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### Correlation of glycated hemoglobin in lower extremity amputation in diabetes mellitus

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#### Abstract

Lower extremity amputation (LEA) in patients with diabetes are associated with high postoperative mortality and a high rate of secondary amputation. Glycated Hemoglobin reflects average plasma glucose over the previous 8 to 12 weeks and is an excellent marker for disease control in diabetes. However, a direct link between the level of quality of diabetic care—as measured by hemoglobin A1c—and amputation risk has yet to be documented. In this retrospective time bound study study, we sought to examine the relationship between the use of hemoglobin A1c testing and amputation risk using a hospital database. Diabetic patients registered at our centre who have underwent lower extremity amputation, their HbA1c levels were collected from the Medical records department between 2016-19. A total of 150 patients were included in the study, majority of the cases showed elevated levels of glycated hemoglobin while only 1.3% had normal values. There was a significant association between patients undergoing LEA and their glycated hemoglobin levels ( $p<0.047$ ). LEA is associated with elevated levels of glycated hemoglobin and this makes it crucial to have regular follow up and close monitoring of patients to ensure high quality diabetic care.

**Keywords:** Diabetes mellitus; glycosylated hemoglobin; lower extremity amputation

#### Introduction

According to the International Diabetes federation (IDF), there are 463 million people around the world diagnosed with diabetes and this number is projected to increase to 578 million by 2030 [1]. India has an estimated 77 million diabetics and is second in place, following China, among top 10 countries with diabetic patients.

Demographic changes, social and economic development have contributed to increased number of cases in India [3]. Reduced exercise, sedentary lifestyle and unhealthy diet are also contributing factors for diabetes in the Indian subcontinent [4].

Hyperglycemic state through a complex process causes inflammation of arterial walls which eventually gives rise to atherosclerosis [5]. It can affect both the microvascular and macrovascular circulation which is then responsible for various complications such as retinopathy, nephropathy, neuropathy, coronary artery disease and peripheral vascular disease [6]. Fortunately, peripheral vascular disease as a result of diabetes mellitus is not common in India and according to CURES cohort [7], it accounts for 8.6% of cases with diabetes. One of the dreaded complications associated with PVD is lower extremity amputation (LEA) which in turn not only affects the quality of life but also causes a significant economic setback for the patient. An important blood marker to determine the degree of blood glucose control is glycated hemoglobin (HbA1c). A value less than 7% indicates good glyceic control while a value greater than 9% shows poor control [8]. There have been studies that showed patients with poor glyceic control have had LEA [9] but the exact relationship between HbA1c and LEA has not been clear.

Our study aims to determine if glycated hemoglobin is associated with lower extremity amputation in patients with diabetes. We also aimed to see if there was an association between glycated hemoglobin and repeated amputations in the same patient.

#### Materials and Methods

We retrospectively reviewed all patients that had undergone lower extremity amputation in the department of general surgery over a period of three years from 2016-19. Inclusion criteria included patients diagnosed with type 2 diabetes mellitus and had undergone LEA.

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Cases with type 1 diabetes mellitus and cases that underwent traumatic LEA were excluded from the study. Institutional ethics committee approval was taken prior to starting the study.

Following data was recorded: age, sex, type of surgical procedure, level of HbA1c, type of medication (insulin, oral antidiabetic drugs (OAD)) the patient was receiving and number of amputations the patient had undergone. Based on levels of HbA1c patients were classified into 3 groups: G1(<5.7%), G2(5.7-10%) and G3(>10%). Data was analyzed using SPSS version 25 for Windows. Categorical data were stated as percentages while continuous variables were described as mean

and standard deviation. Fisher exact test was used to assess association between the different variables. A p value of less than 0.05 were considered significant.

### Results

A total of 150 patients were included in the study. There were larger number of males (82.7%) as compared to females (17.3%). Most of the cases (37.3%) were found to be between 61 to 70 years of age. 53.6 % of patients in this group had HbA1c between 5.7% to 10% while 46.4% of patients had glycated hemoglobin greater than 10% (p=0.105) (Table 1).

**Table 1:** Patient Demographics

		Glycated Hemoglobin (HbA1c)					
		<5.7% (G1)		5.7-10% (G2)		>10% (G3)	
		No	%	No	%	No	%
Sex	Female	1	3.8	18	69.2	7	26.9%
	Male	1	0.8	65	52.4	58	46.8%
	Total	2	1.3	83	55.3	65	43.3%
Age (Years)	< 51	0	0	7	46.7	8	53.3%
	51 - 60	1	2	23	46	26	52.0%
	61 - 70	0	0	30	53.6	26	46.4%
	71 - 80	1	4.8	16	76.2	4	19.0%
	> 80	0	0	7	87.5	1	12.5%
	Total	2	1.3	83	55.3	65	43.3%

Majority of the cases in our study showed elevated levels of glycated hemoglobin while only 1.3% had normal values. Out of 150 cases, 93.3% underwent digital amputation while the remainder 6.7% underwent below knee amputation.

There was a significant association between patients undergoing LEA and their glycated hemoglobin levels ( $p<0.047$ ). 55.3% of LEA had a HbA1c between 5.7 -10%, 43.3% had a HbA1c greater than 10% and only 1.3% of cases had a glycated hemoglobin less than 5.7% (Table 2).

Majority of patients in our study were receiving insulin (69.3%) as compared to OAD (30.7%). 50% of patients with a glycated hemoglobin >10% were on insulin while 69.6% of patients with HbA1c between 5.7% to 10% were taking OAD ( $p= 0.044$ ) (Table 2).

11.3% of patients had undergone a second amputation and 10% of patients had undergone more than two amputations (Table 2). However, our study failed to show any association between number of amputations and HbA1c.

**Table 2:** Type of procedure, Medical Treatment Received and Number of Amputations

		Glycated Hemoglobin (HbA1c)					
		<5.7% (G1)		5.7-10% (G2)		>10% (G3)	
		No	%	No	%	No	%
Procedure	BKA	1	10.0	5	50	4	40
	Digital Amputation	1	0.7	78	55.7	61	43.6
	Total	2	1.3	83	55.3	65	43.3
Medical Treatment Received	Insulin	1	2.2	32	69.6	13	28.3
	OAD	2	1.3	83	55.3	65	43.3
	Total	2	1.7	65	55.1	51	43.2
Number of Amputations	One	2	1.7	65	55.1	51	43.2
	Two	0	0	9	52.9	8	47.1
	More than two	0	0	9	60	6	40
	Total	2	1.3	83	55.3	65	43.3

### Discussion

Ever since glycated hemoglobin was used in clinical laboratories in 1977, it has revolutionized the way diabetes is managed [10]. It became a diagnostic tool for diabetes in 2009 and was later incorporated into the World Health Organization (WHO) and American Diabetic Association (ADA) guidelines [11, 12].

Numerous studies has shown that reduction in levels of glycated hemoglobin can reduce the risk of microvascular complication associated with diabetes mellitus [13, 14]. In our study we found that patients with high levels of HbA1c had a strong association with LEA. Meta-analysis by Zhou *et al.* [15], found that LEA risk increased as the level of glycated hemoglobin increased. Various

other studies also showed that for every 1% rise in HbA1c the risk of LEA also increased [15, 16, 17]. Other than microvascular complications associated with elevated levels of HbA1c, diabetic patients are invariably prone to infection following minor injuries and this may also attribute to LEA.

Most of the patients in our study who had undergone LEA more than once had high levels of glycated hemoglobin. Although this was not found to be statistically significant, it still warrants further prospective studies and longer follow up of patients before an outcome can be established. Non the less, it still points to glycated hemoglobin being a marker for repeated amputations.

We also had a much larger number of patients undergoing digital amputation as compared to below knee amputation. The main factor that might have contributed to this is autonomic and sensory neuropathy associated with elevated glycated hemoglobin [18]. These patients with peripheral neuropathy have dry skin and also fail to recognize minor trauma to the foot and toes which eventually results in ulceration, infection and subsequently digital amputation [19].

As per the ADA [20], patient with glycated hemoglobin more than 10% should receive insulin. Since most of our patients had a glycated hemoglobin more than 10% this could be the reason for larger number of patients receiving insulin as compared to OAD. It is also strongly recommended that patient with type 2 diabetes in addition to their medication should partake in lifestyle modification that focuses on diet, weight reduction and physical activity [21].

One of the limitations of our study is that we did not take into consideration associated contributing factors such as smoking and dyslipidemia which could have also contributed to peripheral vascular disease and eventually LEA.

### Conclusion

Diabetes is responsible for a large number of diseases among which LEA produces a significant impact on the patients physical and psychological status. LEA is associated with elevated levels of glycated hemoglobin and this makes it crucial to have regular follow up and close monitoring of patients to ensure high quality diabetic care.

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