ORIGINAL ARTICLE

GLYCOSYLATED HEMOGLOBIN AS PREDICTOR FOR LOWER EXTREMITY AMPUTATION IN DIABETIC PATIENTS

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ABSTRACT

Background: About 10% of patients with diabetes mellitus present with diabetic foot ulcers. The objective of the study was to determine the predictive role of HbA1c level on progression to lower limb amputation in diabetic patients.

Material & Methods: This was a case-control study conducted between January, 2014 and December, 2015. We collected a matched-pair data for patients with diabetic foot ulcers with or without amputation. Thirty-five patients from each group were statistically analyzed to see the predictive role of HbA1c for amputation.

Results: The mean age of all patients included was 56.06 ±4.6 years with 30(42.9%) males and 40(57.1%) females with a ratio of 1:1.3. Mean HbA1c was found to be 8.85 ±1.4%. A univariate logistic regression showed HbA1c as a predictor of amputation, sensitivity was 60%, specificity was 71.4%, positive predictive value 64.3% and negative predictive value 67.6%. For each unit decrease in HbA1c, the odds of reduction of amputation, reduced by 2.5 times (OR 0.40, 95% CI 0.24 to 0.66, $p<0.001$). The area under the curve was estimated at 77.9% (95% CI 66.9 to 88.9). The cut-off value of HbA1c for the above stated sensitivity and specificity was at 9.15%.

Conclusion: HbA1c can be effectively used as a laboratory parameter in evaluating diabetic foot ulcer patients and it can be employed as a target to reduce the amputation risk.

KEY WORDS: Diabetic foot; Amputation; Glycosylated hemoglobin.

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INTRODUCTION

Peripheral arterial disease (PAD) is one of the sequelae in uncontrolled diabetic patients. Patients in our society are usually unaware of the consequences of poor diabetic control and foot hygiene.[1] About 10% of patients with diabetes mellitus (DM) present with one of the complications of diabetic foot ulcers (DFU).[1, 2] The commonest risk factors for DFUs are poor foot hygiene, poor diabetic control, neuropathy, vasculopathy and incidental injury to the foot. These ulcers are one of the commonest risk factors for admission of diabetic patients. Infective complications of DFUs lead to osteomyelitis of the lower limbs, generalised sepsis and death.[3,4]

In the general population, it is estimated that more than 80% of amputations are carried out in diabetic patients, the majority of which are a consequence of DFUs.[5,6] Lower limb amputation is regarded as a risky procedure to control localised infection sepsis.[7,8]

Glycosylated hemoglobin (HbA1c) has emerged as one of the potential modifiable risk factor which is observed to be frequently elevated in patients with DFUs. The knowledge base and evidence for this is, however, limited.[9-11]

Only a handful of studies have evaluated the predictive power of HbA1c in lower limb amputation of DFUs. Determining a cut-off level for the HbA1c proportion will help in classifying high risk and low risk patients with regard to lower limb amputation.

The objective of the study was to determine the predictive role of HbA1c level on progression to lower limb amputation in diabetic patients,

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MATERIAL AND METHODS

This was a case-control study from the Department of Endocrinology and Metabolic Diseases at Hayatabad Medical Complex, Peshawar, Pakistan. Patients data for the year 2014 and 2015 was obtained from record. We collected a matched-pair data for patients with diabetic foot ulcers with or without amputation. Thirty-five patients from each group were statistically analyzed to see the predictive role of HbA1c for amputation. demographic variables were gender and age. research variables were duration of diabetes in years, duration of ulcer in days, wagner grades (1-5) and HbA1c level.

A DFU was defined as any foot lesion with full-thickness breakage of skin distal to the malleoli ranging from grade 1 to grade 5 according to the Wagner classification. The decision to amputation was based on consultation with the general surgeon, orthopaedic surgeon and endocrinologist. Criteria for amputation considered severity of soft tissue infection, bone involvement and/or frank gangrene.

The data was analyzed in SPSS version 22.0. Patients demographics, clinical and laboratory parameters were presented in frequencies and percentages. Continuous variables were presented as mean±standard deviation. The ability of the HbA1c levels to predict the risk of Lower Extremity Amputation(LEA) was analyzed using the receiver operating characteristic curve with 95% confidence interval. Independent t-test and chi-square analysis were used to determine significant association and to determine any significant mean differences.

RESULTS

A total of 70 patients were included in the study; 35 with Lower Extremity Amputation (LEA) and 35 without LEA. The mean age of all patients was 56.06 ±4.6 years. The mean age of patients with LEA was 55.57 ±4.94 years and patients without LEA was 56.54 ±4.39 years (p=0.38). Regarding the gender 30 (42.9%) were males and 40 (57.1%) females in a ratio of 1:1.3. In the LEA group there were 16 (45.7%) males and 19 (54.3%) females (p=0.62).

The mean duration of diabetes was 10.9 ±6.4 years. The mean duration of diabetes with LEA was 9.66 ±5.96 and without LEA 12.31 ±6.69. The main duration of ulcer at the time of presentation was 21 ±6.5 days. The mean ulcer duration with LEA was 22.29 ±6.18 days and without LEA was 19.71 ±6.66 days. The median Wagner grade at presentation was 3 (deep ulcers with infection); where 11 (15.7%) patients presented in grade I (superficial ulcers), 16 (22.9%) grade II (deep ulcers with exposed tissues), 20 (28.6%) grade III (deep ulcers with infection), 18 (25.7%) grade IV (partial gangrene), and 5 (7.1%) patients presented in grade V (complete gangrene). The mean HbA1c was found to be 8.85 ±1.4%. The mean HbA1c with LEA was 9.437 ±1.36% and without LEA was 8.26 ±1.25%. (Table 1)

Univariate logistic regression was performed to ascertain the effects of HbA1c level on the likelihood that patients will undergo LEA after suffering from foot ulcer. The model was statistically significant, $\chi^2(4) = 18.19$, $p < 0.001$. The model effectively explained 32.6% (NagelkerkeR^2) of the variance in amputation rate and could classify correctly 66.2% cases of amputation. The sensitivity was 60.0%, specificity was 71.4%, positive predictive value was 64.3% and negative predictive value was 67.6%. For each unit decrease in HbA1c, the odds of reduction of amputation after having a foot ulcer, reduced by 2.5 times (OR: 0.40, 95% CI; 0.24 to 0.66, p<0.001). The area under the curve was estimated at 77.9% (95% CI; 66.9 to 88.9). The cut-off value of HbA1c

Table 1: Group-wise statistics for continuous variables.

Variable	Study Group	Number	Mean	SD	p value
Age (Years)	Amputation	35	55.57	4.94	0.38
	No Amputation	35	56.54	4.39	
Diabetes duration (Years)	Amputation	35	9.66	5.96	0.08
	No Amputation	35	12.31	6.69	
Ulcer duration (Days)	Amputation	35	22.29	6.18	0.09
	No Amputation	35	19.71	6.66	
Wagner grade	Amputation	35	3.80	0.67	<0.001
	No Amputation	35	1.91	0.74	
HbA1c	Amputation	35	9.437	1.36	<0.001
	No Amputation	35	8.260	1.25	

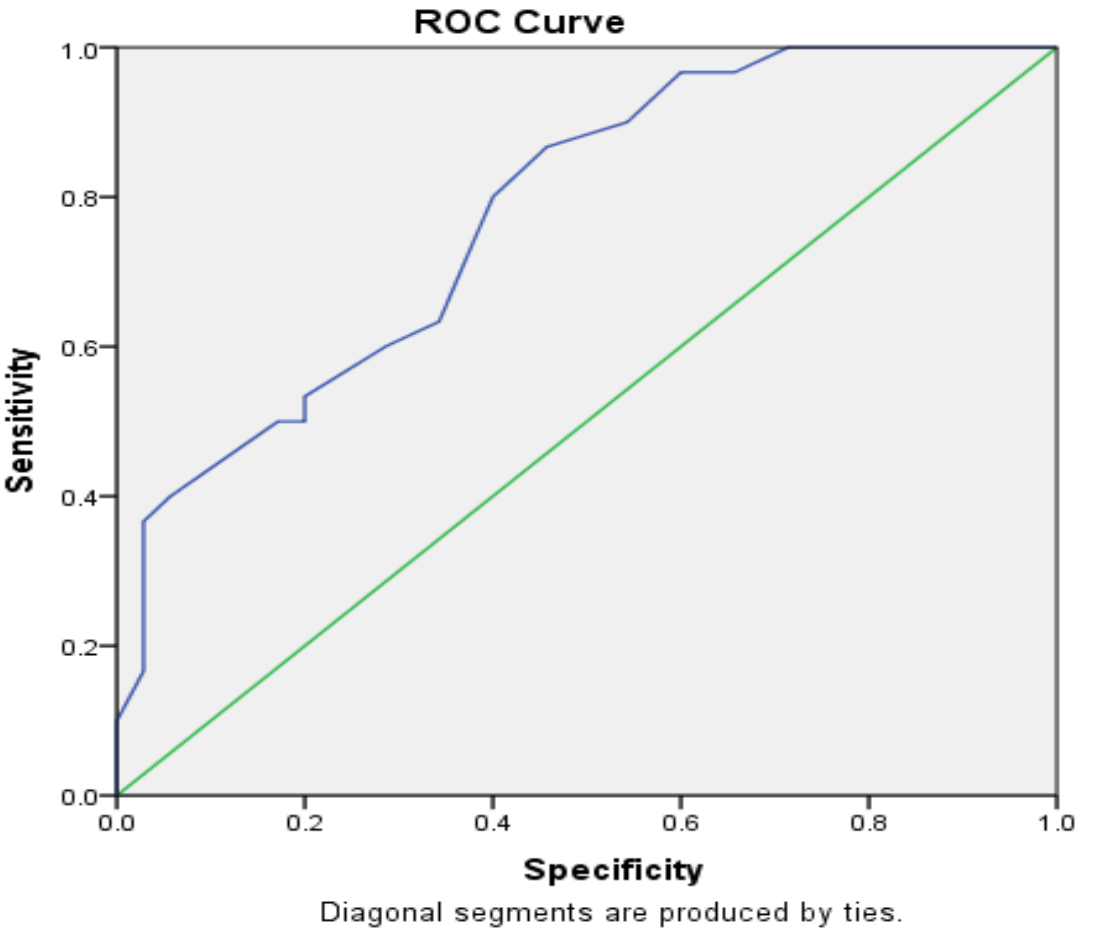

Figure 1: ROC curve showing area under the curve (77.9%, 95% CI 66.9 to 88.9, p<0.001), sensitivity (60%), and specificity (71.4%).

for the above stated sensitivity and specificity was at 9.15%.

DISCUSSION

Various predictors of progression from ulcer to osteomyelitis and gangrene have been identified over the previous years, among which peripheral vascular disease, neuropathy, hypertension and HbA1c are the major ones.[12] Identification of modifiable risk factors is the need of the moment to target a particular risk factor.[13, 14]

One of the well-known grading system for diabetic foot ulcers is Wagner classification.[15]Yesil et al[16] has reported the high predictive power of Wagner classification in terms of end results such as amputation or recovery. In this study we found that almost 90% of these ulcers were grade 4 or below. Only 5 cases were a completely gangrenous foot which is grade 5 and the best modality for its treatment is amputation. Pemayun et al[14] in their study has stated that there was a 10-fold risk of amputation when Wagner grade at admission was at least 4 as compared to the lower grades.Peripheral arterial disease is also a well-known risk factor for progression to lower limb gangrene and resultant amputation.[4] In our study, there was significant mean difference between Wagner grades for the two study groups.

Pemayun et al[14] has shown that HbA1c levels directly correlate with the risk of progression and negative likelihood of healing of DFUs. HbA1c elevation implies chronic elevation of blood glucose determining the incidence of neuropathy, peripheral vascular disease severity and lower immune function to counteract infective organisms.[17, 18]

Zhao et al[19] in their large prospective cohort study has shown in a mean 6.8 years of follow-up, the hazard ratio of lower limb amputation was closely associated with different grades of HbA1c (OR; 1, 1.73, 1.65, 1.96, 3.02 and 3.3 for HbA1c of <6%, 6-6.9, 7-7.9, 8-8.9, 9-9.9 and >10% respectively). Selvin et al[20] from Johns Hopkins, observed that the relative risk of admission related to peripheral vascular disease with tertile of HbA1c were 2.7 and 4.5 (p < 0.001). In a meta-analysis of 14 studies with a total of 94,460 patients, Al Adler and co-workers[21] have

shown that for each percentage increase in HbA1c levels, the relative risk of lower limb amputation increases 1.26 times (95% CI; 1.16-1.26) however the difference was not statistically significant. In our study, we observed that HbA1c reduction can significantly reduce the risk of progression of DFUs to amputation. Additionally, in ROC curve analysis, we observed that HbA1c levels above 9.15% can predict progression to amputation with moderate to strong sensitivity and specificity.

The mechanisms of chronic glycaemia as a cause of increased risk of lower limb amputation are well-known, namely, impaired wound healing, neuropathy and higher risk of infection.[22,23]

Further studies are required to validate the value of HbA1c levels as predictor of amputation in DFUs, as it will help bed-side monitoring of the risk and help diabetologists target it to reduce the risk for amputation.

CONCLUSION

HbA1c with a moderate sensitivity and specificity can be effectively used as a laboratory parameter in evaluating diabetic foot ulcer patients and it can be employed as a target to reduce the amputation risk in patients with diabetic foot ulcer.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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None declared.

AUTHORS' CONTRIBUTION

Conception and Design:	KU,
Data collection, analysis & interpretation:	KU, SK, MI
Manuscript writing:	SK, MI, TGK