International Journal of Multiphysics
Volume 18, No. 3, 2024
ISSN: 1750-9548

An Overview on Role of Insulin in Wound Healing

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Abstract:

Wound healing is a complex, multi-phase physiological process involving hemostasis, inflammation, proliferation, and remodeling. Proper coordination of cellular and molecular mechanisms is essential to restore tissue integrity. Insulin, a key anabolic hormone primarily known for its role in glucose metabolism, has emerged as a significant modulator of wound repair due to its cellular effects on proliferation, differentiation, and inflammation. Insulin stimulates the proliferation of keratinocytes and fibroblasts, which are vital for re-epithelialization and extracellular matrix formation. It enhances endothelial cell migration, supporting angiogenesis, which is crucial for supplying nutrients and oxygen to the healing tissue. Insulin promotes collagen synthesis and supports the formation of granulation tissue. It modulates the expression of matrix metalloproteinases (MMPs), enzymes involved in the remodeling of the extracellular matrix. Insulin has been shown to reduce pro-inflammatory cytokines (e.g., TNF-α, IL-6) and increase anti-inflammatory mediators. This effect helps in controlling excessive inflammation, which is often detrimental to proper wound healing, especially in chronic wounds. Insulin enhances the expression of vascular endothelial growth factor (VEGF) and other angiogenic factors, stimulating the formation of new blood vessels. By facilitating glucose uptake into cells, insulin ensures that energy requirements for wound healing processes are met, especially in high-demand cells like macrophages and fibroblasts. Topical insulin therapy has been investigated in both animal models and clinical trials, showing accelerated healing in acute and chronic wounds. It holds potential particularly in diabetic wound care, where impaired insulin signaling contributes to delayed healing.

Keywords: Insulin, Wound healing, Diabetic wounds, Angiogenesis, Inflammation.

Introduction:

Wound healing is a dynamic and complex biological process essential for restoring the integrity and function of injured tissue. It involves a coordinated sequence of overlapping phases—hemostasis, inflammation, proliferation, and remodeling—regulated by numerous cytokines, growth factors, and hormones **(1).** Among these regulators, insulin, a peptide hormone primarily known for its role in glucose metabolism, has been increasingly recognized for its significant influence on tissue repair mechanisms.

Beyond its metabolic actions, insulin exerts mitogenic and anti-inflammatory effects, modulating cell proliferation, protein synthesis, angiogenesis, and glucose utilization—each critical to effective wound healing **(2).** In individuals with diabetes mellitus, impaired insulin signaling contributes to delayed wound closure, chronic inflammation, and an increased risk of infection, highlighting the hormone's potential therapeutic relevance in wound management **(3).** Recent studies have explored both systemic and topical insulin applications, demonstrating improved wound healing outcomes in both diabetic and non-diabetic contexts.

The role of insulin in wound healing process

Insulin is a peptide hormone with multiple physiological roles. It regulates blood glucose levels and is known to have a beneficial role in wound healing. Insulin may be able to aid in the restoration of the integrity of injured skin, thus it's important to area of wound repair, especially given its low-cost relative to other growth factors, thus it is more likely to be considered for incorporation into wound dressings, bioadhesive films and hydrogels **(4).**

Since surgeons discovered variations in the postoperative wound healing between diabetes and non-diabetic patients in the early 20th century, the therapeutic benefits of insulin in wound repair have been documented across many decades. Wounds in the former group would have a higher probability of not healing normally, leaving them open to infection. More problems developed as the resulting infection extended to the circulation throughout the body**.**

The effects of insulin on cutaneous wounds have been studied using a range of cell and molecular techniques. These studies have demonstrated that insulin can stimulate keratinocyte migration in a dose- and time-dependent manner, working in a manner that is EGF/EGF-R-independent but insulin-receptor-dependent. On the other hand, if insulin and insulin growth factor 1receptors may be stimulated simultaneously, insulin may be more widely applied to many types of wounds, especially if one receptor is possible to be malfunctioning (as in type II diabetes). It is crucial to comprehend how insulin promotes faster wound healing because it will offer understanding of the various possible uses for the healing process **(5).**

The significance of the insulin receptor, a transmembrane protein triggered by insulin, insulin growth factor 1, and insulin growth factor 1i, has been repeatedly demonstrated by research. it is a member of a broad class of tyrosine kinase receptors that are present in fibroblasts and keratinocytes, and other cell types **(6).**

Liu, et al. showed that topical application of insulin to excision wounds stimulates keratinocyte migration. This migratory enhancement involves the PI3KAkt pathway, and identifies Rac1, a small GTPase, as a molecule activated downstream of PI3K-Akt. Activation leads to translocation of Rac1 to the plasma membrane, followed by activation of Rac1 substrate, the integrin α3 and the extracellular matrix molecule laminin 332. Due to the way insulin affects keratinocyte migration, insulin-accelerated wound healing is associated with elevated integrin α3β1 expression in keratinocytes and elevated LN332 levels **(7).**

Compared to intact skin, the tissue of wounds has higher expression of the insulin receptor, IRS-1, IRS-2, ERK, and Akt, indicating that the insulin signaling pathway may be important in this process. Especially Akt is capable of phosphorylating proteins that control the production of lipids, glycogen, and cell survival **(8).**

Recent findings reveal that, via a post-transcriptional process in keratinocytes, Akt activation is a critical step for vascular epidermal growth factor release in skin wounds and is required for vascular maturation and angiogenesis during cutaneous wound healing **(9).**

According to Lima et al., insulin signaling pathways are enhanced in injured skin of normal rat, but in diabetic animals, insulin deficiency causes these pathways to be attenuated. On the other hand, topical insulin cream treatment for diabetic rats' wounded skin speeds up wound healing and restores the insulin signaling cascade's protein levels. Therefore, expression of proteins involved in the early phase of insulin exposure, namely, IRS-1,2 and Akt, are increased in healing tissue when compared to healthy skin **(10).**

Insulin stimulates Ras which functions as a molecular switch once it is engaged, triggering a cascade of serine kinases that involves the sequential activation of Raf, MEK (a protein kinase that stimulates MAP kinases), and ERK. In order to initiate a transcriptional program that results in cellular proliferation or differentiation, activated ERK can translocate into the nucleus and catalyze the phosphorylation of transcription factors **(11).**

Other proposed mechanisms of action for insulin in wound healing exist, such as the enhancement of expression of neutrophil adhesion molecules to reinforce the cellular functions of migration, phagocytosis and bactericidal actions **(12).**

Chen, et al. offered data of neutrophil counts and functions in the presence or absence of topical low-dose insulin as well as a preliminary analysis of the underlying mechanisms. It has been demonstrated that topical insulin administration reduces neutrophil infiltration by blocking the expression of MIP-2 and promoting accelerated neutrophil resolution. Therefore, research suggests that both local and systemic insulin delivery may be useful in the treatment of skin wound incisions. Insulin modulates the inflammatory response during wound healing **(13).**

A study by Cruz-Cazarim in 2019 reported that daily application of insulin-loaded microparticles (50µL, 1 IU/mL insulin) to the eyes of diabetic rats for 15 days normalized tear fluid volume, corneal thickness, and protected corneal cell morphology in cases of dry eye syndrome and corneal injuries **(14).**

A study by Apikoglu-Rabus in 2010 showed that the application of insulin solution twice daily for 15 days enhanced wound healing in both diabetic and non-diabetic rats by shortening the time required for complete epithelialization **(15).**

Azevedo et al. (16) has investigated the effect of insulin cream (0.5 U/100 g) applied daily for 26 days on second-degree burns in control and diabetic rats. The results showed that insulin cream increased inflammatory cell infiltration and collagen deposition in diabetic rats, whereas non-diabetic rats did not exhibit these effects **(16).**

Several clinical trials have specifically compared topical insulin with normal saline for wound healing. Rezvani et al. (17) conducted a randomized, double-blind, placebo-controlled trial on 45 patients with acute and chronic extremity wounds. Patients received crystalline insulin sprays (10 U) or saline solution twice daily. The insulin-treated group had a mean healing rate of 46.09 mm^2/day, significantly higher than the 32.24 mm^2/day observed in the normal saline group ($P = 0.029$). No hypoglycemia, wound infections, or local pain were reported **(17).**

Stephen et al. (18) performed a randomized controlled trial comparing normal saline gauze dressings with insulin dressings in 50 patients with pressure ulcers. By day 7, the mean wound area decreased significantly in the insulin group (from 9.61 ± 6.39 cm^2 to 6.24 ± 4.33 cm^2, $P < 0.01$), while in the saline group, the wound area remained nearly unchanged (from 11.79 ± 8.97 cm^2 to 11.43 ± 9.06 cm^2, $P = 0.566$). This highlights insulin's superior wound-healing potential **(18).**

Attia et al. (19) compared topical regular insulin, zinc chloride solution, and saline in 90 patients with open cutaneous wounds. Both insulin and zinc chloride accelerated healing, but insulin had the most pronounced effect, demonstrating superior wound closure and no significant impact on blood glucose levels **(19).**

A study, conducted over 20 months, evaluated the efficacy of topical insulin in the treatment of Diabetic foot ulcers. A total of 110 patients were included and randomized into two groups: one receiving a solution of 30 IU insulin in 30 ml normal saline (experimental group) and the other undergoing conventional saline dressing (control group). The wound healing process was assessed on days 7, 14, and 21, with complete healing time determined through follow-up visits. The results demonstrated a significant reduction in wound diameter in the insulin-treated group compared to the control group. The mean post-treatment wound diameter was notably smaller in the topical insulin group (2.46 ± 0.57 cm) compared to the placebo group (3.90 ± 0.76 cm) ($P = 0.022$). Additionally, the mean percent reduction in wound size was significantly higher in the insulin group ($49.7 \pm 5.2\%$) compared to the control group ($19.2 \pm 4.6\%$) ($P = 0.001$). These findings highlight the potential efficacy of topical

insulin in accelerating wound healing in Diabetic foot ulcers, supporting its role as a promising adjunct therapy in diabetic wound management **(20).**

A prospective study evaluated the efficacy of local insulin, topical phenytoin, and normal saline dressings in the management of Diabetic foot ulcers. Among the three groups, a particular focus on the comparison between the normal saline and insulin groups revealed a significant difference in wound healing outcomes. The mean reduction in wound size was notably greater in the insulin group (4.98 cm^2) compared to the normal saline group (3.74 cm^2), with a statistically significant difference ($P < 0.001$). Similarly, the reduction in wound depth was remarkably higher in the insulin group (47.005 cm^2) than in the normal saline group (4.945 cm^2) ($P < 0.001$). Furthermore, the mean time required for complete wound healing was shorter in the insulin group (20 days) compared to the normal saline group (26 days), again demonstrating statistical significance ($P < 0.001$). These findings suggest that local insulin application is significantly more effective than normal saline in promoting faster and more substantial wound healing in Diabetic foot ulcers **(21).**

References:

1. Guo, S., & DiPietro, L. A. (2010). Factors affecting wound healing. Journal of Dental Research, 89(3), 219–229. https://doi.org/10.1177/0022034509359125
2. Gore, M. A., & Akhuemonkhan, J. E. (2004). Insulin and wound healing. Wounds, 16(1), 6–11.
3. Maruyama, K., Asai, J., Ii, M., Thorne, T., Losordo, D. W., & D'Amore, P. A. (2007). Decreased macrophage number and activation lead to reduced lymphatic vessel formation and contribute to impaired diabetic wound healing. The American Journal of Pathology, 170(4), 1178–1191. https://doi.org/10.2353/ajpath.2007.060925
4. Bhittani MK, Rehman M, Altaf HN, Altaf OS. Effectiveness of Topical Insulin Dressings in Management of Diabetic Foot Ulcers. World J Surg. 2020 Jun 9;44(6):2028–33.
5. Katiar V, Prem Shanker, Anil Kumar Verma, Mishra Y, Gaur M. Efficacy of topical application of insulin versus platelet rich plasma versus normal saline dressings in the healing of diabetic foot ulcers: A study from a tertiary care center in India. Asian J Med Sci. 2022 Nov 1;13(11):82–7.
6. Hrynyk M, Neufeld RJ. Insulin and wound healing. Burns. 2014 Dec;40(8):1433–46.
7. Liu Y, Petreaca M, Yao M, Martins-Green M. Cell and molecular mechanisms of keratinocyte function stimulated by insulin during wound healing. BMC Cell Biol. 2009 Dec 12;10(1):1.
8. Ghayour L, Irem F, ullah B, Riaz A, Ali AA. Comparative Analysis of Topical Insulin Dressing Vs Normal Saline Dressing in Diabetic Foot Ulcers Wound Healing. Pakistan Journal of Medical and Health Sciences. 2024 Feb 1;18(1):32–4.
9. Kido Y, Nakae J, Accili D. The Insulin Receptor and Its Cellular Targets [1]. J Clin Endocrinol Metab. 2001 Mar;86(3):972–9.
10. Mahmoud Elrefaey N, Abdou Abd El-Monem El-Deeb H. Effect of Topical Insulin on Diabetic Wound Healing among Patients with Diabetic Foot Ulcer. Egyptian Journal of Health Care. 2019 Mar 1;10(1):340–56.
11. Goren I, Müller E, Schiefelbein D, Gutwein P, Seitz O, Pfeilschifter J, et al. Akt1 Controls Insulin-Driven VEGF Biosynthesis from Keratinocytes: Implications for Normal and Diabetes-Impaired Skin Repair in Mice. Journal of Investigative Dermatology. 2009 Mar;129(3):752–64.
12. Larouche J, Sheoran S, Maruyama K, Martino MM. Immune regulation of skin wound healing: mechanisms and novel therapeutic targets. Advances in wound care. 2018;7(7):209-31.
13. Chen X, Zhang X, Liu Y. Effect of topical insulin application on wound neutrophil function. Wounds. 2012 Jul;24(7):178–84.
14. Cruz-Cazarim EL, Cazarim MS, Ogunjimi AT, Petrilli R, Rocha EM, Lopez RFJEJoP, Biopharmaceutics. Prospective insulin-based ophthalmic delivery systems for the treatment of dry eye syndrome and corneal injuries. 2019;140:1-10.
15. Apikoglu-Rabus S, Izzettin F, Turan P, Ercan FJC, Dermatology E. Effect of topical insulin on cutaneous wound healing in rats with or without acute diabetes. 2010;35(2):180-5.
16. Azevedo F, Pessoa A, Moreira G, Santos MD ,Liberti E, Araujo E, et al. Effect of topical insulin on second-

degree burns in diabetic rats. 2016;18(2):181-92.
17. Rezvani O, Shabbak E, Aslani A, Bidar R, Jafari M, Safarnezhad SJOwm. A randomized, double-blind, placebo-controlled trial to determine the effects of topical insulin on wound healing. 2009;55(8):22.
18. Stephen S, Agnihotri M, Kaur SJOWM. A randomized, controlled trial to assess the effect of topical insulin versus normal saline in pressure ulcer healing. 2016;62(6):16-23.
19. Attia EA ,Belal DM, El Samahy MH, El Hamamsy MHJWR, Regeneration. A pilot trial using topical regular crystalline insulin vs. aqueous zinc solution for uncomplicated cutaneous wound healing: Impact on quality of life. 2014;22(1):52-7.
20. Bhittani MK, Rehman M, Altaf HN, Altaf OSJWJoS. Effectiveness of topical insulin dressings in management of diabetic foot ulcers. 2020;44:2028-33.
21. Nagaraj J, Subbiah VJC. The Efficacy of Local Insulin Versus Topical Phenytoin or Normal Saline in Diabetic Foot Ulcer Management :A Prospective Comparative Study. 2022;14(10).