al. discovered that metformin can reduce NO levels and O2- production, increase circulating EPCs and improve cellular function of EPCs, and improve angiogenesis. Wounds in db/db mice pretreated with metformin underwent progressive healing until complete closure.[15] Bagheri found that metformin decreased neutrophils on day 4 and macrophages on day 7, and increased new epidermal basal cells, fibroblasts, and blood vessels in type 2 diabetic rats.[33] Yu et al discovered that metformin improves the angiogenic function of EPC by increasing activation of AMPK/eNOS dependent pathway, improves impaired BM-EPC functions, and increases both phosphorylated-AMPK and phosphorylated-eNOS expression in BM-EPCs from STZ-induced diabetic mice. Metformin has been shown in vitro to improve high glucose-impaired BM-EPC functions and increase phosphorylated-eNOS expression.[36] According to Lamiaa's research results, metformin has a synergistic effect when combined with BM-MSCs on wound healing in an animal model of STZ-induced diabetes, accelerating wound healing progress by stimulating surface re-epithelization and differentiation, and promoting angiogenesis.[37]

Another study revealed that metformin treatment had no effect on the number of circulating EPCs and even slowed wound healing in people with diabetes. Metformin treatment has also been reported to reduce keratinocyte proliferation, alter the cell cycle, particularly in the S phase, and alter wound re-epithelization, resulting in delayed healing in diabetic foot ulcers, but on the other hand, metformin has an anti-inflammation effect that protects against amputation.[38] Other factors must be considered because diabetic ulcers have a complex pathogenesis with several factors affecting wound healing such as peripheral neuropathy, autonomic neuropathy, gravity, abnormal pressures, foot deformity, abnormal joint mobility, trauma, and peripheral arterial disease (PAD).[39-41]

Metformin has been shown in plenty of research to cause delayed healing due to impaired angiogenesis and keratinocyte proliferation; however, when combined with a gravity factor for blood perfusion, it can have a beneficial effect by controlling the formation of granulation tissue and avoiding excessive cell proliferation and scarring.[31,38-39,41-42] Because the use of metformin for wound healing is still controversial, more research is needed to provide better evidence of metformin and its association with wound healing as a treatment modality for the management of diabetic ulcer patients and reduce the risk of wound progression to become more severe.

CONCLUSION

Metformin is a first-line therapy for type 2 diabetes that has been used for a long time. Metformin, in addition to being an anti-hyperglycemic agent, has a pleiotropic effect that aids in wound healing. Although the use of metformin for wound healing is still controversial, it is important to remember that wound healing is influenced by a variety of many factors and to consider the beneficial effect of metformin for wound healing. We recommend metformin as an oral diabetes treatment for type 2 diabetes with ulcers.

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