



## EFFECT OF INJECTABLE INSULIN ON ACUTE DIABETIC WOUND HEALING

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### ABSTRACT

This study investigates if different diabetic treatment regimens affect diabetic foot fresh ulcer healing after debridement and/or VAC (vacuum assisted closure) therapy. From January 2018 to December 2021, 74 diabetic foot ulcers in patients were followed until wound healing, amputation or SSG (Split skin grafting). Demographic data, diabetic treatment regimens, wound characteristics and outcome were collected. Systemic insulin treatment can improve wound healing in diabetic ulcers after adjusting for multiple confounding covariates.

**KEY WORDS :** Sheehan's Syndrome, Pancytopenia, Hypopituitarism

### INTRODUCTION

Globally, an estimated 463 million adults are living with diabetes; India, with 77 million patients, has the second-highest number of patients after China [1]. Diabetic foot disease represents a real challenge to national health systems and healthcare providers in general [2]. The lifetime risk of a person with diabetes having a foot ulcer has been reported to be as high as 25%, with foot ulcers being the most frequent reason for hospitalization of patients with diabetes (about 30%) [3]. Moreover, treating diabetic foot ulcers is costly, accounting for 20% of total healthcare costs for diabetes, which is more compared to the cost for any other diabetic complication [3]. In India, the numbers of diabetic foot patients are increasing in both urban and rural settings, with 85% of amputations preceded by foot ulcers. Almost 75% of these amputations are performed on neuropathic feet with secondary infection, which is potentially preventable. In India, neuropathic lesions account for 80% of foot ulcers, with neuro-ischemic making up the remaining 20% [4]. The prevalence of the peripheral arterial disease is 3.2% in diabetic patients aged <50 years, but it increases to 33% in those aged >80 years, with the increase being associated with both age and the duration of diabetes [5]. In India, approximately 100,000 legs are amputated every year, and the numbers are increasing [3].

Insulin remains the cornerstone of therapy in a substantial number of patients with type 2 diabetes mellitus (T2DM). Inadequate knowledge regarding insulin usage is likely to influence its acceptance and adherence, and outcome of therapy, underscoring great need to investigate knowledge, attitude, and practice of insulin usage in patients with T2DM.

According to recent estimates till 2020, roughly 4 of 10 patients with T2DM in India are using insulin alone or in combination with OADs at any given point of time. Besides controlling glucose levels, insulin has been shown to have wound healing effects (5). The objective of this study is to evaluate the effects of systemic insulin treatment on healing of acute onset foot and leg ulcers.

### Materials and methods:

This was a prospective study of 74 subjects who were referred for treatment of diabetic foot acute wounds to general surgery between January 2018 and December 2021 were included. All 74 patients admitted and treated with debridement, daily dressings or Vac Therapy. Demographic information, medical history, imaging data, current medication, and foot ulcer characteristics were obtained from the patient's history and examination.

All selected patients for study were non tobacco users and without any addictions. All patient underwent arterial colour doppler study and without any evidence of additional peripheral vascular disease. Patients with Wagner's grade 2 classification selected for this study which represents deep ulcers involving skin, subcutaneous tissue, muscles, tendons but no osteomyelitis or gangrene. The ulcers were followed until complete healing after SSG, amputation or until last clinical follow-up.

All 74 Patients were Diabetes mellitus type 2 and glycosylated haemoglobin HB1C between 5.9 to 12.6 with average of 9.25 at the beginning of the treatment Out of 74 patients 60 patients were known DM and 14 were detected DM first time after admission. All 60 patients were on oral antidiabetic drugs. Out of 74, newly detected 14 and known 23 Diabetes mellitus were shifted on insulin and remaining 37 DM continued with oral antidiabetic treatment as their blood sugar levels were well controlled.

We started with short acting insulin subcutaneously for first 7 days followed by mixture of 70% intermediate-acting insulin (isophane) and 30% short-acting insulin (regular). The doses were adjusted between 8 to 20 units twice a day (along with oral antidiabetic agents in 20/37 patients).

The standard wound-care practice for impaired wound healing includes control of the infection together with debridement, off-loading to relieve pressure, and maintenance of a moist wound bed.

**Table 1 Baseline Characteristics of the Patients and Ulcers on Referral**

Age (years)		52.5 (45–60)
Gender	Female	16 (21.62%)
	Male	58 (78.37%)
Type of diabetes	Type 2	74 (100%)
Insulin treatment	Yes	37 (50%)
	No	37 (50%)
Serum haemoglobin A1C level (%)		9.25 (5.9–12.6)
Hypertension	Never smoked	74 (100%)
	Yes	16 (21.62)
	No	58 (78.38)

Numerical measures are summarized as median (min-max), and categorical variables are shown as frequency (percentage)

### Results:

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Among the patients who were receiving insulin treatment 32/37 ulcers (91.8%) had complete early healing compared to 24/37 (64.86%) among those who were treated with oral medication only. Median age was 52.5 years (range: 45 –60) and 58 cases (78.37%) were males. 58 cases reached a complete healing (healing rate: 78.37%). Median follow-up period in subjects with classified as having acute wounds was 23 days (range: 1-45 days). Insulin treatment was a part of diabetes management in 37 (50%) cases, remaining 37 cases were on oral antidiabetic drugs. Insulin therapy significantly increased the wound healing rate (91.8% [34/37 ulcers] vs. 64.86 [24/37 ulcers]). healing in days were 45 to 60 days (average 52.5). In multivariate random-effect logistic regression model, adjusting for age, gender, hypertension, wound infection, involved side and serum haemoglobin A1C levels, insulin treatment was associated with a higher chance of complete healing.

Outcome	Complete healing	58 (78.37%)
	Minor amputation	8 (10.81%)
	Major amputation	0 (0 %)
	Chronic wound	4 (5.40%)
Time to outcome (days)	57.5 (25-90)	

### Discussion:

Diabetic foot and diabetic foot infections are commonly encountered complications of diabetes [1]. Diabetic foot infections may be limb threatening or life threatening if not corrected in time. The principles of managing foot infections are simple and straightforward. Apart from wound care, antimicrobial therapy, and off-loading, the correction of metabolic abnormalities, including hyperglycemia, acidosis, azotemia, and electrolyte disturbances, is of utmost importance [2].

The results of our study indicated that after adjusting for multiple confounding covariates, insulin therapy positively affects wound healing in people with diabetes.

It has been demonstrated that different glucose-lowering medications have promising effects on diabetic wound healing mainly through decreasing inflammation and promoting healing (6). The idea of application of insulin in favour of wound healing was presented for the first time in 1930 by Joseph in a case series of complicated bed sore patients (6). Later in 1968 Rosenthal in an experimental study showed that insulin-treated rats had increasingly higher tensile strengths of wounds compared to their non-treated controls (7). Pierre in 1998 has shown using systemic insulin in patients with burns improves wound matrix formation (8). More recently topical application of insulin has been shown to accelerate healing of diabetic ulcers (9,10), however its mechanism was not fully understood.

Recent guidance on the medical management of diabetic foot ulcers focuses only on antimicrobial therapy [11-13]. Comprehensive reviews suggest that existing oral antidiabetic drugs and insulin regimens must be intensified in diabetic foot infection, but do not offer detailed instructions on how to do this. Especially missing from current literature is clear-cut information on the indications for starting and intensifying insulin regimens in diabetic foot ulcers [14]. This is unfortunate, as evidence reveals that non-insulin using males have a higher risk of amputation than those who receive insulin while being treated for diabetic foot infection [15]. Recent studies have demonstrated the beneficial effects of systemic insulin therapy [16] and insulin pump therapy [17] on wound healing in diabetic foot. Pathophysiologic studies also support the use of insulin in infection [18].

Further requirement of insulin is linked to the course of the foot infection. Refractory ulcers, onset of systemic inflammation, and clinical worsening are indications to intensify insulin regimens and optimize insulin dosage. A stable foot ulcer, heading towards recovery, implies that the chosen glucose-lowering strategy is adequate. A fully healed ulcer, with no risk factors for recurrence,

may allow de-escalation of insulin therapy and an eventual return to oral antidiabetic therapy.

In our study using systemic insulin therapy was associated with higher rates of complete wound healing even after adjusting for multiple confounding covariate which includes age, sex, hypertension, different HB1AC, wound infection and including blood glucose control. The independent association of insulin therapy with higher rates of complete wound healing contends mechanisms other than blood glucose control for insulin.

As strengths, our study is the first population-based study to show the effects of systemic insulin treatment on diabetic wound healing. Also long duration of follow-up assures precise categorization of non-healing wound types. Additionally, adjusting statistical models for a broad range of potentially confounding factors including inherent patient effect increases the validity of the observed independent associations.

As limitations, our study we selected only category 2 of Wagner's staging relative to the exposure (insulin treatment) assures the cause-and-effect nature of the observed association, still more prospective blinded studies are required to evaluate the efficacy of systemic insulin treatment in diabetic wound healing with osteomyelitis, gangrene and associated PVD.

Select indications for insulin use in diabetic foot ulcer.
<p>Ulcer phenotype</p> <ul style="list-style-type: none"> <li>• Deep involvement of bone/joint/tendon</li> <li>• Inflammation &gt;2 cm around wound</li> <li>• Crepitus</li> <li>• Bullae</li> <li>• Gangrene</li> <li>• Ecchymosis/petechiae</li> <li>• Presence of foreign body</li> </ul> <p>Ulcer behavior</p> <ul style="list-style-type: none"> <li>• Acute onset</li> <li>• Rapidly progressive</li> <li>• Refractory to treatment</li> </ul> <p>Limb phenotype</p> <ul style="list-style-type: none"> <li>• Arterial insufficiency</li> <li>• Venous insufficiency</li> <li>• Lymphedema</li> </ul> <p>Systemic health</p> <ul style="list-style-type: none"> <li>• Altered dietary intake</li> <li>• Acidosis</li> <li>• Azotemia</li> <li>• Electrolyte disorders</li> <li>• Septicemia</li> </ul> <p>Microbiological phenotype: Multidrug-resistant organisms</p> <ul style="list-style-type: none"> <li>• Methicillin-resistant Staphylococcus aureus</li> <li>• Gram-negative bacteria with extended-spectrum <math>\beta</math>-lactamases and carbapenamase</li> <li>• Vancomycin-resistant Staphylococcus aureus</li> </ul>

### CONCLUSIONS

Insulin is an important tool in the management of diabetic foot ulcers. We can use insulin in following situations.

1. In persons with a life-threatening or limb-threatening foot ulcer, insulin must be initiated or intensified to achieve rapid and sustained glycaemic control.
2. In persons with seemingly non-threatening ulcers and poor glycaemic control, insulin must be initiated or intensified to achieve rapid and sustained glycaemic control.
3. In persons with seemingly non-threatening ulcers and adequate glycaemic control, insulin may be considered in the presence of risk factors for recurrence, such as anatomical deformity or lymphedema.

4. Guidelines for asymptomatic adults with diabetes may not be relevant to persons with diabetic foot infections.
5. The choice of insulin regimens will depend upon various factors, including need for hospitalization, dietary pattern glucose profile, presence of comorbidities, and behaviour of the foot ulcer.
6. Insulin regimens which provide both fasting and postprandial control should be preferred.
7. Insulin preparations which are associated with minimal hypoglycemia and glycaemic variability should be preferred.

In summary, systemic insulin treatment can improve wound healing in diabetic ulcers after adjusting for multiple confounding covariates. Future prospective clinical studies are required to more elucidate this association.

**Fig 1: BEFORE INSULIN THERAPY**



**Fig 2: AFTER INSULIN THERAPY**



#### REFERENCES:

1. Clayton W, Elasy TA. Clin Diabetes A review of the pathophysiology, classification, and treatment of foot ulcers in diabetic patients. 2009;27:52–58. [Google Scholar]
2. Pendsey S. New Delhi, India: Jaypee Brothers Medical Publishers; 2003. Diabetic Foot: A Clinical Atlas. [Google Scholar]
3. Sinharay K, Paul UK, Bhattacharyya AK, Pal SK. Prevalence of diabetic foot ulcers in newly diagnosed diabetes mellitus patients. <https://pubmed.ncbi.nlm.nih.gov/23741832/> J Indian Med Assoc. 2012;110:608–611. [PubMed] [Google Scholar]
4. Tripathy JP, Thakur JS, Jeet G, et al. Diabetic Metab Syndr Prevalence and risk factors of diabetes in a large community-based study in North India: results from a STEPS survey in Punjab, India. 2017;9:8. [PMC free article] [PubMed] [Google Scholar]
5. Schaper N, van Netten J, Apelqvist J, et al. IWGDF Guidelines on the prevention and management of diabetic foot disease. [Jun;2020].; <https://iwgdfguidelines.org/wp-content/uploads/2019/05/IWGDF-Guidelines-2019.pdf> 2019:1–194.
6. Joseph B. Insulin in the Treatment of Non-Diabetic Bed Sores. Ann Surg. 1930;92(2):318–319. [PMC free article] [PubMed] [Google Scholar]
7. Rosenthal SP. Acceleration of primary wound healing by insulin. Arch Surg. 1968;96(1):53–55. [PubMed] [Google Scholar]
8. Pierre EJ, Barrow RE, Hawkins HK, Nguyen TT, Sakurai Y, Desai M, et al. Effects of insulin on wound healing. J Trauma. 1998;44(2):342–345. [PubMed] [Google Scholar]
9. Apikoglu-Rabus S, Izzettin FV, Turan P, Ercan F. Effect of topical insulin on cutaneous wound healing in rats with or without acute diabetes. Clin Exp Dermatol. 2010;35(2):180–185. [PubMed] [Google Scholar]
10. Lima MH, Caricilli AM, de Abreu LL, Araujo EP, Pelegrinelli FF, Thirone AC, et al. Topical insulin accelerates wound healing in diabetes by enhancing the AKT and ERK pathways: a double-blind placebo-controlled clinical trial. PLoS One. 2012;7(5):e36974. [PMC free article] [PubMed] [Google Scholar]
11. Lipsky BA, Berendt AR, Cornia PB et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54:e132–173.
12. Lipsky BA, Aragón-Sánchez J, Diggle M et al. IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. Diabetes Metab Res Rev 2016;32(Suppl 1):45–74.
13. IDF Clinical Practice Recommendations on the Diabetic Foot 2017. Available at [www.idf.org/e-library/guidelines/119-idf-clinical-practice-recommendations-on-diabetic-foot-2017.html](http://www.idf.org/e-library/guidelines/119-idf-clinical-practice-recommendations-on-diabetic-foot-2017.html). [Accessed 10 December 2017].
14. Bader MS. Diabetic foot infection. Am Fam Physician 2008;78:71–79.
15. Criado E, De Stefano AA, Keagy BA, Upchurch GR Jr, Johnson G Jr. The course of severe foot infection in patients with diabetes. Surg Gynecol Obstet 1992;175:135–140.
16. Vatankhah N, Jahangiri Y, Landry GJ, Moneta GL, Azarbal AF. Effect of systemic insulin

treatment on diabetic wound healing. Wound Repair Regen 2017;25:288–291.

17. Fan HJ, Yu JH, Cui GM, Zhang WY, Yang X, Dong QJ. Insulin pump for the treatment of diabetes in combination with ulcerative foot infections. J Biol Regul Homeost Agents 2016;30:465–470.
18. Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: A review of pathogenesis. Indian J Endocrinol Metab 2012;16(Suppl 1):S27.