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## ***Potential Use of Topical Insulin in Chronic Diabetic Wound Healing***

Potensi Penggunaan Insulin Topikal untuk Tata Laksana Luka Diabetik Kronis

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*Received: May 5, 2021*

*Accepted: December 19, 2021*

### ***Abstract***

*Wound healing disturbances that occur in chronic diabetic wounds result in various complications and cause a significant burden. With the increasing prevalence of diabetes mellitus, it is estimated that the numbers of chronic diabetic wounds and their complications will also continue to increase. One of the latest managements using growth factors for chronic diabetic wounds gives satisfactory results, but their use is still limited because of the high costs. This study aims to explore the effectiveness of using topical insulin as a cheaper and effective alternative therapy in chronic diabetic wounds. The method of this study is a literature review sourced from Google Scholar and ProQuest search engine. Eight articles were obtained that are relevant to be discussed in this study. According to studies conducted so far, topical insulin can improve wound healing through the modulation of inflammation and insulin signaling pathways. In conclusion, there is improved wound healing in diabetic chronic wounds patients that were given topical insulin. Therefore topical insulin should be considered as part of chronic diabetic wounds management.*

***Keywords:*** *wound healing; chronic diabetic wounds; growth factors; topical insulin*

### ***Abstrak***

Gangguan penyembuhan luka yang terjadi pada luka diabetik kronis mengakibatkan berbagai macam komplikasi dan beban kesehatan. Dengan terus meningkatnya prevalensi penyakit diabetes melitus, diperkirakan angka kejadian luka diabetik kronis dan komplikasinya juga akan terus meningkat. Salah satu penatalaksanaan luka diabetik kronis terkini adalah dengan menggunakan faktor pertumbuhan yang memberikan hasil memuaskan, namun penggunaannya masih terbatas karena harganya yang mahal. Tujuan kajian ini adalah untuk membahas efek penggunaan insulin topikal sebagai alternatif yang lebih murah dan efektif dalam tatalaksana luka diabetik kronis. Metode penelitian berupa tinjauan pustaka terhadap literatur yang bersumber dari Google Scholar dan ProQuest. Sebanyak delapan artikel relevan untuk dibahas pada studi ini. Dari studi yang telah dilakukan, insulin topikal mempromosikan penyembuhan luka melalui modulasi proses inflamasi dan jalur pensinyalan insulin. Sebagai simpulan, ditemukan adanya peningkatan penyembuhan luka pada pasien dengan luka diabetik kronis yang diberikan insulin topikal. Oleh karena itu insulin topikal seharusnya dipertimbangkan sebagai bagian dari tatalaksana luka diabetik kronis.

***Kata kunci:*** *penyembuhan luka; luka diabetik kronis; faktor pertumbuhan; insulin topikal*

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**Introduction**

Chronic wounds are wounds that fail to heal within four weeks. Chronic wounds generally occur due to systemic disease, vascular disorders, or perfusion disorder in the injured area. Diabetes mellitus is one of the major diseases that cause chronic wounds, dubbed as chronic diabetic wounds. The incidence of chronic diabetic wounds has increased due to the increasing worldwide prevalence of diabetes mellitus and the prolonged life expectancy of diabetic patients.<sup>1</sup> The number of people with diabetes mellitus globally in 2017 is estimated to be around 425 million adults and projected to increase to 629 million adults by 2045.<sup>2</sup>

Complications of chronic diabetic wounds are the leading cause of hospitalization and amputation in diabetic patients with an average annual cost of \$8659 per patient.<sup>3</sup> Of all amputations in diabetic patients, around 85% preceded by prolonged chronic wounds that subsequently deteriorate to severe gangrene or infection.<sup>3</sup> Thus chronic diabetic wounds are a major issue that put a significant burden not only on social and medical but also on economic aspects of the patients and health system.

Data from the 2018 Indonesian National Health Survey (Riset Kesehatan Dasar) showed that the prevalence of people aged > 15 years with diabetes mellitus increased from 1.1 percent in 2007 to 2.0 percent in 2018.<sup>4</sup> Chronic diabetic wounds are the most common reason for diabetic patients to be admitted to hospitals in Indonesia. An estimated 7.3-24 % of people with chronic diabetic wounds in Indonesia will have a foot amputated.<sup>5,6</sup> Based on the data above, it is estimated that the prevalence of chronic diabetic wounds and its complications will also continue to increase even further.

Wound healing in diabetic patients is far more complex than in healthy people. This is because disturbances on macrovascular, microvascular, peripheral nerve, and immune systems in diabetic patients.<sup>7,8</sup> Vascular disorders complicate tissue perfusion, hindering wound healing capability. Poor wound healing will increase the risk of contracting an infection that will worsen the wound site injury. The hyperglycemic environment also triggers a prolonged inflammatory response, causing excessive proinflammatory cytokines, which inhibit wound healing from entering the proliferation stage. At present, topical chronic diabetic wounds management includes the potential use of growth factors such as epidermal growth factor (EGF), transforming growth factor (TGF)- $\beta$ , and platelet-derived growth factor (PDGF).<sup>9</sup> Although some studies suggested that topical growth factors had a benefit in chronic diabetic wounds. But issues regarding its optimal dose, reduced utility in chronic wounds, and ultimately its cost-effectiveness needs to be further clarified.<sup>10</sup>

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Insulin is easier to obtain, more affordable, and has been used as topical wounds treatment since the early 20<sup>th</sup> century.<sup>11</sup> It has been shown that topical insulin produced faster wound healing and minimal systemic side effects in some studies<sup>12,13</sup> Despite that, topical insulin is still not widely used for chronic diabetic wounds management.

This study aims to explore the mechanism and effectiveness of using topical insulin in wounds healing, hence the possibility of using topical insulin in chronic diabetic wounds.

### Method of Study

The research method is a literature review from the literature searched with Google Scholar and ProQuest. The literature selected is of an experimental method. Journal searching was performed using keywords *topical insulin*, *chronic diabetic wound*, *chronic diabetic wound healing*, *insulin signaling pathway*. After the search is done, duplication of articles was done using Mendeley, an open source-based journal manager system.

Inclusion criteria for this study were journals that discussed topical insulin, chronic wound healing, published between 2010-2017 in English, and published in a peer-reviewed journal. The exclusion criteria for this study were articles that did not provide full text, not in English or Indonesian, and did not discuss the mechanism of topical insulin in wound healing.

### Result and Discussion

#### Wound healing in chronic diabetic wounds

Wound healing is a process that consists of 3 overlapping phases, namely the coagulation and inflammation, proliferation, and remodeling phases.<sup>14</sup> Disturbance in one of the three phases will cause a delay in wound healing, inadequate healing, and increase the risk of complications due to loss of protective function of the skin. Although all three phases can happen in an overlapping fashion, the sequence of this process remains critical since a pathological state in one of the phases will inhibit the work of the next phase.

The first phase of wound healing is the coagulation and inflammation phase, which starts immediately after the wound is being formed. Platelet aggregation and coagulation factors will form fibrin blockages consisting of polymerized fibrinogen (fibrin), fibronectin, vitronectin, and thrombospondin to patch the wound.<sup>15</sup> Coagulation is needed for wound protection and as a foundation framework that supports the healing process in the next phase. Besides forming blockages, platelet aggregation also produces various growth factors such as PDGF and TGF that are important for cells proliferation in the later stage. These growth factors are activated

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depending on pH and other parameters and play a role in the recruitment of immune cells to the wound site.

Recruitment of immune cells to wound tissue marks the start of the inflammatory phase. Neutrophils and macrophages play a role in phagocytosing infectious agents and discarding necrotic tissues.<sup>14</sup> Wound debris clearance by immune cells takes around 2-3 days. After the inflammatory process subsides, the macrophages will undergo phenotypic changes from M1 to M2 that are anti-inflammatory. M2 macrophages then produce various growth factors such as TGF- $\beta$ , vascular endothelial growth factor (VEGF), and cytokines which will trigger the proliferation of fibroblasts and endothelial cells.<sup>16</sup> Macrophages thus play a role in creating a clean wound environment for cells proliferation so that fibroblasts and endothelial cells can form granulation tissue as a basis for wound healing.

The next phase is the proliferation phase. This phase is characterized by angiogenesis, collagen deposition, formation of extracellular matrix (ECM), and re-epithelialization of the epidermis to cover the wound surface. After about 2-3 weeks, the wound will enter the remodeling or maturation phase. In this phase, collagen will change from type III to type I, and wound tissue is patched up, almost as its original structures.<sup>14</sup> Cell proliferation and vascularity in wound tissue then regress, marking the completion of the wound healing process.

The wound healing process needs to be supported by sufficient oxygen supply, good vascularization in wound tissue, and adequate nutrients such as protein and vitamins. Pathological conditions such as diabetes mellitus will interfere with the healing process. Hyperglycemic neuropathy leads to sensory loss of diabetic patients and causes unawareness of extremities trauma. This problem is complicated by microangiopathy that reduces perfusion to the area of wounds. Calluses are formed due to excessive pressure in the injured area, increasing the risk of infection. The three factors above that consist of neuropathy, ischemia, and trauma are called pathogenic triage of chronic diabetic wounds.<sup>3</sup>

At the cellular level, the main issue of chronic diabetic wounds is in the inflammatory phase, characterized by an increase in the number of immune cells at the site of injury and macrophage dysfunction. The macrophages recruited to the wound site are intrinsically more inflammatory, but they have a reduced phagocytosis activity. These altered properties interfere with the cleaning process of the wound area, leaving necrotic tissues, and causing persistent inflammation.<sup>17</sup> Macrophages also show a decrease in pro-proliferative cytokine production, such as interleukin (IL) -1 $\beta$  and VEGF.<sup>18</sup> Combination of chronic inflammation and decreased pro-proliferative cytokine production causes delayed progression to the next phase.

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Persistent inflammation as a response to hypoxia at the injury site causes disorganized angiogenesis. High sugar levels in endothelial cells cause damage to macrovascular and microvascular endothelium due to increased glycosylation and superoxide end product in the mitochondrial electron transport chain.<sup>19</sup> These factors together with inadequate perfusion due to microangiopathy, cause chronic hypoxic conditions in chronic diabetic wounds. Chronic hypoxia will then increase the formation of free radicals, inflammation, and damage to cells and tissues at the wound site.<sup>20</sup> In addition to the inflammatory phase disorder, the proliferation phase is also disrupted in chronic diabetic wounds. This is because of the reduced activity of fibroblasts. They experience irreversible growth inhibition called replicative senescent. These cause interference of matrix formation by fibroblasts and reduced VEGF production needed in angiogenesis for adequate granulation tissue formation.

Hyperglycemia also alters the balance between matrix metalloproteinases (MMPs) and their inhibitors, namely  $\alpha$ 2-macroglobulin and tissue inhibitors of matrix metalloproteinases (TIMPs). In chronic diabetic wounds, there are an increased expression and activity of MMP8 and MMP9 that cause damages to several matrix proteins and growth factors needed in the proliferation phase.<sup>21</sup> Hyperglycemia is also associated with a decrease concentration of plasminogen urokinase activators and increase tissue plasminogen activator inhibitors that result in a disturbance of fibrinolysis and matrix deposition disorders. These conditions cause suboptimal ECM production, resulting in disturbed adhesion, motility, growth, and differentiation of cells involved in wound healing, causing the wounds to become chronic.

Hyperglycemia also triggers interference with the insulin signaling pathway through phosphorylation of insulin receptor substrate (IRS). The IRS acts as a signal transmitter from insulin to the intracellular phosphoinositide-3-kinase/protein kinase B (PI3K/Akt) and extracellular signal-regulated kinase/ mitogen-activated protein (ERK/ MAP) kinase signaling pathways. This disruption of the signaling pathway is associated with a decrease in cell proliferation and differentiation activities.<sup>12</sup>

### **The role of growth factors in chronic diabetic wounds**

Growth factors are signaling molecules in the form of proteins and steroid hormones that regulate cell activity through bonding with cell transmembrane receptors. Growth factors play a role in cell regeneration through their ability to stimulate proliferation, differentiation, migration, and cellular gene expression. Growth factors can work as autocrine, paracrine, or endocrine depending on the target receptor. The onset of growth factors is usually rapid and of short

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duration. Because of those properties, the use of growth factors has been studied for wound healing. The growth factors studied in depth include epidermal growth factor (EGF), TGF- $\beta$ , and PDGF.<sup>22</sup> Application of growth factors to the wound showed faster tissue regeneration compared to wound healing that relies on natural growth factors released by cells and wound tissue.<sup>8,10,22</sup>

However, in cases of chronic diabetic wounds, it has been discussed that the mechanism of the occurrence of healing disorders is not only caused by a deficiency of growth factors. Multifactorial circumstances related to prolonged hyperglycemia result in a pathological complex. In addition, the high cost of producing growth factors makes it impractical in daily clinical practice. The high cost is due to the requirement of exclusive recombinant technology for growth factors production, not owned by all pharmaceutical manufacturers. As a result, the average price of growth factors on the market, such as PDGF can be more than 1,000 USD per package.<sup>9</sup> All of these factors cause limited use of these agents as topical management in chronic diabetic wounds.<sup>10,23</sup>

### Insulin

Insulin was first discovered in 1921 to reduce blood sugar levels in patients with type I diabetes. This discovery was made by Frederick Banting and Charles Best, who managed to isolate insulin from the pig pancreas. The administration of extracted insulin proved successful in reducing blood sugar levels. Currently, with the rapid development of recombinant DNA technology, insulin can be mass-produced at a low cost of around 1 USD/mg.<sup>9</sup> Crystallization techniques using zinc molecules produce stable insulin molecules. This technique results in insulin with a longer duration of activity and can be stored for a long time without reducing its bioactivity.

In addition, besides reducing blood sugar levels, insulin also has the protective property to vascular endothelium. Insulin also has anti-platelet aggregation and anti-atherosclerosis properties. Cellular insulin increases extracellular matrix and collagen synthesis by increasing myofibroblast proliferation and increasing activation of macrophages in the inflammatory phase of wound healing.<sup>24</sup> Insulin also accelerates wound healing by increasing keratinocyte differentiation and cell migration in the reepithelialization stage.

The use of insulin in wound healing can be traced back to the 1930s when insulin was the only drug that could reduce blood glucose concentration in diabetic patients. The surgeons at that time noticed differences in the speed of postoperative wound healing in diabetic and nondiabetic patients.<sup>9</sup> Through observations, the application of systemic insulin on diabetic patients showed

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an increased speed of wound healing. This phenomenon gave the clinician an idea that there was a pathological process that caused a decrease in the rate of wound healing in diabetic patients, which could be corrected with insulin. Since then, research on the effect of insulin on wounds has kept going. In the 1960s, insulin began to be used topically to treat chronic diabetic wounds in humans.<sup>9</sup> Insulin has also been investigated to treat burns in animal samples in the form of mice with a satisfying result.<sup>25</sup> It is known from *in vivo* studies that insulin has similar molecules to insulin-like growth factor (IGF) and can stimulate the proliferation and migration of keratinocytes, endothelial cells, and fibroblasts, also the excretion of extracellular matrix by fibroblasts, thereby promoting the formation of granulation tissue.

Until now, there has been no standard method for topical insulin administration. Various studies had been carried out using various administration methods. Topical insulin can be given in the form of cream, hydrogels, spray, and subcutaneous injection. The results of all of the methods are generally satisfactory.<sup>12,13,24,26</sup> Therefore, the choice of topical insulin administration method is based on the needs and available resources. Hereafter, studies that used topical insulin as a therapy for chronic diabetic wounds will be discussed.

### Research on Topical Insulin in Wound Healing

After considering the inclusion and exclusion criteria, eight articles were found relevant articles to be discussed in this study (Table 1). All the articles in this study are listed in the references sources.

Kargin et al. conducted a study on mice by dividing the sample into two groups, each of which consisted of 10 rats that were injured. The wound in the first group was given 0.3 IU of regular insulin which was diluted with 20  $\mu$ L of single-dose sterile water for 20 days. Meanwhile, normal saline was given to the control group rat wounds. Wound closure rates were found to be higher in the first group on all days of the experiment. The period of complete wound closure is shorter in the first group, with a mean of 4 days.<sup>13</sup> This study also found increased organized collagen fibrils on the epidermis and dermis layers of samples taken from the wounds of the insulin-given rats.

Lima et al. examined the regulation of insulin signaling pathways in diabetic wounds of rats with a double-blind placebo-controlled clinical trial.<sup>12</sup> His study divided rats into six groups which consist of control groups and groups that were given topical insulin to the excision wound site. The insulin cream used was regular insulin prepared into 0.5 U/ 100 g cream produced in the pharmacy of University of Campinas, Brazil, and holds the patent number, PI 0705370-3. The

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dose used didn't cause any increase in plasma glucose. Tissue extracts from excision wounds were obtained for immunoblotting with anti-IRS-1 antibodies and anti-Akt. Results showed that there was a consistent increase in both proteins two days after the initial excision of the wound.<sup>12</sup>

**Table 1 Summary of Studies Conducted on The Topic of Insulin Use in Chronic Diabetic Wounds**

Study by (Year of Publication)	Subjects	Type of Insulin	Method of Administration	Results
Liu et al. (2009)	Mice	0.03 U of insulin	Applied topically	Insulin stimulates keratinocyte migration in a time- and dose-dependent manner
Lima et al. (2012)	Rats	Insulin cream (0.5 U/100 g)	Applied topically	Acceleration of wound healing, recovery in proteins of the insulin signaling pathway
Chen et al. (2012)	Mice	0.03U regular insulin in 20 µL saline	Applied topically	Enhanced the cellular functions of neutrophils in the wound area
Goenka et al. (2014)	Human	4U of human insulin (Actrapid) in 1 ml normal saline	Applied topically	Less day needed for wound healing and less men hospital stay in the insulin group
Kargin et al. (2015)	Rats	Diluted regular Insulin (0.3/20 µL saline water)	Applied topically	Higher wound healing in the insulin group
Katagiri et al. (2016)	Mice	Insulin pellet (0.1U/day release)	Applied subcutaneously	Greater reduction in open wound rate and increase epithelialization rate
Zhang et al. (2016)	Human	Human insulin	Injected subcutaneously	Increase growth of granulation tissue
Yu et al. (2017)	Rats	Diluted human insulin (0.1 U/20 µL saline water)	Applied topically	Improve healing, expression of insulin signaling related proteins on wound area

From the study conducted by Lima, when the wounded skin of diabetic rats was treated with a topical insulin cream, an acceleration of wound healing occurred in association with a recovery in the proteins of the insulin signaling pathways. The increased Akt signaling pathway could phosphorylate proteins that regulated lipid synthesis, glycogen synthesis, cell survival, and protein synthesis in the process of regeneration. Data from various sources indicated that activation of the Akt signaling pathway was also an important step for VEGF release in wound tissue for angiogenesis and vascular maturation in keratinocytes during the healing of skin wounds.<sup>27</sup> Insulin activated Ras (a member of a large family of small molecular weight GTP-binding proteins) through tyrosine phosphorylation of IRS proteins. Ras then acted as a molecular



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switch that stimulated a cascade through the stepwise activation of rapidly accelerated fibrosarcoma (Raf), Mitogen-activated protein kinase kinase (MEK, protein kinase that activates MAP kinases), and ERK. Activated ERK could translocate into the nucleus which then catalyzed phosphorylation of transcription factors that lead to cellular proliferation or differentiation. This study also suggested that the abnormal insulin signaling observed in wounded skin of diabetic rats might contribute to the impaired wound healing. Hyperglycemia was shown to inhibit insulin action as a result of serine phosphorylation of IRS through a protein kinase C (PKC) mediated mechanism, which might, in turn, increase the degradation of IRS proteins. Thus, the use of topical insulin reversed the reduction of proteins needed for the insulin signaling pathway.

Katagiri et al. suggested a disruption in tissue granulation in the condition of hyperglycemia by oxidative stress, end-product glycation, and activation of PKC that disrupted the signaling pathway and cell synthesis for tissue regeneration. They tried to intervene in the insulin receptors found in keratinocytes, fibroblasts, endothelial cells, and immune cells.<sup>26</sup> In this study, Katagiri gave insulin to wounded rat tissues and found increased IRS1 expression and PI3K/Akt signaling pathway. That increased expression resulted in increased VEGF production and enhanced angiogenesis in rat wound tissues. These results were similar to the study of Lima et al. that disturbances in chronic diabetic wounds were associated with insulin signaling pathways, and intervention using topical insulin was able to increase signal pathway activity and better wound regeneration.

A study by Yu et al. also showed a significant increase in insulin signaling proteins and growth factors in diabetic rats, as well as the phosphorylated IRS-1 and AKT.<sup>28</sup> Besides that, they also observed increased Glucose Transporter 1 (GLUT1) protein level and translocation of GLUT1 from cytosol to cell membrane of the basal epidermal cells after insulin application. Yu suggested that insulin-induced growth is promoted by increasing the expression of GLUT1 in the plasma membrane via the activation of the PI3K/AKT/mTOR pathway, which could be one of the factors that contributed to the effectiveness of insulin in diabetic skin.

Liu et al. conducted a study on mice with the result showed that topical insulin-induced keratinocyte migration in a dose- and time-dependent manner through the PI3K-Akt-Rac1 pathway.<sup>11</sup> This study also identified Rac1, a small GTPase, an activated downstream molecule of the PI3K-Akt pathway that was needed for the healing process. Inhibition of this molecule inhibited insulin-induced keratinocyte migration. Rac1 was known to be able to regulate actin assembly and to stimulate the formation of lamellipodia, thereby promoting cell movement in response to external signals from cytokines, growth factors, and the ECM. Insulin was also able

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to induce attachment of the epidermis to the dermis, appearance of a well-organized epidermis, numbers of skin appendages, and dermal papilla and epidermal reticular ridges.

Chen, et al. conducted a study on mice by dividing rats into two groups. Insulin 0.03 units dissolved in 20  $\mu$ L saline were given to the wound in the first group, allowed to absorb for 5 minutes, then covered with a dressing.<sup>29</sup> In the second group, only normal saline was given. Wound healing in rats given topical insulin was faster than that of wounds given normal saline. Measurement using the western blot method showed the level of Gr-1, specific biomarkers for neutrophils were found to increase on the first day of injury. However, Gr-1 levels in wounds given topical insulin decreased faster compared to the control group. This finding showed the ability of topical insulin to suppress neutrophil infiltration activity to the wound site and prevent the extension of the inflammatory phase of the wound. Myeloperoxidase (MPO) is a peroxidase enzyme found in many azurophilic granules of polymorphonuclear neutrophils (PMN). MPO is a PMN activation marker because MPO enzyme activity correlates with PMN function. Activated PMN releases ROS to induce the peroxidation of unsaturated fatty acids in cell membranes. Malondialdehyde (MDA) is a product of lipid peroxidation and is useful as an indicator that shows the severity of cell damage. A study by Chen, et al. showed no significant differences in MPO and MDA levels between the groups given insulin and the control group. However, two days after injury, the number of neutrophils in the wound given insulin was significantly lower than the control group. Combining the results above, it is concluded that neutrophils in wounds that had been given topical insulin had increased cellular function. MPO and MDA levels were similar but with fewer cell numbers indicate that insulin increased the ability of neutrophils to destroy pathogens. Increased neutrophil function and decreased neutrophil infiltration in wound tissue resulted in earlier resolution of the inflammatory phase of wound healing.

Zhang et al. studied 32 patients randomly allocated to the insulin group or the control group. In the insulin group, the first half of the biosynthetic human insulin (protamine isophane) was diluted with physiological salts to a total volume of 1 mL and then injected diffusely into the base of the chronic diabetic wounds. Half of the remaining dose of insulin was injected subcutaneously into the abdominal wall. In the control group, insulin doses were injected subcutaneously into the abdominal wall and 1 mL of normal saline was injected diffusely into the base of the diabetic chronic wounds was done twice a day for 7 consecutive days. They found that insulin reduced the local wound blood glucose concentration, thus might reduce the damage caused by the accumulation of glucose metabolic intermediates. Insulin also inhibited the three major proinflammatory transcription factors i.e. nuclear factor- $\kappa$ B (NF- $\kappa$ B), activator protein-1

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(AP-1), and early growth response-1 (EGR-1). The expression of regulating monocyte chemotactic protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), MMP-2, MMP-9, tissue factor (TF), and plasminogen activator inhibitor-1 (PAI-1), which were regulated by the previous three transcription factors, were also inhibited by insulin. These proteins are important components of NADPH oxidase, which produces superoxide radicals with potent oxidative effects leading to the damage of the tissue cells. By reducing the inflammatory factors, insulin prevents an excessive inflammatory reaction.<sup>30</sup> The study showed that local wound insulin injection also had a marked effect on systemic blood glucose and could achieve the purpose of lowering blood glucose.<sup>31</sup> Wounds in the group given insulin locally showed an increase in the speed of granulation tissue formation and increased microvessel density (MVD).

Goenka et al. conducted a study with 50 samples of chronic wound patients, such as decubitus wounds, chronic postoperative wounds, chronic diabetic wounds with wounds measuring less than 10 cm<sup>2</sup>. Patients were divided into four groups: diabetic patients, divided again into a group that was treated with topical insulin and the other with normal saline. The non-diabetic groups were also divided again in the same fashion. This study showed a faster recovery in patients treated with topical insulin than without insulin. A similar result was found in either group, with diabetes mellitus or not.<sup>32</sup>

Based on studies conducted, insulin has a positive effect on multiple pathways leading to enhanced wound healing, including Akt, ERK, PI3K, MAPK signaling pathway, increased IRS1 expression, and increased neutrophil function.<sup>11-13,26,28,31-33</sup> Studies on humans showed positive results but there were no studies that used randomized controlled trials (RCT) on human patients as their method.<sup>15</sup> Lack of samples and clinical baseline characteristics of the patients in current studies, such as area of the wounds, chronicity, and level of target blood glucose, made the results difficult to interpret.<sup>34</sup> This encourages the need for more research on topical insulin for chronic diabetic wounds to produce a more conclusive result.

### Conclusion

In conclusion, topical insulin administration modulates the immune system and insulin signaling pathways and improves wound healing in chronic diabetic wounds. Thus, topical insulin can potentially be used as an alternative therapy for chronic diabetic wounds. The authors suggest more randomized controlled trial studies to be conducted, considering the lack of high quality studies on human subjects. With the finding of more conclusive data, it is hoped that the use of topical insulin will be a part of standard therapy for patients with chronic diabetic wounds.

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