

# **THE EFFICIENCY OF TOPICAL INSULIN IN MANAGING OF CHRONIC DIABETIC FOOT ULCERS**

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## **INTRODUCTION**

Despite insulin treatment and a meticulously controlled diet, approximately 15% of all patients with diabetes will, at some time, have non-healing wounds and this is the leading cause of lower extremity amputation. Wound healing involve cell adhesion, migration, proliferation, differentiation, and apoptosis. Abnormalities of distinct factors of wound healing like decreased growth factor production, angiogenic response, macrophage function, collagen accumulation, epidermal barrier function, and fibroblast migration and proliferation contribute to defective healing in diabetes. Relative or absolute lack of insulin or its action is a hallmark of diabetes disease and defective insulin action in the skin contributes to defects in wound healing [1].

Foot ulcers are common due to underlying angiopathy and neuropathy. Several therapeutic modalities like skin grafts, hydrocolloid dressings, and high-protein diets, but some may not be economically stable or associated with complication. Researches in past has shown that topical insulin accelerates wound healing in the skin of diabetic rats and humans [2].

Insulin stimulates the growth and development of different cell types and affects proliferation, migration, and secretion by keratinocytes, endothelial cells, and fibroblasts [3]. The purpose of this prospective, randomized study was to investigate the efficacy and safety of topical insulin in management of patients with chronic diabetic foot ulcers.

## **MATERIALS AND METHODS**

Present study was conducted in department of general surgery, Vinayaka mission Medical College for period of six months (MARCH 2022 to August 2022). 40 patients were enrolled by simple randomization to participate in study and divided in two groups:

- Group A: Insulin Dressing.
- Group B: Saline Dressing.

All patients with foot ulcer treated daily with topical insulin spray of 1cc saline mixed with 5units regular insulin for each 10cm<sup>2</sup> ulcer. Patients with uncontrolled wound bleeding, severe malnutrition, severe infection, immunodeficiency, age>75 years, renal failure, liver dysfunction, ischemic limbs were excluded from study.

Before the start of the treatment and once in a week thereafter, depth and size of the wounds were recorded. The recordings were carried for a period of 4 weeks or healing of ulcer whichever is earlier. Strict glycemc control was brought in all the patients before study and also underlying anemia and hyper proteinemia were corrected. Systemic antibiotics were given based on pus culture and sensitivity. Dressings were performed once in a day, with normal saline in one group and additionally insulin intra lesional injection in another group. Vernier calipers was used to measure ulcer depth in its biggest diameter and ulcer area was used to define ulcer improvement. All patients participating in the study were informed and their consent taken.

## RESULTS

Present study showed statistically significant improvement in both area and depth of diabetic foot ulcers due to insulin therapy thus establishing the role of insulin in wound healing. The average size of the ulcer was 4.4 cm<sup>2</sup> in insulin group and it was 4.1 cm<sup>2</sup> in saline group. Statistically significant difference (p<0.05) in the improvement of ulcer size was found in study after treatment.

**Table 1 – Depth of ulcer and size of ulcer between the groups**

	Depth of Ulcer (mm)		Size of Ulcer (cm <sup>2</sup> )	
	Before Treatment	After Treatment	Before Treatment	After Treatment
<b>Group A</b> Insulin Group	<b>7.2</b>	<b>2.2</b>	<b>4.4</b>	<b>1.4</b>
<b>Group B</b> Saline Group	<b>7.4</b>	<b>6.1</b>	<b>4.1</b>	<b>3.1</b>



Figure 1 – Picture showing the pattern of healing

## DISCUSSION

Wound healing is a complex biological process that involves chemotaxis and neovascularization that comprises synthesis of extracellular matrix protein, components and remodeling of tissues. Present study showed statistically significant improvement in both area and depth of diabetic foot ulcers due to insulin therapy thus establishing the role of insulin in wound healing. Experimental researches on animals in past shows that insulin signaling pathways are up regulated in the wounded skin of normal rats, but in the wounded skin of diabetic subjects, these up regulations are treated with a topical insulin cream, an acceleration of wound healing occurs, in association with a recovery in the proteins of the insulin signaling pathways. Findings in the present study showing that topical insulin is efficacious for restoring normal re-epithelialization in foot ulcers. Significant difference in present study groups can be explained as direct application of insulin to the injured cutaneous surface restores the decreased levels of DNA synthesis of basal epithelial cells to normal values, thereby stimulates active cell proliferation [4]. Several studies have explored the effect of topical insulin in diabetic wound healing. Lima et al (2012) conducted a double-blind placebo-controlled clinical trial to evaluate the effect of topical insulin

in 22 patients with diabetic wounds. Subjects were randomly assigned to receive treatment with insulin cream (n=11) or placebo cream (n=11) for 8 weeks. By the end of the 8th week, the 10 patients who received insulin cream presented a significant improvement in wound healing, whereas the placebo group showed no such effect [5]. Martinez et al (2013) investigated the effect of local insulin administration in 8 diabetic patients with acute and chronic diabetic wounds. Half of the wound surface in each patient was treated with insulin (10 U) daily for 14 days, whereas the other half was not treated with insulin. There were significant differences in the number of vessels, percentage of fibrosis, and mean temperature between the insulin-treated and placebo sides. Five years later, Martinez's group conducted a similar study in 10 patients with full-thickness acute wounds. A significant difference in new vessel growth was observed in the insulin-treated site, compared to the saline-treated site; however, there was no significant difference in fibrosis percentage between the two zones [6].

In addition, Zhang et al (2016) explored the effect of local insulin injection on systemic blood glucose level and wound healing in patients with diabetic foot ulcer. The authors injected one-half of the calculated insulin dose into the base of ulcer and injected the other half subcutaneously into the abdomen of the experimental group (n=18), whereas the control group (n=14) was subcutaneously injected with the full insulin dose to abdomen twice daily for 7 days. The insulin group showed significantly enhanced formation of granulation tissue and new vessels, compared to the control group; however, the level of fasting blood glucose in both groups was not significantly different [7].

Recently, insulin delivery system, such as liposomal chitosan gel applied in wound healing have been extensively investigated. Bhattani et al (2019) conducted a double-blind placebo-controlled clinical trial to assess the effect of topical insulin in 110 patients with diabetic foot ulcers. Subjects were assigned to receive treatment with insulin gauze dressings (n=55) or saline gauze dressings (n=55) for 2 weeks. By the end of the 2nd week, the mean wound diameter was  $2.46 \pm 0.57$  cm in the topical insulin group, while it was  $3.90 \pm 0.76$  cm in the saline group ( $P = 0.022$ ). Dawoud et al (2019) explored the effect of insulin mucoadhesive liposomal gel on patients with chronic wounds in different parts of the body.[8] Patients were randomly assigned to receive treatment with insulin-loaded liposomal chitosan gel (n=10) or liposomal chitosan gel (n=5) daily for 8 weeks. The results showed a significant improvement of wound healing rate in the test group ( $36.67 \pm 12.179$  mm<sup>2</sup>/day) than the control group ( $2.27 \pm 1.034$  mm<sup>2</sup>/day), with magnificent reduction in the erythema.

## **CONCLUSION**

The use of topical insulin was found to be safe and effective in patients with diabetic foot ulcers. Results confirm that topically applied insulin can accelerate wound healing without any systemic side effects. Additionally, various wound dressings accelerate the wound healing with controlled and sustained delivery of bioactive insulin. Therefore, topical insulin has been appreciated in field of wound healing, and further studies are needed to improve our understanding of the role of insulin in the healing of various wounds.

## References

1. Zhang X-j, Wu X, Wolf SE, Hawkins HK, Chinkes DL, Wolfe RR. Local insulin-zinc injection accelerates skin donor site wound healing. *Journal of Surgical Research*. 2007; 142(1):90-6.4.
2. Hallam M-J, Pitt E, Thomas A, Nduka C. Low-Dose insulin as an antiscarring therapy in breast surgery: A randomized controlled trial. *Plastic and reconstructive surgery*. 2018; 141(4):476e-85e.5.
3. Zhang Z, Lv L. Effect of local insulin injection on wound vascularization in patients with diabetic foot ulcer. *Experimental and therapeutic medicine*. 2016; 11(2):397-402.6.
4. Aghdam SY, Eming SA, Willenborg S, Neuhaus B, Niessen CM, Partridge L, et al. Vascular endothelial insulin/IGF-1 signaling controls skin wound vascularization. *Biochemical and biophysical research communications*. 2012; 421(2):197-202.7.
5. Liu Y, Petreaca M, Martins-Green M. Cell and molecular mechanisms of insulin-induced angiogenesis. *Journal of cellular and molecular medicine*. 2009;13(11-12):4492-504.8.
6. Falanga V. Wound healing and its impairment in the diabetic foot. *The Lancet*. 2005; 366(9498):1736-43.9.
7. Swaminathan R. Effectiveness of topical insulin in management of chronic diabetic foot ulcers. *Indian Journal of Basic and Applied Medical Research*. 2014; 3(3):455-9.10.
8. Bing M, Da-Sheng C, Zhao-Fan X, Dao-Feng B, Wei L, Zhi-Fang C, et al. Randomized, multicenter, double-blind, and placebo-controlled trial using topical recombinant human acidic fibroblast growth factor for deep partial thickness burns and skin graft donor site. *Wound repair and regeneration*. 2007; 15(6):795-9.11.