DOI: 10.7860/JCDR/2023/65875.18681

Original Article

Surgery Section

Association of Glycosylated Haemoglobin and Wound Healing in Diabetic Foot Ulcer: A Prospective Cohort Study

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ABSTRACT

Introduction: Diabetes Mellitus (DM) is a disease that, over time, can affect practically all organ systems in the body, including the skin and circulatory systems. An estimated 15% of all diabetic patients develop a foot ulcer in their lifetime. Although it is clear from the literature review that strict glycaemic control prevents complications, the relationship between Glycosylated Haemoglobin (HbA1c) value and wound healing in diabetic foot patients is less well-defined.

Aim: To determine the association between Glycosylated Haemoglobin (HbA1c) and wound healing rate in Diabetic Foot Ulcers (DFUs).

Materials and Methods: This prospective cohort study was conducted in the Department of General Surgery, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur, India, between August 2018 and July 2020. All patients between 18 and 70 years old, diagnosed with diabetic foot according to the World Health Organisation definition, and presenting with a lower limb ulcer were included as study participants. A detailed clinical history, examination of the patient, limb, and ulcer, and baseline HbA1c assessment were performed. The ulcer wound was graded and staged according to the University of Texas Wound classification system. All selected patients were divided into two groups. Group-A (n=15) comprised patients with HbA1c ≤7%, and Group-B (n=15) consisted of patients with HbA1c >7%. The primary outcome was the wound healing rate per day in relation to HbA1c levels at baseline and subsequent follow-up. The secondary outcomes were the demographic profile and predisposing factors affecting the healing of DFUs. Student's t-test (two-tailed, independent) and Chi-square/Fisher's-exact tests were performed for statistical analysis.

Results: The mean age of the subjects was 57.33±7.43 years in Group-A and 56.20±7.51 years in Group-B. There was a male preponderance in both Group-A (9) and Group-B (11). A total of 11 (36.7%) patients had a history of smoking, all of them being male. The mean healing rate per day was 0.09±0.02 cm^2/day in Group-A patients, which is higher compared to Group-B with 0.02±0.01 cm^2/day.

Conclusion: Strict glycaemic control is a mainstay in preventing the progression of foot ulcers to gangrene and, therefore, amputation. A lower baseline HbA1c at the presentation of DFU is indicative of a favourable outcome in terms of wound healing, with comprehensive treatment and follow-up efforts.

Keywords: Control, Healing, Hyperglycaemia, Risk factors, Wound

INTRODUCTION

Diabetes is a major public health problem that is approaching epidemic proportions globally. The prevalence of diabetes in India has risen to 8.9% in 2019 [1]. The northeastern states have a prevalence of 6.38% [2]. DM is a disease that, over time, can affect practically all organ systems in the body, including the skin and circulatory systems. An estimated 15% of all diabetic patients develop a foot ulcer in their lifetime [3,4].

Diabetic foot complications remain a major medical, social, and economic problem. Globally, DFU prevalence is 6.3%, with a male (4.5%) preponderance over females (3.5%) [5]. The primary underlying risk factors in the development of foot ulcers were neuropathy and ischaemia, the two common complications of diabetes, while hyperglycaemia contributes to delayed and impaired wound healing [6]. The majority of foot ulcers remain unrecognised at initial stages due to associated neuropathy and ischaemia, and then rapidly progress to a stage where limb salvage becomes difficult, leading to amputation. Consequently, this leads to repeated hospitalisation and economic burden on the patients [7]. In addition to impairment in the quality of life, DFUs are associated with reduced life expectancy, with 5-year mortality rates as high as 55% for ischaemic ulcers and 77% for those with a previous lower limb amputation [8].

Neuropathy in diabetic patients involves the motor, autonomic, and sensory components of the nervous system [9]. Due to the loss of sensation as a part of peripheral neuropathy, patients are unable to detect the trauma occurring in the affected area, which exacerbates the development of ulcers [10]. DFUs, if not managed properly, progress and lead to amputation of the affected foot. Routine monitoring of blood glucose levels is a hallmark of diabetic care with the goal of maintaining a normoglycaemic or near-normoglycaemic level of blood glucose control. The American Diabetes Association has included HbA1c in the diagnosis of DM, with a cut-off value of 6.5 [11]. HbA1c levels are considered as a gold standard measurement of patients' glycaemic control over the previous three months [12].

Many studies conducted by Christman AL et al., Akbar N and Bilal N., Zhao W et al., have shown a positive correlation between glycaemic control and improved wound healing and a lower incidence of limb amputation due to DFUs [13-15]. Although it is clear from the literature that strict glycaemic control prevents complications, the relationship between HbA1c value and wound healing in diabetic foot patients is less well-defined.

Thus, the present study was conducted with the objective to determine the association of HbA1c and wound healing in DFUs. Improving glycaemic control may improve ulcer outcomes. The authors' hypothesised that Group-A patients would have a much better outcome than Group-B patients in terms of wound healing. Therefore, the prediction of outcomes may be helpful for healthcare professionals in individualising and optimising the clinical assessment and management of patients, resulting in improved

health outcomes, improved quality of life, and fewer diabetes-related foot complications.

MATERIALS AND METHODS

This prospective cohort study was conducted in the Department of General Surgery, Regional Institute of Medical Sciences, Imphal, Manipur, India, between August 2018 and July 2020. The study was carried out after obtaining approval from the Research Ethics Board, Regional Institute of Medical Sciences, Imphal (A/206/REB-Comm(SP)/RIMS/2015/471/89/2018), and strict confidentiality and privacy were maintained.

Inclusion and Exclusion criteria: All patients older than 18 years and less than or equal to 70 years, diagnosed with diabetic foot according to the World Health Organisation definition [16], and presenting with a lower limb ulcer (DFUs grade 1, 2, and 3, University of Texas Wound classification) [17] and admitted to the surgical ward, RIMS, Imphal, were included in the study. Pregnant and lactating women, patients with S. Creatinine >2 mg/dL, patients with venous ulcers, peripheral arterial diseases, autoimmune and rheumatic diseases, and those unwilling to participate and follow the study protocol were excluded from the study.

Sample size calculation: The sample size was calculated based on the formula:

$$n=\frac{s_1^2+s_2^2}{e^2}$$

$$\approx 30$$

Where s_1=2.03 {Standard Deviation (SD) for HbA1c}

s_2=0.86 (Standard deviation for HbA1c)

e=L/2, L is the allowable error and equals to 1.7/2

(The values for the standard deviation were taken from a similar study conducted by Zubair M et al.,) [18]

Therefore, 30 patients were included in the study.

Study Procedure

Clinical examination included palpation of all peripheral pulses, calculation of Ankle Brachial Index (ABPI) using a handheld Doppler machine, and assessment of the ulcer for signs of infection (swelling, exudates, odour, tissue necrosis, crepitation, and pyrexia). Ulcer size was determined by multiplying the maximum and minimum dimensions and expressed in square centimetres. Complete haemogram, fasting and postprandial blood sugar levels, renal function tests, and baseline HbA1c assessment were done at the time of initial presentation.

All the selected patients were divided into two groups. One group comprised patients with DFU with HbA1c ≤7% (Group-A), and the other group comprised patients with DFU with HbA1c >7% (Group-B).

Each patient was managed as an inpatient in the ward and followed-up until the ulcer was healed or a minimum of 12 weeks, after which the work-up at the initial presentation was reassessed. During the follow-up period, the patient was under strict glycaemic control, ulcer debridement was done in necessary cases, antibiotic therapy started after pus culture and sensitivity report, and wound area assessment was done once a week in all cases.

The wound healing rate in cm^2/day was calculated using the formula:

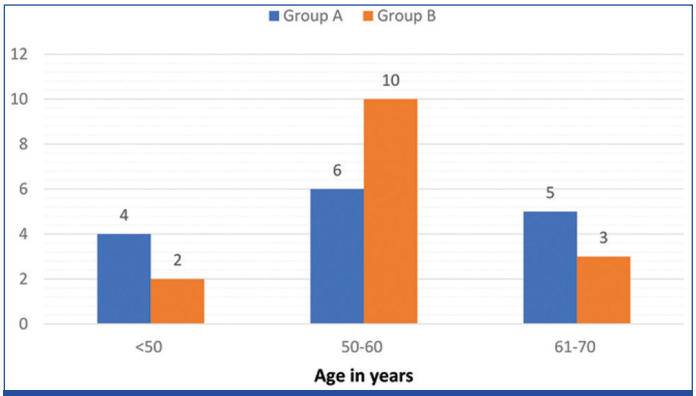
$$=\frac{\text{Wound area at visit 1-Wound area at subsequent visit}}{\text{No. of days between the two visits}}$$

STATISTICAL ANALYSIS

Descriptive and inferential statistical analyses have been carried out in the present study. Results on continuous measurements were presented as Mean±SD, and results on categorical measurements were presented as Number (%). Significance was assessed at a 5% level of significance. Chi-square/Fisher's-exact test was used to find the significance of study parameters on a categorical scale between two or more groups. Student's t-test was used for continuous variables. The statistical software, namely Statistical Package for Social Sciences (SPSS) 22.0 and R environment ver.3.2.2, were used for the analysis of the data.

RESULTS

The mean age of subjects in Group-A was 57.33±7.43 years, while in Group-B it was 56.20±7.51 years (p=0.681) [Table/Fig-1].



[Table/Fig-1]: Age distribution pattern in Diabetic Foot Ulcer (DFU).

The majority of patients (63.3%) had a long history of DM (more than 5 years) in general. When comparing the two groups, 8 (53.3%) patients in Group-A and 11 (73.3%) patients in Group-B had a long duration of diabetes before the development of foot ulcer (p-value of 0.26). The majority (53.3%) had grade I ulcer at presentation, while the remaining (46.7%) had grade II ulcer at presentation. Fisher exact test was used to analyse the data, and with a p-value of 0.715, both groups were evenly matched [Table/Fig-2].

Parameters	Group-A	Group-B	Total	p-value
History of smoking				
Yes	4 (26.7%)	7 (46.7%)	11 (36.7%)	0.256
No	11 (73.3%)	8 (53.3%)	19 (63.3%)	
Total	15 (100%)	15 (100%)	30 (100%)	
History of trauma present or not				
Yes	9 (60%)	11 (73.3%)	20 (66.7%)	0.439
No	6 (40%)	4 (26.7%)	10 (33.3%)	
Total	15 (100%)	15 (100%)	30 (100%)	
Duration of diabetes				
More than 5 years	8 (53.3%)	11 (73.3%)	19 (63.3%)	0.26
Less than 5 years	7 (46.7%)	4 (26.7%)	11 (36.7%)	
Total	15 (100%)	15 (100%)	30 (100%)	
Associated history of hypertension				
Present	8 (53.3%)	9 (60%)	17 (56.7%)	1
Not present	7 (46.7%)	6 (40%)	13 (43.3%)	
Total	15 (100%)	15 (100%)	30 (100%)	
Duration of ulcer in days				
<10	7 (46.7%)	11 (73.3%)	18 (60%)	0.242
10-15	8 (53.3%)	4 (26.7%)	12 (40%)	
Total	15 (100%)	15 (100%)	30 (100%)	
Grade of ulcer at presentation				
Grade-I	7 (46.7%)	9 (60%)	16 (53.3%)	0.715[#]
Grade-II	8 (53.3%)	6 (40%)	14 (46.7%)	
Grade-III	0 (0%)	0 (0%)	0 (0%)	
Total	15 (100%)	15 (100%)	30 (100%)	

Stage of ulcer at presentation				
Stage-A	1 (6.7%)	6 (40%)	7 (23.3%)	
Stage-B	13 (86.7%)	9 (60%)	22 (73.3%)	
Stage-C	00	00	00	0.715≠
Stage-D	1 (6.7%)	0 (0%)	1 (3.3%)	
Total	15 (100%)	15 (100%)	30 (100%)	

[Table/Fig-2]: Distribution of patients according to various factors.
≠: Fisher's-exact test was used. In rest chi-square test was used

The HbA1c value was reassessed after 12 weeks of holistic treatment in both study groups. There was a mean decrease of 0.260 in Group-A and a mean decrease of 1.747 in Group-B. With a p-value of <0.001, the difference was highly significant in Group-B [Table/Fig-3].

The mean ulcer area at presentation in Group-A was 9.59 (±2.28) cm^2, while in Group-B it was 10.52 (±2.32) cm^2. Student's t-test was used to compare the means, and with a p-value of 0.278, there was no statistically significant difference between the two groups [Table/Fig-3].

HbA1c%	At presentation	After 12 weeks	difference	t value	p-value
Group-A	6.49±0.49	6.23±0.23	0.260	3.060	0.008**
Group-B	10.24±1.71	8.49±1.00	1.747	5.838	<0.001**

[Table/Fig-3]: HbA1c at presentation and after 12 weeks.

The ulcer healing rate per day was calculated by considering the size of the wound on the first visit and subsequent visits, dividing the number of days between the two visits. Wound assessment was done once weekly, and the results showed that the mean healing rate per day was much higher (0.09±0.02 cm^2/day) in Group-A patients compared to Group-B (0.02±0.01 cm^2/day) patients. Student's t-test was used to compare the means, and with a p-value of <0.001, the difference was highly significant. This confirms authors' hypothesis that Group-A patients would have a much better outcome than Group-B patients in terms of wound healing [Table/Fig-4].

Variables	Group-A	Group-B	p-value
Ulcer area (cm^2)	9.59±2.28	10.52±2.32	0.278
Ulcer healing rate (cm^2/day)	0.09±0.02	0.02±0.01	<0.001**

[Table/Fig-4]: Table showing ulcer area at presentation and daily healing rate in both the group.
Student's t-test was used

DISCUSSION

The DFU was found to be more common in the 6th decade of life, with a mean age of 56.77±7.37 years, which is similar to the studies conducted by Kumar B et al., and Ravinthar A et al., where the mean age at presentation was 53.4±11.9 years and 55 years, respectively [19,20]. This comparable mean age may suggest certain time-dependent risk factors in the evolution and course of DFU disease that are common to diabetes in any environment. There was a male preponderance in the current study, which is consistent with the results obtained in studies conducted by Christman AL et al., Fesseha BK et al., and Vella L et al., [13,21,22].

In the current study, 36.7% of the patients presented with a history of smoking. Akbar N et al., and Ravinthar A et al., also concluded in their study that smoking has a poor prognosis in patients with foot ulcers [14,20]. Smoking affects the small blood vessels and slows down wound healing. Trauma has been established as one of the important causative factors for DFU [23]. In the study conducted by Kumar B et al., 70% of the patients had a preceding history of trauma.

Hypertension is a risk factor in the disease process of DFU [19]. Ogbuawa O et al., found hypertension to be an independent risk factor for macrovascular disease and subsequent foot ulceration [24]. Many other previously conducted studies have shown conflicting results, with some failing to show any association between blood pressure and DFUs [25-27]. In accordance with the haemodynamic hypothesis, early hyperaemia and capillary hypertension promote more severe late functional abnormalities with increasing duration of diabetes. These late functional abnormalities include loss of autoregulation and reduced hyperemic responses, which interact with the loss of neurogenic flow regulation, disturbed endothelial function, and abnormal rheology to produce the familiar clinical picture of the diabetic foot [28].

The mean HbA1c at presentation in the current study was 8.37 (±2.27), which is similar to the results reported by Fesseha BK et al., and Shashanka R and Palachandra A [21,29]. However, Kumar B et al., in their study reported a lower mean HbA1c of 6.6±0.7 [19].

Christman AL et al., and Ravinthar A et al., observed in their studies that patients with low HbA1c values had faster healing [13,20]. Many physiological factors are thought to contribute to poor wound healing in individuals with diabetic foot, including decreased or impaired keratinocyte and fibroblast migration and proliferation, cytokine and growth factor function, angiogenic response, and response to infection. Hyperglycaemia reduces keratinocyte migration and proliferation and contributes to oxidative stress through the production of reactive oxygen [20]. Markuson M et al., in their study, concluded that healing does occur regardless of HbA1c levels, but ulcers in individuals with higher HbA1c levels take significantly longer to heal [30]. However, in a long-term prospective clinic-based study of DFUs conducted by Fesseha BK et al., they did not observe any association between baseline HbA1c and wound healing [21]. Similarly, they concluded that changes in HbA1c measures during wound treatment were generally not associated with accelerated wound healing. However, in the studies by Zubair M et al., and Shashanka R and Palachandra A, it was concluded that slower wound healing is associated with increased HbA1c levels, and HbA1c can be considered as an independent biomarker in assessing wound healing in patients with DFU [18,29]. This is similar to the present study, which showed a strong significance (p-value of <0.001) between HbA1c levels and wound healing.

The present study can help predict the outcome of DFUs in association with HbA1c. A lower HbA1C at presentation and good control of hyperglycaemia would lead to a favourable outcome and better wound healing of the ulcer. A detailed study on the pathogenesis and the relationship of hyperglycaemia with wound healing would lead to a better understanding of this aspect. Studies on the demographic and geographic profiles of other parts of India in relation to the healing of DFUs would also be helpful in such research.

Limitation(s)

The follow-up period was short in the present study. Therefore, the findings cannot be generalised to the entire population as it was a single-centre study.

CONCLUSION(S)

The study demonstrates that HbA1c can be used as a predictive marker for wound healing in patients with DFU. Specifically, the baseline HbA1c value is more effective in predicting the outcome of DFU treatment, particularly in terms of wound healing. Therefore, a lower baseline HbA1c at the presentation of DFU indicates a favourable outcome in terms of wound healing, provided that there are directed efforts to optimise wound healing through comprehensive treatment and follow-up, especially by focusing on bringing diabetes under control to improve conditions for healing.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jun 09, 2023
- Manual Googling: Aug 30, 2023
- iThenticate Software: Sep 16, 2023 (15%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jun 07, 2023**
Date of Peer Review: **Aug 11, 2023**
Date of Acceptance: **Sep 20, 2023**
Date of Publishing: **Nov 01, 2023**