Published in final edited form as:

Wound Repair Regen. 2017 April ; 25(2): 288–291. doi:10.1111/wrr.12514.

Effect of Systemic Insulin Treatment on Diabetic Wound Healing

Nasibeh Vatankhah, M.D.¹, Younes Jahangiri, M.D.², Gregory J Landry, M.D.¹, Gregory L Moneta, M.D.¹, and Amir F Azarbal, M.D.¹

¹Division of Vascular Surgery, Knight Cardiovascular Institute, Oregon Health & Science University, Portland, Oregon

²Dotter Interventional Institute, Oregon Health and Science University, Portland, Oregon

Abstract

This study investigates if different diabetic treatment regimens affects diabetic foot ulcer healing. From January 2013 to December 2014, 107 diabetic foot ulcers in 85 patients were followed until wound healing, amputation or development of a non-healing ulcer at the last follow-up visit. Demographic data, diabetic treatment regimens, presence of peripheral vascular disease, wound characteristics and outcome were collected. Non-healing wound was defined as major or minor amputation or those who didn't have complete healing until the last observation. Median age was 60.0 years (range: 31.1–90.1) and 58 cases (68.2%) were males. Twenty-four cases reached a complete healing (healing rate: 22.4%). Median follow-up period in subjects with classified as having chronic wounds was 6.0 months (range: 0.7–21.8). Insulin treatment was a part of diabetes management in 52 (61.2%) cases. Insulin therapy significantly increased the wound healing rate (30.3% [20/66 ulcers] vs. 9.8% [4/41 ulcers]) ($P=0.013$). In multivariate random-effect logistic regression model, adjusting for age, gender, smoking status, type of diabetes, hypertension, chronic kidney disease, peripheral arterial disease, oral hypoglycemic use, wound infection, involved side, presence of Charcot's deformity, gangrene, osteomyelitis on x-ray, and serum hemoglobin A1C levels, insulin treatment was associated with a higher chance of complete healing ($\text{beta} \pm \text{SE}$: 15.2 ± 6.1 , $P=0.013$). Systemic insulin treatment can improve wound healing in diabetic ulcers after adjusting for multiple confounding covariates.

Keywords

Diabetic wound; Diabetic foot; Amputation; Insulin

Introduction

Diabetes affects approximately 29 million people in the US in 2014 (1). Impaired wound healing is a critical problem in diabetes that affects 1%–4% of patients with diabetes annually (2). The mechanisms of poor healing in diabetic foot ulcer are not fully understood.

Corresponding Author: Nasibeh Vatankhah, M.D., Division of Vascular Surgery, Knight Cardiovascular Institute, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, OP-11, Tel: 503 494-7593, Fax: 503 494-4324, vatankha@ohsu.edu.

Duality of Interest: No potential conflicts of interest relevant to this article were reported.

However, studies suggest that impaired leukocyte function, cytokines and growth factors dysregulation, neuropathy, and vasculopathy have important roles in non-healing diabetic foot ulcers (3, 4). According to CDC, 6 million patients use insulin to control their diabetes (1). 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 foot ulcers.

Methods

Study subjects

The protocol was approved by Institutional Review Board of Oregon Health and Science University. This was a retrospective study of 85 subjects who were referred for treatment of diabetic foot ulcer to the vascular surgery clinic between January 2013 and December 2014 were included. Demographic information, medical history, imaging data, current medication, and foot and ulcer characteristics were obtained from the patients' medical records. All patients' information was recorded at the time of entry into clinic and prescribed by patients' primary care physician or an endocrinologist. The ulcers were followed until complete healing, amputation or until last clinical follow-up.

Definitions

Outcomes were divided into complete wound healing, minor amputation, major amputation, and chronic wounds. Ulcers that did not reach complete healing or amputation during the follow-up were considered chronic wounds. Amputations below the ankle were classified as minor amputations and amputations higher than this level were defined as major amputations.

Treatment for blood glucose control was divided into insulin and non-insulin therapy. Insulin therapy was defined as the presence of insulin on the medications list at the time of admission.

Statistical analysis

Data were summarized as median (min-max) for numerical measures and frequency (percentage) for categorical variables. Comparisons of frequencies between two groups were done by Chi² test and Fischer's exact test.

Uni- and multivariate binary logistic regression models were used to assess the association of insulin therapy with complete healing of the ulcers. Because more than one ulcer was studied in some of the patients, there was a possibility of predisposition in the subjects themselves for one particular outcome (endogenous patient effect). To cope with this issue we used random-effect logistic regression models for longitudinal (panel) data with considering patient-specific ID as the cluster (patient-identifying) variable.

In regression models, the univariate model was considered as model 1; and model 2 was adjusted for wound characteristics (infection, affected limb, presence of Charcot's deformity, gangrene, and osteomyelitis on x-ray) and the patient's characteristics and comorbid conditions (age, gender, smoking status, type of diabetes, hypertension, chronic kidney

disease and peripheral arterial disease). Model 3 was further adjusted for serum hemoglobin A1C levels.

Results

A total of 107 ulcers in 85 patients included in this study. Table 1 demonstrates a summary of baseline characteristics of the patients and ulcers. The subjects' median age on referral was 60.0 years (range: 31.1–90.1), and 58 (68.2%) cases were males. The diabetes type was type 2 in 70 (82.3%) of the patients. Insulin treatment was a part of diabetes management in 52 (61.2%) cases. Median serum hemoglobin A1C on all referrals was 7.9% (range: 4.9–17.6). Hemoglobin A1C levels were actually higher in the insulin treated group than in the non-insulin treated group (8.54 ± 2.36 vs. 7.70 ± 2.33). The ulcers were complicated with peripheral arterial disease in 24 (28.2%), Charcot's deformity in 8 (7.5%), infection in 54 (50.5%) and gangrene in 42 (39.2%) cases. Osteomyelitis was detected on x-ray imaging in 26 (25.5%) wounds. Final outcome was complete healing in 24 (22.4%), minor amputation in 50 (46.7%), major amputation in 11 (10.3%) wounds, and 22 (20.6%) of the ulcers did not heal during the observation period (chronic). Median time-to-outcome was 1.1 months and median follow-up time in chronic wound group was 6.0 months (range: 0.7–21.8).

Among the patients who were receiving insulin treatment 20 ulcers (30.3%) had complete healing compared to 4 (9.8%) among those who were treated with oral medication only or were not treated for diabetes at all ($P=0.013$) (Figure 1).

Table 2 demonstrates the results of random effect panel binary regression model. Insulin treatment was significantly associated with higher rates of complete wound healing in all models. Even after adjusting for serum hemoglobin A1C levels, insulin therapy was independently associated with complete healing of the ulcers (beta coefficient: 13.69, $P=0.047$). In multivariate model (model 3) higher levels of serum hemoglobin A1C (beta: -4.75 , $P=0.029$) and presence of infection (beta: -14.63 , $P=0.012$) were also significantly associated with lower rates of complete wound healing beside insulin treatment.

On sub-population analysis, after excluding subjects with minor amputation ($n=50$), insulin therapy was associated with higher rate of complete healing versus major amputation or development of a chronic wound ($P=0.013$, χ^2 test) (Figure 2). In regression model analysis, adjusted for insulin treatment and serum hemoglobin A1C levels, insulin therapy remained an independent predictor of complete healing (OR: 9.90, $P=0.008$).

Discussion

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 favor of wound healing was presented for the first time in 1930 by Joseph in a case series of complicated bed sore patients (7). 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 (8). Pierre in 1998 has shown using systemic insulin in patients with burns improves wound matrix formation (9). More recently topical application of insulin has been shown to accelerate healing of diabetic ulcers (10, 11), however its mechanism was not fully understood. Although effect of insulin was ascribed to its glucose control properties (12), later studies revealed different mechanisms through which insulin improves wound healing (13, 14). In our study using systemic insulin therapy was associated with higher rates of complete wound healing even after adjusting for multiple confounding covariate, 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. Increased microvessel density and growth of granulation tissue has been reported in patients with diabetic foot ulcers after topical injection of insulin compared to control group (15). Topical insulin may improve wound healing even in healthy animals, reduce the duration of the inflammatory phase, and improve wound reepithelialization. (14). Topical insulin may accelerate healing of diabetic and non-diabetic wounds by enhancing the serine-threonine kinase (AKT) and extracellular signal-regulated kinase (ERK) pathways and increased expression of endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF) and stromal cell-derived factor (SDF-1 α) (11). A novel combination of negative pressure wound therapy and continuous-instillation of insulin as “wound chemotherapy” has shown promising results in a case of severe diabetic foot ulcer (16).

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 is a retrospective cross-sectional study which challenges the evaluation of cause-and-effect associations. Although, the latency of the outcome measurement (foot ulcer healing) relative to the exposure (insulin treatment) assures the cause-and-effect nature of the observed association, still prospective blinded studies are required to evaluate the efficacy of systemic insulin treatment in diabetic wound healing. Also, the retrospective nature of this study also made it difficult to determine the cause of using insulin or other medications to control hyperglycemia and why HbA1C levels were not being properly managed at the time of admission and data entry. Therefore, the confounding effect of differences in later treatment for blood glucose control cannot be determined from this study.

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.

Acknowledgments

Funding: N. Vatankhah is supported by NIH Postdoctoral Fellowship Award T32-HL094294.

References

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report. 2014. Available from: <http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf>
2. Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons NB. Burden of diabetic foot ulcers for medicare and private insurers. *Diabetes Care*. 2014; 37(3):651–658. [PubMed: 24186882]
3. Pradhan L, Nabzdyk C, Andersen ND, LoGerfo FW, Veves A. Inflammation and neuropeptides: the connection in diabetic wound healing. *Expert Rev Mol Med*. 2009; 11:e2. [PubMed: 19138453]
4. Brem H, Tomic-Canic M. Cellular and molecular basis of wound healing in diabetes. *J Clin Invest*. 2007; 117(5):1219–1222. [PubMed: 17476353]
5. Hrynyk M, Neufeld RJ. Insulin and wound healing. *Burns*. 2014; 40(8):1433–1446. [PubMed: 24810536]
6. Salazar JJ, Ennis WJ, Koh TJ. Diabetes medications: Impact on inflammation and wound healing. *J Diabetes Complications*. 2016; 30(4):746–752. [PubMed: 26796432]
7. Joseph B. Insulin in the Treatment of Non-Diabetic Bed Sores. *Ann Surg*. 1930; 92(2):318–319. [PubMed: 17866367]
8. Rosenthal SP. Acceleration of primary wound healing by insulin. *Arch Surg*. 1968; 96(1):53–55. [PubMed: 5635406]
9. 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: 9498508]
10. 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: 19594766]
11. 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. [PubMed: 22662132]
12. Rubinstein A, Pierce CE Jr. Rapid healing of diabetic foot ulcers with meticulous blood glucose control. *Acta Diabetol Lat*. 1988; 25(1):25–32. [PubMed: 3043987]
13. 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; 10:1. [PubMed: 19134226]
14. Azevedo F, Pessoa A, Moreira G, Dos Santos M, Liberti E, Araujo E, et al. Effect of Topical Insulin on Second-Degree Burns in Diabetic Rats. *Biol Res Nurs*. 2016; 18(2):181–192. [PubMed: 26111834]
15. Zhang Z, Lv L. Effect of local insulin injection on wound vascularization in patients with diabetic foot ulcer. *Exp Ther Med*. 2016; 11(2):397–402. [PubMed: 26893621]
16. Scimeca CL, Bharara M, Fisher TK, Kimbriel H, Mills JL, Armstrong DG. Novel use of insulin in continuous-instillation negative pressure wound therapy as "wound chemotherapy". *J Diabetes Sci Technol*. 2010; 4(4):820–824. [PubMed: 20663443]

Figure 1.
Rate of Complete Wound Healing By Insulin Treatment

Figure 2.
Rate of Complete Wound Healing by Insulin Treatment in a subpopulation of patients excluding minor amputations

Table 1

Baseline Characteristics of the Patients and Ulcers on Referral

		Summary ¹
Age (years)		60.0 (31.1–90.1)
Gender	Female	27 (31.8%)
	Male	58 (68.2%)
Type of diabetes	Type 1	15 (17.6%)
	Type 2	70 (82.3%)
Insulin treatment	Yes	52 (61.2%)
	No	33 (38.8%)
Serum hemoglobin A1C level (%)		7.9 (4.9–17.6)
Smoking status	Current smoker	21 (25.0%)
	Former smoker	33 (39.3%)
	Never smoked	30 (35.7%)
Hypertension	Yes	62 (72.9%)
	No	23 (27.1%)
Chronic kidney disease	Yes	22 (25.9%)
	No	63 (74.1%)
Peripheral arterial disease	Yes	24 (28.2%)
	No	61 (71.8%)
Affected side	Right	53 (49.5%)
	Left	54 (50.5%)
Charcot's deformity	Yes	8 (7.5%)
	No	99 (92.5%)
Wound infection	Yes	54 (50.5%)
	No	53 (49.5%)
Gangrene	Yes	42 (39.2%)
	No	65 (60.8%)
Osteomyelitis on x-ray	Yes	26 (25.5%)
	No	76 (74.5%)
Outcome	Complete healing	24 (22.4%)
	Minor amputation	50 (46.7%)
	Major amputation	11 (10.3%)
	Chronic wound	22 (20.6%)
Time to outcome (months)		1.1 (0–22.8)

¹ Numerical measures are summarized as median (min-max), and categorical variables are shown as frequency (percentage)

Table 2

Uni- and Multivariate Associations of Insulin Treatment and Wound Factors with Complete Healing of Diabetic Ulcers (total n=107)

	Model 1		Model 2 (n=101)		Model 3 (n=92)	
	Beta coefficient ± SE	P value	Beta coefficient ± SE	P value	Beta coefficient ± SE	P value
Insulin treatment	3.50 ± 1.52	0.021	11.58 ± 5.38	0.031	15.19 ± 6.08	0.013
Serum hemoglobin A1C ¹	-1.39 ± 0.97	0.151			-5.33 ± 2.21	0.016
Wound infection	-4.12 ± 1.49	0.006	-13.04 ± 4.68	0.005	-15.75 ± 6.45	0.015
Involved side (left vs. right)	-3.90 ± 1.74	0.025	-3.99 ± 2.51	0.111	-4.70 ± 3.17	0.138
Charcot deformity	-2.51 ± 3.71	0.498	-5.02 ± 6.39	0.433	-7.36 ± 6.14	0.231
Wound gangrene	-1.62 ± 1.46	0.266	-2.30 ± 3.53	0.514	-4.30 ± 4.51	0.340
Osteomyelitis on x-ray	-1.38 ± 1.64	0.400	7.48 ± 5.11	0.143	9.08 ± 5.35	0.090

¹ Standardized odds ratios

Model 1: Univariate model

Model 2: insulin treatment, oral hypoglycemic use, wound infection, involved side, presence of Charcot's deformity, gangrene, osteomyelitis on x-ray, age, gender, smoking status, type of diabetes, hypertension, chronic kidney disease and peripheral arterial disease.

Model 3: Model 2 additionally adjusted for serum hemoglobin A1C; there was no significant interaction between insulin treatment and serum hemoglobin A1C levels.