

ORIGINAL RESEARCH

Evaluation and Comparison of HbA1C Level in Diabetic Patients with and without Foot Ulcer: A Case control Study

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Abstract: **Background:** Diabetic foot is one of the long-term microvascular complications of diabetes mellitus (DM). The prevention of foot ulcers is the most effective way to reduce severe morbidity and mortality in patients with diabetes. Appropriate glycemic control is one of the most important preventive measures for diabetic foot ulcers. Glycosylated hemoglobin (HbA1C) is representative of long-term blood glucose levels over the prior three months. The present study evaluated the relationship between HbA1C levels and the development of diabetic foot ulcers. **Methods:** The present study was an analytical case-control study conducted in Ali-ibn-Abitaleb Hospital in Zahedan, Iran, in 2022. 130 patients comprising 65 DM patients with diabetic foot ulcers and 65 DM patients without foot ulcers were included in this study. Demographic and laboratory information was collected by the researcher using a checklist. The data were analyzed using SPSS software. **Results:** The average age of the control and case groups was 64.1 and 62.6 years, respectively. The results showed a significant relationship between the age of 60-70 years and the onset of diabetic foot ulcers. There was also a significant relationship between the female gender and the occurrence of diabetic foot. No significant relationship was observed between the duration of DM and the onset of diabetic foot. The results showed that 87.7% of the people in the control group had no previous history of diabetic foot. However, 76.9% of the people in the case group had a prior history of diabetic foot. There was a significant relationship between the previous history of the diabetic foot and its recurrence in diabetic patients. Regarding the serum level of HbA1C, 78.5% and 12.3% of patients in the case group had moderate (7-10%) and poor control (10-13%), respectively. 43.1%, 50.7%, and 6.2% of people in the control group had good, moderate, and poor control and in the multivariable model, only the previous history remained in the model, which showed that the probability of infection in people with a previous history is almost 24 times higher than in people without a previous history. **Conclusion:** The results indicate that age, female gender, history of diabetic foot, and high serum level of HbA1c had a significant relationship with diabetic foot. Since the serum level of HbA1c is an important indicator of long-term blood sugar control, it can possibly be used as a reliable factor to predict diabetic foot complications.

Keywords: Diabetes mellitus; Diabetic foot; Foot ulcer; Glycated hemoglobin

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1. Introduction

Diabetes mellitus (DM) is defined as a type of metabolic disorder characterized by increased blood glucose levels(1).

Blood glucose levels increase due to defects in insulin secretion and action. DM is the most common endocrine disorder and a chronic illness with many life-threatening complications. DM is one of the ten leading causes of death worldwide(2).

The World Health Organization estimated that the prevalence of DM will reach 380 million people worldwide in 2025. The Eastern Mediterranean and the Middle East regions have the highest prevalence of diabetes and mortality rates caused by DM. In Iran, there are 3.5 million patients with DM, which

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will reach 3.9 million people in 2030 and the general prevalence of DM in people aged 20-74 years, men and women is about 10.3%, 9.6%, and 11.1%, respectively(3). More than 5 million people in the United States are at risk of DM-related complications(4). The complications of DM are divided into macrovascular and microvascular complications. The microvascular complications include retinopathy, neuropathy, and nephropathy. The macrovascular complications include cardiovascular complications such as coronary artery disease, diabetic foot, atherosclerosis, hypertension, and hyperlipidemia (5). Diabetic foot is a partial or full-thickness skin lesion on the foot of a diabetic person, and most diabetic lower extremity amputations occur due to the diabetic foot(6). Approximately a quarter of patients with DM will experience diabetic foot ulcers in their lifetime. Peripheral artery disease (PAD), peripheral neuropathy, and trauma are associated with an increased risk of diabetic foot ulcers. Diabetic foot complications include infection, lower extremity amputation, and increased risk of mortality(7). Diabetic foot lesions include callus, fissure, edema, dry skin and blisters which occur in 43.7%, 26.5%, 1.8%, 10%, and 1.3% of diabetic foot patients respectively(8). Peripheral neuropathy plays a significant role in the development of the diabetic foot and increases the probability of its development by about 8-18%. The incidence of diabetic foot increases by 4.5% and 13.8% with neuropathy and peripheral vascular disease, respectively (9).

The most important diabetic foot ulcers prevention methods include glycemic control and patient education and training (10).

Glycosylated hemoglobin (HbA1C) is representative of long-term blood glucose levels over the prior 8-12 weeks. Unlike other indicators of glycemic control, HbA1C is not affected by daily blood sugar fluctuations. According to the updated statement from the American Diabetes Association (ADA) and the American Society of Endocrinologists, the HbA1c level of diabetic patients should be measured at least twice a year (11). HbA1c value of less than 7% shows good glycemic control, 7-10% shows moderate, and more than 10% shows poor control (7).

Several studies have been conducted on factors associated with a higher risk of developing diabetic foot ulcers and outcomes that may lead to amputation and death, and few previous articles have shown a possible relationship between HbA1C levels and the development of diabetic foot ulcers(12). Prevention is the first and most effective way of diabetic foot ulcers management (13). However, there is still no standard criterion to prevent the development and expansion of diabetic foot ulcers. This study aims to further strengthen the evidence and identify factors that can be employed in predicting the occurrence of diabetic foot ulcers.

2. Methods

2.1. Study design and patient characteristics

The present case-control study was conducted on 130 patients with type 2 DM over the age of 18 years at Ali-ibn-Abitaleb Hospital in Zahedan, Iran, during the six months from July to December 2022.

According to a similar study conducted in 2012(14), the sample size was determined to be 130 people. Patients were randomly selected and divided into case and control groups. The case group included 65 DM patients with diabetic foot ulcers, and the control group included 65 DM patients without diabetic foot ulcers. People in both groups had no history of smoking or hypertension. Patients with confounding variables were excluded in both groups. Confounding factors include Cushing's syndrome, glucagonoma, corticosteroid therapy, pheochromocytoma, pregnancy, splenectomy, which falsely increase the level of HbA1c, and chronic bleeding, chronic renal failure, and hemolytic anemia, which falsely decrease the level of HbA1c. Patients were subgrouped into three groups of good (HbA1C less than 7%), moderate (HbA1C between 7 to 10%), and poor (HbA1C more than 10%) glycemic control (7). Diabetic foot ulcers was classified using Wagner's grade (15). All eligible participants were assessed after obtaining written informed consent to participate in the study.

2.2. Sampling method and data collection

After obtaining permission from the Medical Ethics Committee and obtaining the patient's consent, all DM patients with diabetic foot ulcers referred to Ali -ibn-Abitaleb Hospital in out-patient clinic were included in the study. Demographic information such as age, gender, duration of diabetes, and laboratory information such as HbA1c serum level were recorded in the checklist by the researcher.

A 2-cc blood sample was collected from each patient to measure the serum level of HbA1C. 1 milliliter of lysing solution (pretreatment) was added to each vial, and centrifuged for 15 minutes. The vial was gently shaken to dissolve the contents, and HbA1C was measured after 2 hours.

2.3. Statistical analysis

Qualitative variables are presented as frequency, and quantitative variables are presented as mean and standard deviation. Chi-squared test was used to investigate the difference regarding each studied variable between case and control groups. Data were analyzed using SPSS software version 20. P-value <0.5% was considered statistically significant.

Table 1: Comparison of studied variable among case and control groups

Variable	Control group (n=65)	Case group (n=65)	P
Age (mean± SD)	64.1 ± 12.1	62.6 ± 7.1	
<20 years old	-	-	0.006
20-30 years old	2 (3.1)	-	
30-40 years old	5 (7.6)	7 (10.7)	
40-50 years old	13 (20)	10 (15.4)	
50-60 years old	15 (23.1)	13 (20)	
60-70 years old	24 (36.9)	30 (46.1)	
70-80 years old	4 (6.2)	5 (7.7)	
80-90 years old	2 (3.1)	-	
Gender			
Male	23 (35.4)	37 (43.1)	0.03
Female	42 (64.6)	28 (43.1)	
Duration of diabetes			
<10 years	20 (30.8)	5 (7.7)	0.06
10-20 years	25 (38.4)	25 (43.1)	
20-30 years	12 (18.4)	26 (40.0)	
30-40 years	5 (7.8)	4 (6.1)	
>40 years	3 (4.6)	2 (3.1)	
Previous history of diabetic foot ulcer			
No	57 (87.7)	15 (23.1)	0.001
Yes	8 (12.3)	50 (76.9)	
Serum level of HbA1C (%)			
<7 % (Good control)	28 (43.1)	6 (9.2)	0.02
7 to 10% (Moderate control)	33 (50.7)	51 (78.5)	
10.1 to 13% (Poor control)	12 (6.2)	8 (12.3)	

3. Results

We enrolled 287 patients in our study. One hundred fifty-seven cases were excluded. A total of 130 patients were included and analyzed (65 DM patients with the diabetic foot ulcers group and 65 DM without diabetic foot ulcers). The average age was 64/1 ± 12/1 years in the control group and 62/6 1/7 ± years in the case groups. 46.1% of patients in the case group and 36.9% of patients in the control group were between 60-70 years old. The results showed a significant relationship between the age group of between 60-70 years and the incidence of diabetic foot ulcers (P=0.006) (Table 1). 56.9% of the case group and 35.4 % of the control group were female, and there was a significant relationship between the female gender and diabetic foot (P=0.03) (Table 1). No significant relationship was observed between the duration of diabetes and the onset of diabetic foot (P=0.06) (Table 1). The results showed that 87.7% of the patients in the control group had no previous history of diabetic foot. However, 76.9% of the people in the case group had a previous history of diabetic foot. There was a significant relationship between the previous history of the diabetic foot and its recurrence in diabetic patients (P=0.001) (Table 1). Regarding the serum level of HbA1c, 9.2% of case group patients had good glycemic control and 78.5% and 12.3% had moderate and poor glycemic control respectively. Whereas 43.1% of

control group patients had good glycemic control and 50.7% and 6.2% had moderate and poor glycemic control respectively. These results indicate a significant relationship between the development of diabetic foot and the lack of long-term blood sugar control (HbA1c level) (P=0.02) (Table 1).

It is worth mentioning that as seen in the univariate model, the four variables of gender, diabetes period, previous history and serum level of HbA1C showed a significant relationship with the variable of diabetic foot. But in the multivariable model, only the previous history remained in the model, which showed that the probability of infection in people with a previous history is almost 24 times higher than in people without a previous history. [OR = 23.75; 95% CI: 9.29 – 60.70] (Table 2).

4. Discussion

In this study, we evaluated and compared HbA1c blood levels in DM patients with and without foot ulcers. The results showed a significant relationship between the patients with age group of 60-70 years and the incidence of diabetic foot ulcers. This result was in line with the study by Armstrong, in which age was presented as an important risk factor in the development of diabetic foot in DM patients(16). The results of a case-control study in Yemen indicated that the probability of developing diabetic foot was higher in diabetic patients

Table 2: Multivariable analysis with Odds Ratio

Variable	Control group (n=65)	Case group (n=65)	Odds Ratio (95% CI)
Age (Years)			
<50	20 (30.7)	17(26.2)	1.00 (Reference)
50-59	15 (23.1)	13 (20.0)	1.02 (0.38 – 2.73)
≥ 60	30 (46.2)	35 (53.8)	1.37 (0.61- 3.09)
Gender			
Female	23 (35.4)	37 (56.9)	2.41 (1.19 – 4.89)
Male	42 (64.6)	28 (43.1)	1.00 (Reference)
Duration of diabetes (Years)			
<10	20 (30.8)	5 (7.7)	1.00 (Reference)
10-19	25 (38.4)	25 (43.1)	7.00 (2.29 – 21.42)
≥ 20	20 (30.8)	32 (49.2)	8.00 (2.63 – 24.30)
Previous history of diabetic foot ulcer			
No	57 (87.7)	15 (23.1)	1.00 (Reference)
Yes	8 (12.3)	50 (76.9)	23.75 (9.29 – 60.70)
Serum level of HbA1C (%)			
<7 % (Good control)	28 (43.1)	6 (9.2)	1.00 (Reference)
7 to 10% (Moderate control)	33 (50.7)	51 (78.5)	7.21 (2.70 – 19.30)
10.1 to 13% (Poor control)	4 (6.2)	8 (12.3)	9.33 (2.11 – 41.38)

over 55 years old. People aged 36-55 and 26-35 years had the lowest percentage of diabetic foot ulcers(17). In a study conducted in Bangladesh by Banik et al. the probability of developing diabetic foot ulcers in diabetic patients over 50 years old is significantly higher than in people under 50 years old (9).

In the present study, there was a significant relationship between the female gender and the incidence of diabetic foot. Bakri et al have reported that males were almost twice more likely to have a foot ulcer compared to women (OR=2.17 (95.0% CI: 1.10, 4.27)) (8).

These results were not consistent with the findings of the present study.

In the study conducted by Bakri et al. the mean duration of DM was 9.7 years and their multivariate analysis revealed that the duration of diabetes was associated with incidence of foot ulcers(8). Almobarak A.O et al. reported that the duration of diabetes was more than ten years is associated with an increase in the diabetic foot probability by 3.16 folds (95% CI: 0.52–10.48 folds increase), $P=0.006$ (18). The results of a study conducted in Australia showed that the duration of DM is a predictive factor for diabetic foot. As the duration of DM increases, the probability of developing diabetic foot increases as well. These results are consistent with the findings of the present study. The present study showed that 87.7% of the patients in the control group had no previous history of foot ulcers. However, 76.9% of the patients in the case group had a previous history of foot ulcers. There was a significant relationship between diabetic foot ulcers and a history of foot ulcers. Lazzarini et al. have also demonstrated similar association. Lazzarini et al. reported that patients referred to healthcare centers with diabetic foot ulcers were more likely

to have a history of diabetic foot ulcers(19).

One of the critical risk factors in developing complications of DM, including diabetic foot, is the lack of blood glucose control. Apelqvist et al. (20) reported that with a 2% increase in HbA1C, the risk of developing diabetic foot increases 1.6 times, and the probability of amputation increases 1.5 times. They also reported that 69.7% and 52.31% of people in the case and control groups had less than 7% HbA1C, respectively.

Ramani et al. conducted a study on 60 diabetic patients and reported that the average HbA1C in diabetic patients with and without diabetic foot was 14.4 ± 3.63 and 9.77 ± 2.34 , these results were statistically significant (21). The results of the present study indicated that 9.2% and 43.1% of patients in the case and control groups had less than 7% HbA1C, respectively.

Other studies investigated the relationship between the severity of diabetic foot ulcers and HbA1C and depicted a statistically significant correlation between grades of diabetic foot ulcer and HbA1C levels of the patients (p -value<0.001) (22).

In contrast to our findings, Moodley, R et al. investigated the relationship between HbA1C levels and foot ulcer development among patients with type 2 DM, indicated that the HbA1c is not an ideal test to readily predict diabetic foot ulcers in patients with Type 2 Diabetes Mellitus (T2DM)(23). Ghanbari et al. evaluated the relationship between serum Hemoglobin A1C level and severity of diabetic foot ulcers. Their results indicate that HbA1c level is a good criterion for evaluating the ulcers incidence and predicting the progression of diabetic foot ulcers in patients, while elevated HbA1c was not significantly associated with age, duration of dia-

betes, underlying disease, and body mass index(24).

5. Conclusion

The results of the present study demonstrate that age, female gender, duration of diabetes, history of diabetic foot, and high serum level of HbA1c have a significant relationship with incidence of diabetic foot ulcers. We propose that HbA1c, an important indicator of long-term glycemic control, can be used as a reliable factor to predict diabetic foot complications and in the multivariable model, only the previous history remained in the model, which showed that the probability of infection in people with a previous history is almost 24 times higher than in people without a previous history.

6. Declarations

6.1. Acknowledgement

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6.2. Conflict of interest

The authors declare no conflicts of interest.

6.3. Funding and supports

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6.4. Author contributions

H.D., A.M., M.A.E., M.K. contributed to the conception, study design, and data collection and evaluation. M.K. and A.B. contributed to the statistical analysis, and interpretation of data. H.D. and A.B. were responsible for overall supervision. M.K. and A.B. drafted the manuscript, revised by A.B. All authors performed editing and approved the final version of this paper for submission, also participated in the finalization of the manuscript and approved the final draft.

6.5. Ethical considerations

The researchers adhered to the principles of the Helsinki Declaration and kept patient information confidential at all stages during the study. The researchers covered all the costs of this project, and the patients incurred no additional costs. This study was approved by the Ethics Committee of Zahedan University of Medical Sciences with code IR.ZAUMS.REC.1401.115.

6.6. Informed consent

Informed consent form was obtained from all patients before their inclusion in the study. Patients were informed that their

participation was voluntary and they were free to withdraw from the study at any point, with no required specific reason, and without any cost. Patients were aware that photographs (audio/video recordings) may be taken during the study and consented to their use in presentations related to this study.

6.7. Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

6.8. Using artificial intelligence chatbots statement

Not used in this article.

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