Hemoglobin A1c Predicts Healing Rate in Diabetic Wounds

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Background

- Lower-extremity wounds and amputations are a major complication of diabetes.
- The identification of clinical factors that can be modified to promote healing will improve patient health.

Objective

- Our objective was to identify which common baseline clinical variable(s) is associated with wound healing rates.
- We hypothesized that elevated hemoglobin A1c (HbA1c) values would be the strongest predictor of poor healing among commonly ordered laboratory and clinical measures.

Methods

- **Study Design:** Retrospective cohort study of 183 diabetic individuals with 310 total wounds treated at the Johns Hopkins Bayview Wound Center.

- **Exposures:**
  - Blood pressure, pulse, and temperature were measured, and peripheral neuropathy status was assessed during clinic visits.
  - Laboratory values (HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and white blood cell count), body mass index, smoking status, and peripheral arterial disease status were obtained from electronic medical record.

- **Outcome:** Wound area healed per day (cm^2/day).

- **Statistical Analysis:** Multiple linear regression with robust standard error and adjustment for the presence of multiple wounds within individuals.
  - Variables in model: age, gender, race, smoking, body mass index, HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, systolic and diastolic blood pressures, pulse, temperature, white blood cell count, peripheral neuropathy, peripheral arterial disease, and wound number.
  - Stratified analyses by peripheral neuropathy and peripheral artery disease status.

Results

Table 1. Characteristics of participants at time of first wound, overall and by HbA1c category.

	All Participants (N=183)	HbA1c <7.0% (n=71)	HbA1c 7.0-8.0% (n=42)	HbA1c ≥8.0% (n=70)
Age (years), mean (SD)	61 (12)	62 (12)	66 (11)	57 (12)
Females, %	45	48	36	49
Race				
White, %	55	61	69	40
Black, %	41	35	31	53
Smoking				
Current smoker, %	28	24	19	37
Former smoker, %	38	52	29	30
Body mass index (kg/m^2), mean (SD)	35 (10)	34 (10)	35 (10)	37 (10)
HbA1c (%), mean (SD)	8.0 (2.3)	6.0 (0.6)	7.4 (0.3)	10.3 (2.0)
Total cholesterol (mg/dL), mean (SD)	154 (45)	148 (45)	153 (41)	160 (47)
LDL cholesterol (mg/dL), mean (SD)	84 (41)	75 (32)	83 (32)	93 (52)
HDL cholesterol (mg/dL), mean (SD)	43 (16)	44 (15)	42 (13)	44 (18)
Triglycerides (mmol/L), mean (SD)	142 (75)	141 (78)	147 (77)	139 (73)
Systolic blood pressure (mmHg), mean (SD)	139 (23)	136 (25)	143 (25)	140 (21)
Diastolic blood pressure (mmHg), mean (SD)	77 (13)	76 (14)	77 (14)	77 (13)
Pulse (bpm), mean (SD)	79 (14)	80 (13)	76 (13)	81 (16)
Temperature (° Fahrenheit), mean (SD)	98.0 (0.6)	97.9 (0.6)	98.0 (0.7)	98.0 (0.6)
White blood cell count (cells/microliter), mean (SD)	7,882 (2,490)	7,949 (2,575)	7,862 (2,380)	7,827 (2,502)
Peripheral neuropathy, %	60	54	55	69
Peripheral arterial disease, %	29	27	29	31
Wound number, mean (SD)	2.3 (1.5)	2.3 (1.6)	2.1 (1.3)	2.4 (1.6)
Wound area (cm^2), mean (SD)	7.2 (13.0)	6.1 (11.4)	7.6 (14.3)	4.1 (5.3)

Table 2. Adjusted ß-coefficients and 95% confidence intervals for the relationship between change in wound area per day and variables.

Variable*	Change in Wound Area Per Day (cm^2/day)	P-Value
Age	0.017 (-0.065, 0.100)	0.68
Female (versus male)	0.038 (-0.132, 0.209)	0.66
Black (versus white)	-0.063 (-0.174, 0.048)	0.26
Current smoker (versus never smoker)	-0.015 (-0.224, 0.067)	0.50
Former smoker (versus never smoker)	0.054 (-0.103, 0.212)	0.86
Body mass index	0.053 (-0.032, 0.139)	0.22
HbA1c (per 1.0%)	-0.028 (-0.054, -0.003)	0.03
Total cholesterol	-0.060 (-0.137, 0.017)	0.13
LDL cholesterol	0.035 (-0.025, 0.094)	0.25
HDL cholesterol	-0.020 (-0.069, 0.029)	0.41
Triglycerides	-0.016 (-0.085, 0.052)	0.64
Systolic blood pressure	0.020 (-0.063, 0.102)	0.64
Diastolic blood pressure	-0.074 (-0.151, 0.003)	0.06
Pulse	0.025 (-0.037, 0.087)	0.43
Temperature	0.015 (-0.048, 0.078)	0.64
White blood cell count	0.118 (-0.085, 0.266)	0.12
Peripheral neuropathy	-0.079 (-0.224, 0.067)	0.29
Peripheral arterial disease	-0.053 (-0.144, 0.038)	0.25
Wound number	-0.001 (-0.059, 0.058)	0.98

*Expressed per SD unless otherwise noted.

Figure 2. Adjusted Mean Change in Wound Area Per Day (cm^2/day) by HbA1c Category.

- Each 1.0% increase in HbA1c was associated with a decrease in healing rate of 0.022 cm^2 per day (95% CI: 0.001, 0.043, p = 0.043) among those with **peripheral neuropathy**, but not among those without peripheral neuropathy.

- Each 1.0% increase in HbA1c was associated with a decrease in healing rate of 0.030 cm^2 per day (95% CI: 0.001, 0.060, p = 0.046) among those with **peripheral arterial disease**, but not among those without peripheral arterial disease.

Results

Figure 1. Wound healing in an individual with HbA1c of 5.6% (a-d) and in an individual with HbA1c of 11.1% (e-i). Wound healing per day is 0.35 cm^2 for the individual with HbA1c of 5.6% (a). The wound is shown at first clinic visit (b, c) and healed at last clinic visit 64 days later (d). Wound-healing per day is 0.001 cm^2 for the individual with HbA1c of 11.1% (e). The wound is shown at first clinic visit (f, g), and at the last clinic visit 727 days later (h, i).
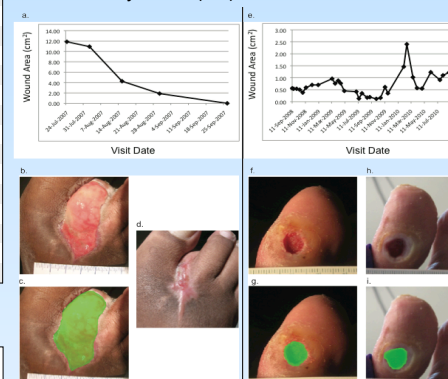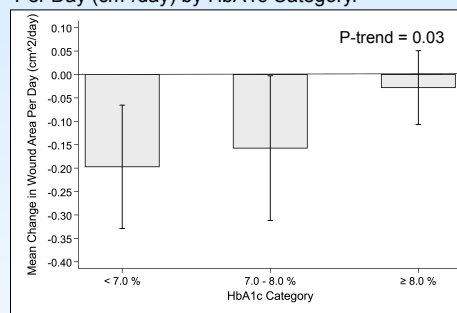

Discussion

- Of the demographic, clinical, and laboratory variables commonly measured in diabetic patients in wound clinics, only elevated HbA1c was significantly associated with poor wound-area-healing rate per day.

- Our study suggests that hyperglycemia, as assessed by HbA1c, is associated with slower wound healing in patients with diabetes, particularly for patients with peripheral neuropathy or peripheral arterial disease.

- Future prospective studies should assess the effect of tight glycemic control to decrease HbA1c levels in wound healing.