Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Association of Hemoglobin-A1c with Healing in Diabetic Cutaneous Wound – A Prospective Study

Arun Basil Mathew[1], Megha Isac[2]

[1]Assistant Professor, Department of CVTS, Division of Adult Cardiac Surgery, Amrita Institute of Medical Sciences, Kochi, Kerala, India, [2]Assistant Professor, Department of General Medicine, MOSC Medical College, Kolenchery, Kerala, India

Abstract

Background: Glycosylated hemoglobin is widely used as a measure for glycemic control in patients. Only very few studies in the literature states that hemoglobin A1c (HbA1c), which is a standard measure of glycemia over 2–3 months, is related to wound-healing rate. Our objective was to identify the common variables most strongly related to wound healing rate in a hospital-based population of individuals with diabetes. We hypothesized that among common laboratory tests, clinical and demographic variables, higher HbA1c values would be the most associated with decreased daily wound-healing rate.

Objective: The objective of the study was to establish the association of HbA1c with healing in diabetic cutaneous wounds.

Methodology: A prospective study in patients who were admitted to the general surgery department for the treatment of diabetic cutaneous wounds at MOSC Medical College was evaluated (from September 2011 to August 2013). Wounds in them were measured using calibrated measuring tape at the time of admission and same procedure repeated at the time of discharge and at follow-up; thereby wound healing rates were measured. A semi-structured questionnaire was also filled while interviewing the patients at the time of admission. Collected data were entered in Excel and analyzed using SPSS version 16. Among all variables analyzed, only HbA1c was significantly associated with wound area healing rate. A change in wound area per day showed for each 1.0% point increase in HbA1c, the wound-area healing rate per day decreased by 0.219 cm^2 (95% confidence interval): –0.290, –0.148, $P = 0.0001$). A sensitivity analysis done stratified by peripheral arterial disease status and neuropathy status showed an improvement in statistical significance.

Conclusion: Hba1c is an important clinical predictor of wound healing rate and the relationship holds stronger particularly in neuropathic wounds and in peripheral arterial diseases.

Key words: Glycosylated hemoglobin, Neuropathy, Peripheral arterial disease

INTRODUCTION

Diabetes mellitus is a metabolic disorder caused by either a lack of insulin, or resistance to its effects, or both. In 2004, an estimated 3.4 million people died from consequences of high fasting blood sugar.[1] Poor glycemic control and presence of diabetic complications are commonly regarded as risk factors for mortality and morbidity.

Diabetic foot infections are one of the major long-term complications of type 2 DM which can result in gangrene and lower extremity amputation.

Access this article online

www.ijss-sn.com

Month of Submission : 11-2020
Month of Peer Review : 11-2020
Month of Acceptance : 12-2020
Month of Publishing : 01-2021

Diagnostic criteria for DM

1. Fasting plasma glucose ≥7 mmol/L (≥126 mg/dl)
2. 2 h PPBS after ingestion of 75g of oral glucose load (OGTT) ≥11 mmol/L (≥200 mg/dl)
3. Hemoglobin A1c (HbA1c) result >6.5%.

Any two out of three criteria or 1 plus symptoms of DM are diagnostic.

Around 1977, the HbA1c was first introduced to clinical laboratories for diabetes monitoring. At the present time, the HbA1c is used worldwide as the marker of long term glycemic control and also a therapeutic target in the prevention and delay of the development of hyperglycemic complications.[2-4]

Over 100 known physiological factors contribute to wound healing deficiencies in individuals with diabetes. These include decreased or impaired growth factor production,[5-7]

Corresponding Author: Dr. Megha Isac, Department of General Medicine, MOSC Medical College, Kolenchery, Kerala, India.

angiogenic response[7,8] macrophage function[9] collagen accumulation, epidermal barrier function, quantity of granulation tissue[7] keratinocyte and fibroblast migration and proliferation, number of epidermal nerves[10] bone healing, and balance between the accumulation of ECM components and their remodeling by MMPS.[11] The wound healing process consists of four highly integrated and overlapping phases: Hemostasis, inflammation, proliferation, and tissue remodeling or resolution.[12] These phases and their bio-physiological functions must occur in the proper sequence, at a specific time, and continue for a specific duration at an optimal intensity.[13] Wounds that exhibit impaired healing, including delayed acute wounds and chronic wounds, generally have failed to progress through the normal stages of healing, such wounds frequently enter a state of pathological inflammation due to a postponed, incomplete, or uncoordinated healing process. Most chronic wounds are ulcers that are associated with ischemia, diabetes mellitus, venous stasis disease, or pressure damage.

The HbA1c level is proportional to average blood glucose concentration over the previous 4 weeks to 3 months. Poor glycemic control is associated with the presence of neuropathy and increased risk for wounds and amputations. Foot problems most often develop when there is neuropathy, poor vascularity, or changes in the shape of toes. In the setting of Kerala, where the study was done, also there is a significant dearth of information regarding association of HbA1c to wound healing.

METHODOLOGY

Materials and Methods

This prospective clinical study was done to identify the common variables most strongly related to wound healing rate in a population of individuals with diabetes admitted in a tertiary care center in the state of Kerala, India. We hypothesized that among common laboratory tests, clinical and demographic variables, and higher HbA1c values would be the most associated with decreased daily wound healing rate.

A total of 101 patients who are diabetic for more than 5 years, with peripheral cutaneous wounds from OP departments and general wards of department of general surgery and plastic surgery between September 2011 and August 2013 were selected for our study as sample group.

Exclusion Criteria

The following criteria are excluded from the study:

1. Seriously ill patients admitted in ICU with multiple comorbidities
2. Diabetic wounds with osteomyelitis (Wagner's classification three and above)
3. Duration of diabetes less than 5 years
4. Patients who are having multiple immunocompromised states. (Tuberculosis, AIDS, severe renal disease, and chronic liver disease).

Wagner's wound classification system:

1. No open lesions, may have deformities or cellulitis
2. Superficial ulcer
3. Deep ulcer to tendon or joint capsule
4. Deep ulcer with abscess, osteomyelitis, or joint sepsis
5. Local gangrene – forefoot or heel
6. Gangrene of entire foot.

Wounds were measured using calibrated measuring tape at the time of admission and same procedure repeated at the time of discharge and after 1 month for follow-up; thereby wound healing rates were measured. The area of wound and the largest width and largest length were traced to obtain wound dimensions. A semi-structured questionnaire was also filled while interviewing the patients for complete information on baseline demographic and clinical variables. Collected data were entered into Excel and analyzed using SPSS version 16. Clinical information collected included vital signs (BP, PR, and temperature), status of neuropathy (Semmer Weinstein filament – Medical Monofilament manufacturing LLC, Plymouth, MA), and peripheral arterial disease status (palpatory and ABPI measurement using a hand held Doppler).

All wound treatments were documented and found to be homogeneous for all patients with diabetic wounds. Standard treatment for diabetic wounds includes removal of non-viable tissue, local dressing (antimicrobial dressings with silver), control of blood glucose levels, offloading with proper shoes if the wound is on the lower extremity and antibiotic treatment if infection is present.

Laboratory test results (HbA1c, Hb, ESR, Platelet count, blood sugars, and white blood cell count) and BMI, smoking status, and alcoholic history data were included in the study.

The change in wound area in cm^2 per day was the outcome for our primary analysis. The change in wound area per day was calculated as the difference between wound area at visit 1 (baseline) and at a subsequent visit divided by the number of days between the two visits (median of 32 days, interquartile range: 18–61). We estimated the change in wound area (cm^2 per day) using a multiple linear regression model with robust SE and adjusted for clustering of wounds within individuals. Model discrimination was assessed with the use of Akaike's Information Criterion values. HbA1c

was expressed per 1% point, for clinical interpretability. Inferences were the same when we log transformed HbA1c to make the variable more normally distributed, so HbA1c was left untransformed for clinical interpretability. Variables of interest included age, gender, pulse, systolic and diastolic blood pressures, body mass index, HbA1c, peripheral neuropathy, peripheral artery disease, smoking, alcoholism, hemoglobin, ESR, RBS wound number, wound location, and white blood cell count. We tested for trends across the medians of HbA1c categories. To assess the possibility of differential healing rates between neuropathic foot wounds, and other wounds in diabetic patients (mainly large surgical non-healing wounds), we performed a sensitivity analysis stratified by wound on weight-bearing portions of the foot in individuals with documented peripheral neuropathy. In addition, we performed a sensitivity analysis stratified by peripheral artery disease status. All reported P-values are two-sided and $P < 0.001$ was considered statistically significant. Analyses were performed using SPSS version 16.

The study was approved by the institutional ethics committee of the hospital.

RESULTS

The demographic and clinical characteristics of the 101 individuals at the time of admission were shown both overall and stratified by HbA1c categories in Table 1. In the entire sample group, the mean age was 59 years, mean HbA1c was 8.6 gm%. Age distribution against Hba1c categories is shown in Figure1.

The mean base line area was 4.872 cm^2, and the mean change in area per day was 0.081 cm^2 per day. Despite being the smallest size (3.902 ± 0.198 cm^2) at baseline, wounds at the highest level of HbA1c (>8 gm%) healed at the slowest rate (0.036 ± 0.002 cm^2 per day). Conversely, ulcers with larger baseline size in the lowest(<7 gm%)(5.305 ± 0.387cm^2) and intermediate(7-8 gm%)(5.783 ± 0.388 cm^2) HbA1c categories both had greater healing rates than did those with smaller baseline size in the highest HbA1c category. Although there trended to be an inverse association between baseline wound size and healing rate, statistical significance was not reached after adjusting for HbA1c and other variables in our model ($P = 0.213$). Association of Hba1c with wound area healing rate (log CAREA) in diabetic cutaneous wounds is shown in Figure 2. Depiction of wound healing pattern in two diabetic individuals is shown in Figure 3. Figure 4 is a Scatter plot depicting a negative correlation of HbA1c and change in wound area per day (log CAREA) and Figure 5 is error plotting showing significance of log CAREA against HbA1c group.

51.5% of our entire study group comes from an urban background, we observed a significant increase (43%) [Table 2] in subjects from rural community who are having their hba1c >8 gm%.

The HbA1c values among different occupations (skilled workers, unskilled workers, unemployed) is explained in Table 3. 45.5% of our entire study group comprised of unskilled unemployed subjects, and in that group around 60% had an HbA1c value >8 gm%.

62.4% of our study group were having smoking addiction in the past (had smoked cigarette/bidis for more than 10 years) of which 28% of the subjects are current smokers. Even though we got an inverse correlation while plotting adjusted beta coefficients and 95% CI for the relationship between change in wound area per day and current smoking status a statistical significant relation was not obtained ($P = 0.859$) [Table 4].

Table 5 shows 60% of our study group having alcoholism as addiction of which 23.8% were frequent alcoholics.

Table 1: Clinical characteristics of all participants at the time of admission stratified by HbA1c

Patient variable	HBA1C group						Total	
	≤7		7–8		>8			
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Age	55.667	2.250	61.174	2.025	61.385	1.317	59.13	1.131
BMI	26.406	0.125	27.001	0.155	27.292	0.128	26.88366	.086300
HBA1C	6.849	0.033	7.791	0.059	10.923	0.115	8.637	.1909
SYSTBP	129.641	1.434	139.261	5.842	145.744	1.605	138.05	1.701
DIABP	73.692	0.803	80.087	0.800	82.256	1.034	78.46	.658
PULSE	73.872	0.394	75.130	0.791	78.846	0.810	76.08	.448
WBC	8383.974	227.656	8213.913	470.224	8786.769	196.103	8500.78	157.737
Hb	11.874	0.175	11.178	0.239	11.372	0.145	11.522	.1063
ESR	6.051	0.913	7.261	1.421	5.923	0.752	6.28	.556
PLATC	2.500	0.078	2.719	0.144	2.425	0.082	2.5210	.05520
WOUNDNO	2.128	0.098	2.304	0.183	2.385	0.108	2.27	.070
RBS	155.842	5.824	232.391	7.897	174.974	7.969	180.91	5.120

Adjusted beta coefficients and 95% CI for the relationship between change in wound area per day and current frequent alcoholic status didn't show a statistical significant association ($P = 0.24$).

The most common location for wounds in our study population was the lower extremity, with 42% of wounds occurring on the leg or ankle and 42.5% of wounds occurring on the foot. The remainder of the wounds occurred on the buttocks (5.5%), the abdomen or chest (3%), the arms(3.5%), the groin (3.0%), and the back (0.5%) [Figure 6].

69% of the total individuals were males, and majority of the patients belong to Christian and muslim community.

There was a mean of 2.3 wounds per individual (232 wounds in total). We divided the wounds into two broad categories of foot wounds with documented neuropathy ($n = 155$) that are classic diabetic wounds versus chronic wounds elsewhere ($n = 77$), which are predominately surgical wounds that have failed to heal. Participants who are having neuropathy and those who are not having neuropathy differed by HbA1c, baseline wound size and area and change in wound size per day.

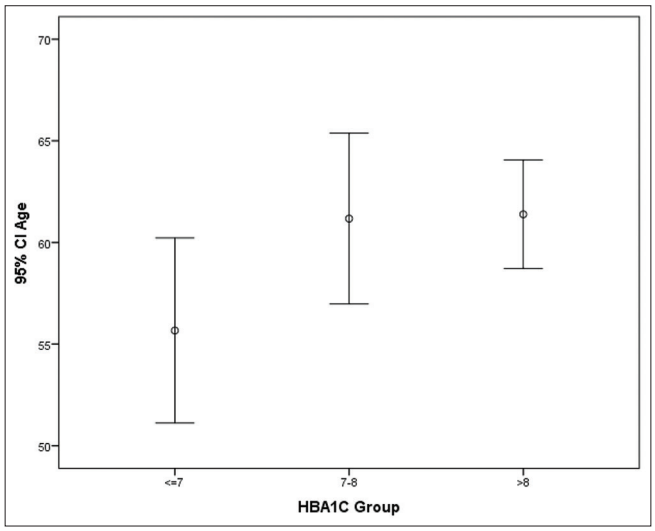

Figure 1: Age distribution

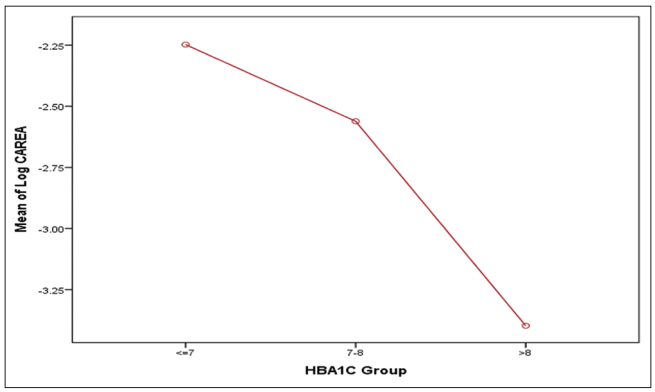

Figure 2: Association of Hba1c with wound area healing rate (log CAREA) in diabetic cutaneous wounds

Mean BMI of our study group was 26.8 which was in the over weight category . Adjusted beta coefficients and 95% CI for the relationship between change in wound area per day and BMI showed there is no statistical significance ($P = 0.664$).

The mean systolic and diastolic BP of our study group were 138 mm of Hg and 78 mm of Hg respectively. Adjusted beta coefficients and 95% CI for the relationship between change in wound area per day and blood pressure values (both systolic and diastolic) showed a borderline significance for diastolic BP ($P = 0.011$) and no statistical significance for systolic BP($P = 0.901$). P value which we assigned in our study for statistical significance being <0.001.

Mean ESR in our study group was 6 mm. Adjusted beta coefficients and 95% CI for the relationship between

Table 2: Residential distribution

Residence	HBA1C group				
	≤7	7-8	>8	Chi-square	*P*-value
Rural	16	12	21	1.443	0.486
Urban	23	11	18		
Total	39	23	39		

Table 3: Occupational distribution

Occupation	HBA1C group				
	≤7	7-8	>8	Chi-square	*P*-value
Unemployed	11	8	6	7.063	0.133
Skilled	15	5	10		
Unskilled	13	10	23		
Total	39	23	39		

Table 4: Distribution of smoking status

Smoking	HBA1C group				
	≤7	7–8	>8	Chi-square	*P*-value
Never	15	11	12	6.162	0.187
Former	16	8	11		
Current	8	4	16		
Total	39	23	39		

Table 5: Distribution of alcoholism status

Alcoholism	HBA1C group				
	≤7	7–8	>8	Chi-square	*P*-value
Never	12	11	17	3.785	0.436
Occasional	18	8	11		
Frequent	9	4	11		
Total	39	23	39		

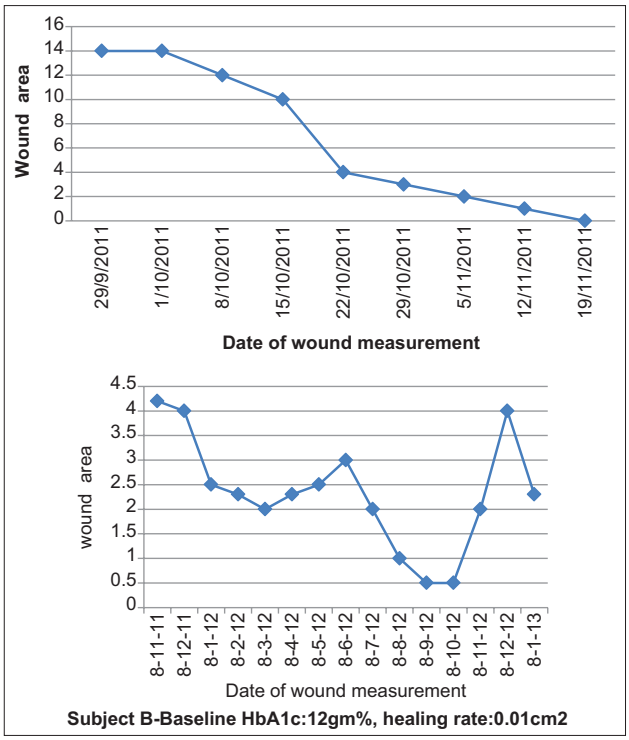

Figure 3: Depiction of wound healing pattern in two diabetic individuals

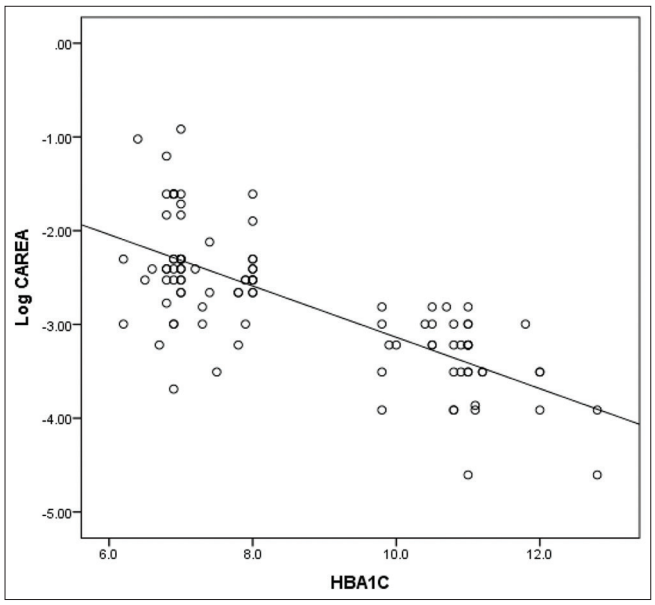

Figure 4: Scatter plot depicting a negative correlation of hba1c and change in wound area per day (log CAREA)

change in wound area per day and ESR showed a statistically insignificant association ($P = 0.220$).

Our results from multiple linear regression models (adjusted beta coefficients and 95% confidence intervals for the relationship between change in wound area per day and other clinical variables) showed HbA1c to have an inverse correlation with wound area healing rate. For each 1.0%

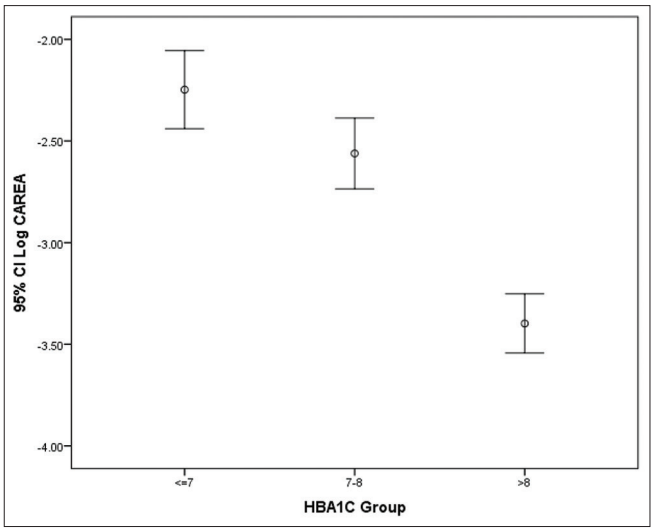

Figure 5: Error plotting showing significance

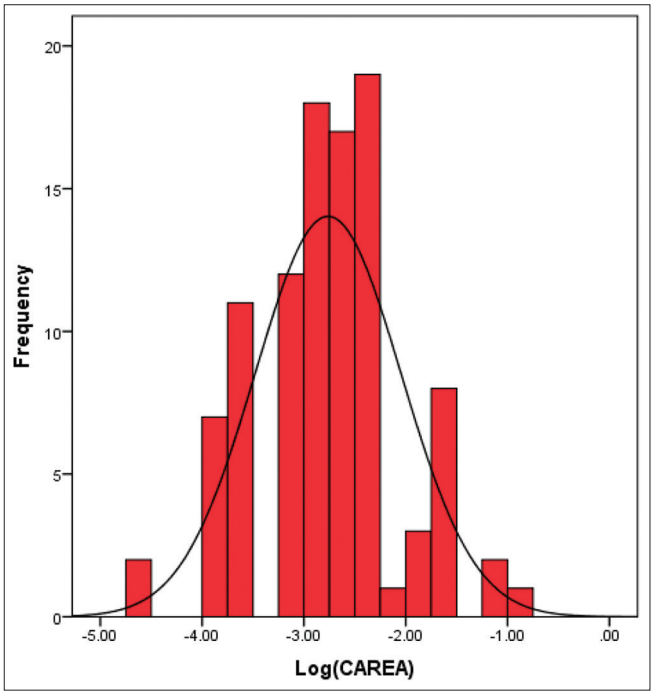

Figure 6: Frequency distribution plot of our study

point increase in HbA1c, the wound-area healing rate per day decreased by 0.219 cm^2 (95% confidence interval (95% CI): -0.290, -0.148, $P = 0.0001$). Age, sex, Hemoglobin, ESR, smoking, Alcoholism, body mass index, wound number, systolic blood pressure, pulse, white blood cell count, peripheral artery disease, and neuropathy status showed no statistically significant association. Diastolic blood pressure was also inversely associated with wound-area healing rate per day ,but the association was of borderline statistical significance ($P = 0.011$) (P value assigned in our study is $P < 0.001$.) Therefore, the only characteristically significant association with wound-area healing rate per day was for HbA1c. Adjusted beta –coefficients and 95%

Table 6: Adjusted beta-coefficients and 95% confidence intervals for the relationship between change in wound area per day and other variables

Patient variable	B	Std. Error	*t*	*P*-value	Lower bound	Upper bound
Constant	–0.668	2.103	–0.318	0.751	–4.851	3.514
Age	–0.003	0.005	–0.657	0.513	–0.013	0.006
BMI	0.027	0.062	0.436	0.664	–0.097	0.151
HBA1C	–0.219	0.036	–6.130	0.000	–0.290	–0.148
SYSTBP	0.000	0.003	–0.124	0.901	–0.007	0.006
DIABP	–0.028	0.011	–2.612	0.011	–0.049	–0.007
PULSE	0.013	0.014	0.887	0.378	–0.016	0.041
WBC	0.000	0.000	–1.279	0.205	0.000	0.000
Hb	0.067	0.058	1.157	0.251	–0.048	0.182
ESR	0.012	0.010	1.235	0.220	–0.007	0.031
WOUNDNO	–0.057	0.072	–0.801	0.426	–0.200	0.085
PAD	–0.199	0.124	–1.607	0.112	–0.444	0.047
RBS	0.002	0.001	1.541	0.127	0.000	0.004
Current Smoker	–0.022	0.122	–0.178	0.859	–0.265	0.221
Alcohol _Frequent	0.149	0.125	1.184	0.240	–0.101	0.398
NEUR	–0.158	0.117	–1.349	0.181	–0.390	0.075

Table 7: Association of Hba1c with wound area healing rate (log CAREA) in diabetic cutaneous wounds

Log CAREA	*n*	Mean	Std. deviation	Std. Error	95% Confidence interval for mean		Minimum	Maximum
					Lower bound	Upper bound		
≤7	39	–2.2477	0.59196	0.09479	–2.4396	–2.0558	–3.69	–0.92
7–8	23	–2.5614	0.40268	0.08396	–2.7355	–2.3872	–3.51	–1.61
>8	39	–3.3979	0.44847	0.07181	–3.5433	–3.2525	–4.61	–2.81
Total	101	–2.7633	0.71788	0.07143	–2.9050	–2.6215	–4.61	–0.92

Table 8: ANOVA testing

Log CAREA	Sum of Squares	df	Mean Square	F	Sig.
Between groups	27.010	2	13.505	53.961	0.000
Within groups	24.526	98	0.250		

confidence intervals for the relationship between change in wound area per day and other variables is shown in Table 6. Association of Hba1c with wound healing rate (log CAREA) in diabetic cutaneous wounds is shown in Table 7. Results of ANOVA testing is shown in Table 8.

Frequency distribution plot of our study showed a normal distribution without skewing of data and we obtained a bell shaped curve. Observed Power of our study being 1.000. Power of study is explained in Table 9.

In our study group 67% had peripheral neuropathy at the time of first examination [Table 10]. In HbA1c >8 gm% category 72% had neuropathy at admission. However, 32% of our study group had features of peripheral arterial disease at the time of admission [Table 11]. Our results from multiple linear regression models for the change in wound area per day shows no statistical significance for peripheral neuropathy ($P = 0.181$) and peripheral arterial disease status ($P = 0.112$). Association of peripheral arterial disease with change in wound area per day (log CAREA) is

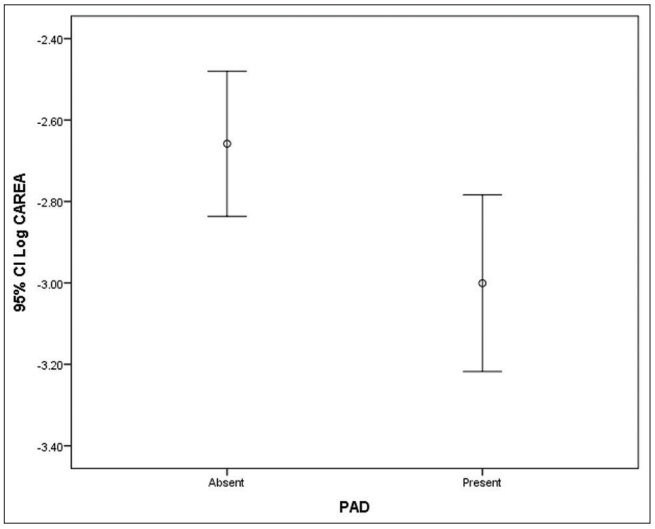

Figure 7: Association of peripheral arterial disease with change in wound area per day (log CAREA)

shown in Figure 7 and Table 12. Table 13 shows association of peripheral arterial disease with change in wound area per day. Assessment of differential healing rate by performing sensitivity analysis stratified by peripheral arterial disease status is shown in Table 14.

To study the possibility of differential healing rates between neuropathic foot wounds that are predominantly diabetic wounds versus wounds in other locations, we performed

Table 9: Power of our study

Dependent variable: Log CAREA			Mean square	F	Sig.	Noncent. parameter	Observed power[b]
Source	Type III sum of squares	df					
Corrected model	27.010[a]	2	13.505	53.961	0.000	107.923	1.000
Intercept	710.785	1	710.785	2840.108	0.000	2840.108	1.000
HBA1C1	27.010	2	13.505	53.961	0.000	107.923	1.000
Error	24.526	98	0.250				
Total	822.735	101					
Corrected total	51.536	100					

Table 10: Distribution of neuropathy status

Neuropathy	HBA1C group				
	≤7	7–8	>8	Chi-square	*P*-value
Absent	15	8	10	1.517	0.468
Present	24	15	29		
Total	39	23	39		

Table 11: Distribution of peripheral arterial disease status

PAD	HBA1C group				
	≤7	7–8	>8	Chi-square	*P*-value
Absent	28	17	25	0.839	0.657
Present	11	6	14		
Total	39	23	39		

Table 12: Association of peripheral arterial disease with change in wound area per day (log CAREA)

Dependent variable	PAD	*n*	Mean	Std. Deviation	Std. Error Mean
Ln_CAREA	Absent	70	–2.6581	0.74731	0.08932
	Present	31	–3.0008	0.59098	0.10614

a sensitivity analysis stratified by wound location and documented neuropathy. For neuropathic foot wounds, each 1.0% point increase in HbA1c was associated with a decrease in wound-area healing rate of -0.306 cm^2 per day ($P = 0.003$). For all other wound locations, each 1.0% point increase in HbA1c was associated with a decrease of -0.261 cm^2 per day ($P = 0.022$). Documented peripheral neuropathy alone was not significantly associated with healing rates, but when combined with HbA1c they are found to be statistically significant. Assessment of differential healing rate by performing sensitivity analysis stratified by neuropathy status is shown in Figure 8 and Table 15. Table 16 shows association of neuropathy status with change in wound area per day.

A sensitivity analysis was also performed stratified by peripheral artery disease status. In participants without peripheral artery disease, HbA1c was not significantly

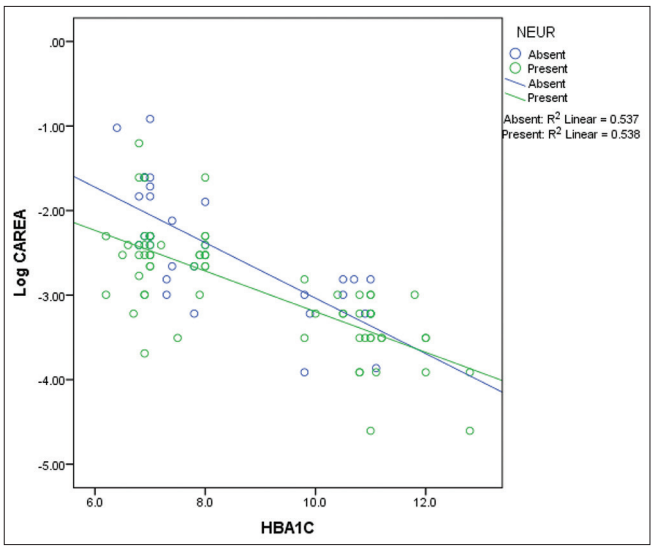

Figure 8: Assessment of differential healing rate by performing sensitivity analysis stratified by neuropathy status

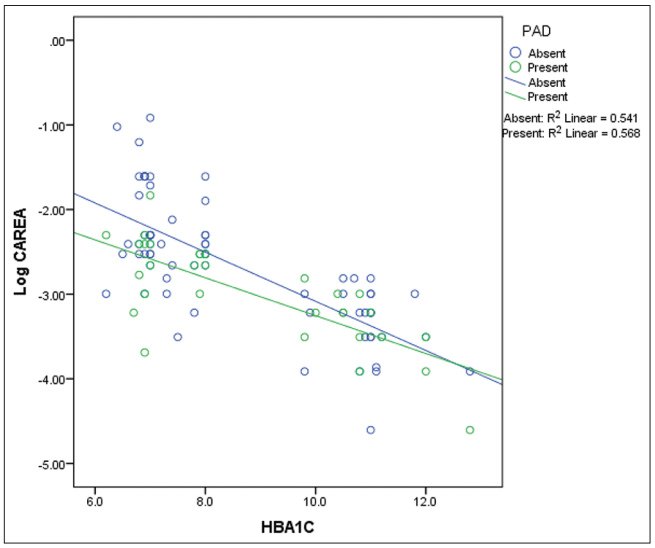

Figure 9: Assessment of differential healing rate by performing sensitivity analysis stratified by peripheral arterial disease status

related to wound-healing rate ($P = 0.026$). In participants with peripheral artery disease, each 1.0% point increase in HbA1c was associated with a decrease of -0.252 cm^2 per day ($P = 0.017$) thereby showing an improvement

Table 13: Association of peripheral arterial disease with change in wound area per day

Ln_CAREA	t	df	*P*-value	Mean difference	Std. error difference	95% Confidence interval of the difference	
						Lower	Upper
Equal variances assumed	2.258	99	0.026	0.34270	0.15180	0.04150	0.64390
Equal variances not assumed	2.470	71.865	0.016	0.34270	0.13872	0.06615	0.61925

Table 14: Assessment of differential healing rate by performing sensitivity analysis stratified by peripheral arterial disease status

Patient variable	B	Std. Error	t	Sig.	Lower bound	Upper bound
Constant	–0.364	0.222	–1.640	0.104	–0.804	0.076
HBA1C	–0.269	0.025	–10.709	0.000	–0.319	–0.219
PAD	–0.252	0.104	–2.423	0.017	–0.458	–0.046

in statistical significance when combined with HbA1c. Assessment of differential healing rate by performing sensitivity analysis stratified by peripheral arterial disease status is shown in Figure 9.

DISCUSSION

According to our study there is definite association between wound healing and HbA1c values. The mean base line area was 4.872 cm^2, and the mean change in area per day was 0.081 cm^2 per day. Despite being the smallest size (3.902 ± 0.198 cm^2) at baseline, wounds at the highest level of HbA1c (>8 gm%) healed at the slowest rate (0.036 ± 0.002 cm^2 per day) .Conversely, ulcers with larger baseline size in the lowest (<7 gm%)(5.305 ± 0.387 cm^2) and intermediate(7-8 gm%) (5.783 ± 0.388 cm^2) HbA1c categories both had greater healing rates than did those with smaller baseline size in the highest HbA1c category. Although there trended to be an inverse association between baseline wound size and healing rate, statistical significance was not reached after adjusting for HbA1c and other variables in our model ($P = 0.213$).

Subjects from rural community who are having their hba1c >8 gm%,which in turn shows a poor glycemic control and lack of diabetic education among subjects hailing from rural background. Strategies should focus on patient education with emphasis on lifestyle modification and compliance with medical therapy.

62.4% of our study group were having smoking addiction in the past (had smoked cigarette/bidis for more than 10 years) of which 28% of the subjects are current smokers. Even though we got an inverse correlation while plotting adjusted beta coefficients and 95% CI for the relationship between change in wound area per day and current smoking status a statistical significant relation was not obtained ($P = 0.859$) [Table 4]. The documented effects of the toxic constituents of cigarette smoke-particularly nicotine, carbon monoxide, and hydrogen cyanide-suggest potential mechanisms by which smoking may undermine expeditious wound repair. Nicotine is a vasoconstrictor that reduces nutritional blood flow to the skin, resulting in tissue ischemia and impaired healing of injured tissue. Nicotine also increases platelet adhesiveness, raising the risk of thrombotic microvascular occlusion and tissue ischemia. In addition, proliferation of red blood cells, fibroblasts, and macrophages is reduced by nicotine. Carbon monoxide diminishes oxygen transport and metabolism, whereas hydrogen cyanide inhibits the enzyme systems necessary for oxidative metabolism and oxygen transport at the cellular level. Compared with non-smokers, smokers have a higher incidence of unsatisfactory healing after facelift surgery, as well as a greater degree of complications following breast surgery. Smokers should be advised to stop smoking prior to elective surgery or when recovering from wounds resulting from trauma, disease or emergent surgery. Adjusted beta coefficients and 95% CI for the relationship between change in wound area per day and current frequent alcoholic status didn't show a statistical significant association ($P = 0.24$).

Our results from multiple linear regression models for the change in wound area per day shows no statistical significance for peripheral neuropathy ($P = 0.181$) and peripheral arterial disease status ($P = 0.112$). These results are consistant with the study of Andrea L *et al*[14] in which they also got a statistical insignificant association for peripheral neuropathy and peripheral arterial disease to change in wound area per day.

The mean base line area was 4.872 cm^2, and the mean change in area per day was 0.081 cm^2 per day. Even the smallest size at baseline, wounds at the highest level of HbA1c (>8 gm%) healed at the slowest rate .Conversely, ulcers with larger baseline size in the lowest (<7 gm%) and intermediate (7-8 gm%) HbA1c categories both had greater healing rates than did those with smaller baseline size in the highest HbA1c category. Although there trended to be an inverse association between baseline wound size and healing rate, statistical significance was not reached after adjusting for HbA1c and other variables in our model ($P = 0.213$).

Table 15: Assessment of differential healing rate by performing sensitivity analysis stratified by neuropathy status

Dependent variable	NEUR	*n*	Mean	Std. Deviation	Std. Error mean	*t*	*P*-value
Ln_CAREA	Present	68	–2.8767	0.70537	0.08554	2.328	0.022
	Absent	33	–2.5296	0.69652	0.12125		

Table 16: Association of neuropathy status with change in wound area per day

Variable	B	Std. Error	t	Sig.
Constant	–0.301	0.22	–1.367	0.175
HBA1C	–0.261	0.025	–10.445	0
NEUR	–0.306	0.102	–3.006	0.003

45.5% of our entire study group comprised of unskilled unemployed subjects, and in that group around 60% had an HbA1c value >8 gm%. Poor glycemic control is more seen in people who are less educated and skilled and in whom diabetic awareness will be scanty.

CONCLUSION

From our entire study conducted at MOSC Medical College, Kolenchery, its been evident that only elevated HbA1c was significantly independently associated with wound-area healing rate. This relationship was stronger for wounds located on the foot, which was insensate neuropathic wounds (67% of all wounds). When our analysis was restricted to these foot wounds, the association with HbA1c remained significant, but when restricted to wounds at all other locations, the association was no longer significant statistically. The relationship was also stronger among participants with peripheral artery disease. Our results suggest that HbA1c is an important clinical predictor of wound-healing rate, particularly in those with neuropathic foot wounds and in those with peripheral artery disease.

REFERENCES

1. World Health Organization. Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks. Geneva: World Health Organization; 2009.
2. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, *et al*. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160-7.
3. Edelman D, Olsen MK, Dudley TK, Harris AC, Oddone EZ. Utility of hemoglobin A1c in predicting diabetes risk. J Gen Intern Med 2004;19:1175-80.
4. Sato KK, Hayashi T, Harita N, Yoneda T, Nakamura Y, Endo G, *et al*. Combined measurement of fasting plasma glucose and A1C is effective for the prediction of Type 2 diabetes: The Kansai Healthcare Study. Diabetes Care 2009;32:644-6.
5. Galkowska H, Wojewodzka U, Olszewski WL. Chemokines, cytokines, and growth factors in keratinocytes and dermal endothelial cells in the margin of chronic diabetic foot ulcers. Wound Repair Regen 2006;14:558-65.
6. Goren I, Müller E, Pfeilschifter J, Frank S. Severely impaired insulin signaling in chronic wounds of diabetic ob/ob mice: A potential role of tumor necrosis factor-alpha. Am J Pathol 2006;168:765-77.
7. Falanga V. Wound healing and its impairment in the diabetic foot. Lancet 2005;366:1736-43.
8. Galiano RD, Tepper OM, Pelo CR, Bhatt KA, Callaghan M, Bastidas N, *et al*. Topical vascular endothelial growth factor accelerates diabetic wound healing through increased angiogenesis and by mobilizing and recruiting bone marrow-derived cells. Am J Pathol 2004;164:1935-47.
9. Maruyama K, Asai J, Ii M, Thorne T, Losordo DW, D'Amore PA. Decreased macrophage number and activation lead to reduced lymphatic vessel formation and contribute to impaired diabetic wound healing. Am J Pathol 2007;170:1178-91.
10. Gibran NS, Jang YC, Isik FF, Greenhalgh DG, Muffley LA, Underwood RA, *et al*. Diminished neuropeptide levels contribute to the impaired cutaneous healing response associated with diabetes mellitus. J Surg Res 2002;108:122-8.
11. Lobmann R, Ambrosch A, Schultz G, Waldmann K, Schiweck S, Lehnert H. Expression of matrix-metalloproteinases and their inhibitors in the wounds of diabetic and non-diabetic patients. Diabetologia 2002;45:1011-6.
12. Gosain A, DiPietro LA. Aging and wound healing. World J Surg 2004;28:321-6.
13. Mathieu D, Linke JC, Wattel F. Non-healing wounds. In: Mathieu DE, editor. Handbook on Hyperbaric Medicine. Netherlands: Springer; 2006.
14. Christman AL, Selvin E, Margolis DJ, Lazarus GS, Garza LA. Hemoglobin A1c predicts healing rate in diabetic wounds. J Invest Dermatol 2011;131:2121-7.

How to cite this article: Mathew AB, Isac M. Association of Hemoglobin-A1c with Healing in Diabetic Cutaneous Wound – A Prospective Study. Int J Sci Stud 2020;8(10):83-91.

Source of Support: Nil, **Conflicts of Interest:** None declared.