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Glycosylated Hemoglobin in Diabetic Foot and its Correlation with Clinical Variables in a North Indian Tertiary Care Hospital

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Abstract

HbA1c reflects glycemia over 2-3 months and is the standard measure used to monitor glycemia in diabetic patients, but studies have not shown an association of HbA1c with DFU. We hypothesized that elevated HbA1c would be most associated with extremity of DFU/DFI. To test this hypothesis we conducted a prospective study of 161 DFU individuals treated at the R G Centre for Diabetes & Endocrinology, AMU. 64.8% were males and the 37.0% had ulcer >1 month. The majority of ulcer was neuropathic (50%) and amputation was done in 28.4%. HbA1c >6.5% were significantly associated with Wagner grades, UTG, BMI, retinopathy, nephropathy, hypertension, neuropathy and smoking. A significant correlation was found between UTG (r=-0.219, p=0.005), ulcer duration >1 month (r=-0.233, p=0.002), BMI (r=0.154, p=0.05), ESR (r=-0.169, p=0.031), Neuropathy (r=-0.007, p=0.048), nephropathy (r=-0.165, p=0.036), hypertension (r=0.207, p=0.007), retinopathy (r= 0.167, p=0.037) and smoking (r=0.164, p=0.034) with HbA1c >6.5%. The diabetic patients with A1c>6.5% showed a high risk of ulcer development in their foot. A significant correlation was observed with the clinical variables (ulcer duration >1 month, BMI, ESR, Neuropathy, nephropathy, hypertension, retinopathy and smoking with A1c>6.5% which is independent of concomitant infections in DFU patients.

Keywords: Diabetic foot ulcer; HbA1c; Correlation

Introduction

The increasing incidence of diabetes mellitus which represents a group of chronic diseases characterized by high levels of blood glucose resulting from defects in insulin action, production or both has become a major health concern worldwide. One of the most common complications of diabetes in the lower extremity is the diabetic foot ulcer. An estimated 15% of patients with diabetes develop a lower extremity ulcer during the course of their disease [1,2]. Diabetic foot is a complex and heterogeneous disorder that affects 1 out of 5 patients with diabetes at least once in his or her lifetime with relevant consequences both on lower limb survival and general morbidity [3]. According to the international consensus guidelines' protocols [4], such a complex pathology necessitates the participation of a multidisciplinary team, including the diabetologist, the podiatrist, the vascular surgeon, the radiologist, and the infectious disease specialist, to manage and address all the various aspects and presentations of the pathology. Only about half of patients actually notice the lesion themselves, with the majority occurring on the digits [5]. Ill-fitting footwear frequently contributes to foot ulceration [6,7]. Inadequate shoe fitting cannot be felt in those patients with sensory neuropathy. Ulcers can form because of tight-fitting shoes causing constant pressure. However, loose shoes also cause ulcers, as a result of friction [8]. Neuropathy is a major contributing risk factor for foot ulcers and can involve both somatic and autonomic fibres. The myelinated (A-type) sensory fibres are associated with proprioception, sensation of light touch, pressure, and vibration, and motor innervations of the muscle spindles. Neuropathy of the A-type nerve fibre results in ataxic gait and intrinsic weakness of the foot muscles. Neuropathy of the C-type sensory fibres is the loss of protective sensation; it results in the loss of pain threshold with prolonged and increased shear forces and repeated trauma. In addition, loss of protective sensation due to peripheral neuropathy is the most common cause of ulceration. The HbA1c has several advantages to the FPG, including greater convenience, since fasting is not required; evidence to suggest greater pre-analytical stability; and less day-to-day perturbations during periods of stress and illness [9]. Blood glucose levels are clearly a major determinant of HbA1c levels, which ultimately shows the diabetes control for the past 2 months. It has been mentioned in the past clinical trials that uncontrolled diabetes or elevated HbA1c levels are associated with the development of retinopathy and as well as other complications [10]. On the basis of research literature mentioned above, the current study was designed to find out the association between HbA1c & diabetic foot in North Indian patients.

Materials and Methods

The study was a prospective cohart hospital based. We recruited 162 diabetic subjects with foot ulceration (group A) hospitalized between 2009 and 2012 at the Rajiv Gandhi Centre for Diabetes and Endocrinology, of Jawaharlal Nehru Medical College Hospital, Aligarh Muslim University, Aligarh. India. We also recruited 162 diabetic patients without foot ulceration (group B) admitted for other causes between 2009 and 2012. All patients gave informed consent to take part in this study. Foot ulcer was defined as a full-thickness skin defect that required ≥14 days for healing [11]. Every subject with diabetic foot was matched for age (± 3 years), sex, and BMI. Patients with inflammatory or infectious diseases, autoimmune and rheumatic diseases, cancer, haematological diseases and those who were under treatment with anti-inflammatory drugs, pregnant and lactating female

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patients were excluded. We also excluded patients with recent venous thromboembolism.

A detailed history and physical examination was carried out for every subject. Age, Sex, anthropometric measurements (body mass index), duration of diabetes, glycemic control prior to and during the hospital stay, lipid profile, presence of retinopathy, nephropathy (creatinine >1.5 mg% or presence of albuminuria), neuropathy (absence of perception of the Semmes-Weinstein monofilament at 2 of 10 standard planter sites on either foot), peripheral vascular disease (ischaemic symptoms and intermittent claudication of rest pain, with or without absence of pedal pulses or posterior tibial pulses). The ankle-brachial index (ABI) was calculated as the ratio of the ankle systolic blood pressure (defined as the higher of the dorsalis pedis or posterial tibialis measurement,) divided by the higher brachial systolic pressure. Subject was classified as having PAD when they had an ABI ≤ 0.9 and/or when they had undergone a peripheral arterial bypass or amputation [8]. ADA criteria for hypertension was used (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg in subjects who are not taking antihypertensive medication or antihypertensive treatment yet present on admission). Hypercholesterolemia was defined as total serum cholesterol ≥150 mg/dL and hypertriglyceridemia as total serum triglyceride ≥200 mg/dL on the basis of ADA-2010 criteria [12]. Coronary artery disease was determined on the basis of history of physician-diagnosed angina, myocardial infarction, or any previous revascularization procedure assessed by questionnaire. Cerebrovascular disease (TIA/ischaemic stroke) was assessed by history, specific neurological examination executed by specialists, and hospitalized or radiological (brain computed tomography or brain magnetic resonance) records of definitive TIA or stroke. All patients had blood pressure, serum glucose, creatinine, serum cholesterol levels, serum triglyceride levels, and urinary albumin excretion (UAE) values measured on first day of admission to the hospital. Duration of ulcer, site, and size of ulcer, history of smoking, history of previous amputation and clinical outcome were noted in every patient. Clinical assessment for signs of infection (swelling, exudates, surrounding cellulitis, odor, tissue necrosis, crepitation and pyrexia) was made by one researcher classifying the ulcers and determining the presence of clinical signs of infection. Ulcer size was determined by multiplying the longest and the widest diameters and expressed in centimetres square. The wound was graded and staged at the time of hospitalization according to the University of Texas Wound classification system as grade 1 (superficial wound, not involving, tendon, capsule or bone), grade 2 (wound penetrating to tendon or capsule) and grade 3 (wound penetrating bone or joint). Grade 0 patients (pre- or post-ulcerative site that has healed) were excluded from the study. Diagnosis of extension to the bone was made in majority of patients by probing with a sterile steel probe. In the absence of sinus tract or an exposed bone, a standard radiograph showing signs of osteomyelitis in the bone was considered definitive and later on MRI was done to confirm the osteomyelitis in suspected patients. Amputation was defined as the complete loss in the transverse anatomical plane of any part of the lower limb [13].

Sample collection and determination of HbA1c

Blood samples were collected for the clinical investigations, between 8 am to 10 am after an overnight fast of 10-12 hours for all the routine investigation. Blood samples were collected:-

- In EDTA Na vials for HbA_1c,
- In sodium fluoride vials for plasma glucose,
- In plain vials for serum lipids and lipoproteins.

Glycohaemoglobin [HbA1c]

The D-10 Hemoglobin A1c Program utilizes principles of ion-exchange high-performance liquid chromatography (HPLC). The assay procedure was followed as per directives of the kit, Bio–Rad Laboratories Inc., Hercules, California, USA.

Statistical methodology

The results were analysed using the SigmaPlot Version 11.1 program. The Shapiro-Wilk test was used to evaluate normality of variables. The differences between the groups were calculated with Student *t* or the nonparametric U-Mann-Whitney tests. Results are expressed as median (lower Quartile ↔ upper Quartile) for continuous variables and percentages for categorical data, with P<0.05 considered significant. A logistic forward regression analysis, multiple linear regression and one way analysis was used to assess the association between all clinical variables and HbA1c% that independently predicted foot ulcer development with a P<0.05. Risk for ulcer development was also estimated by odds ratio (OR) and risk ratio (RR) with 95% confidence intervals (CIs) that independently predict the foot ulcer.

Results

Baseline characteristic of subjects with diabetic foot in comparison with subjects without diabetic foot are given in Table 1. In group A, 82.7% of subjects had T2DM, while in group B T2DM was present in 90.1% of subjects. Regarding the duration of diabetes, 68.6% of subjects in group A vs 75.7% of subjects in group B could be diabetic by >10 years; the 31.4% vs 24.0% for <10 years in respective groups. Subjects in group A also presented, in comparison with those in group B, increased mean ± sd levels of HbA1c % [9.6 ± 2.03 % vs 7.9 ± 0.86], serum creatinine (mg/dl) [1.24 ± 0.56 vs 1.11 ± 0.52], LDL-C (mg/dl) [75.89 ± 18.34 vs 104.38 ± 30.1], HDL-C (mg/dl) [34.6 ± 3.34 vs 44.3 ± 7.7], Total cholesterol (mg/dl) [136.93 ± 13.7 vs 181.9 ± 32.3], and triglycerides (mg/dl) [95.6 ± 21.7 vs 157.0 ± 83.1] (Table 1). The values of HbA1c and blood glucose levels in Group A and Group B at the time of admission and discharge were shown in Figures 1 and 2, which shows improvement in the hospital stay in both group A & group B also.

Univariate analysis

In a univariate analysis OR and RR were calculated between Group A and Group B patients in which HbA1c were calculated. The predictive factor that were associated with predicting the foot ulcer were summarized in Table 2. The significant factors that were most likely to have an association in prediction foot ulcer were HDL-C (<40 mg/dl) [OR1.188(1.12-3.15); RR 1.61(1.09-2.38); p=0.02], LDL-C (>100 mg/dl) [OR 1.96(126-3.04); RR 1.40(1.11-1.75); p=0.003], Triglycerides (>200 mg/dl) [OR 1.86(1.12-3.10); RR 1.59(1.08-2.34); p=0.021], Neuropathy [OR 2.50(1.58-3.96); RR 1.74(1.31-2.31); p=0.0001], Hypertension [OR 1.86(1.19-2.89); RR 1.37(1.09-1.72); p=0.007], on OHA [OR 3.31(2.07-5.29); RR 2.07(1.53-2.78); p=0.006] and smoking cessation [OR 2.57(1.64-4.05); RR 1.50(1.23-1.84); p=0.001]. In chi square test, following were the risk factors that were most likely to have an association in prediction foot ulcer were HDL-C (<40 mg/dl) [p=0.014], LDL-C (>100 mg/dl) p=0.007], Triglycerides (>200 mg/dl) [p=0.015], Neuropathy [p<0.0001], Retinopathy [p<0.001], Hypertension [p=0.005], on OHA [p<0.0001] and smoking cessation [p<0.001].

Multivariate analysis

On multivariate analysis, the factors which showed a positive

Factors	Group A Patients with Ulcer 162	Group B Patients without ulcer 162	*P value*
Age (years)	46.29±13.19	47.10±12.13	NS
T2DM/T1DM	134(82.7)/28(17.28)	146(90.1)/16(9.8)	NS
Male/Female	103(63.5)/59(36.4)	102(62.9)/58(37.0)	NS
Duration of Diabetes			
<10 yrs	111(68.5)	123(75.9)	0.065
>10 yrs	51(31.4)	39(24.0)	0.048
Smoking (Yes/No)	110(87.6)/52(32.0)	73(45.0)/89(54.9)	0.005
BMI (kg/sqmt)	24.84±4.54	24.03±4.23	<0.001
<18.5	4(2.4)	12(7.4)	
18.5—22.9	63(38.8)	67(41.3)	
23.0—24.9	68(41.9)	57(35.1)	
>24.9	27(16.6)	26(16.0)	
Systolic BP (mmHG)	130.46±18.32	133.33±18.82	0.172
Diastolic BP (mmHG)	85.24±16.8	86.34±11.36	0.485
HbA1c (%)	9.6±2.03	7.9±0.86	<0.005
Plasma creatinine (mg/dl)	1.24±0.56	1.11±0.52	0.032
LDL-C (mg/dl)	75.89±18.34	104.38±30.1	<0.001
HDL-C (mg/dl)	34.60±3.34	44.30±7.7	<0.005
Total cholesterol (mg/dl)	136.93±13.7	181.9±32.3	<0.005
Triglycerides (mg/dl)	95.96±21.7	157.01±83.1	<0.005
Neuropathy	82(50.6)	47(29.0)	<0.0001
Retinopathy	82(50.6)	38(23.4)	<0.0001
Nephropathy	72(54.4)	31(19.13)	<0.0001
Hypertension	92(56.7)	67(41.3)	<0.0001
Therapy			
Insulin	62(38.2)	93(57.4)	<0.05
OHA	87(53.7)	42(25.9)	<0.005
Both	13(8.1)	27(16.7)	<0.005
Grade of ulcer			
Grade 1	48(29.6)	-	-
Grade 2	94(58.0)	-	-
Grade 3	20(12.3)	-	-
Ulcer size			
<4cm^2	38(23.4)	-	-
>4cm^2	124(76.5)	-	-
Bacterial infection type			
superficial	48(29.6)	-	-
subcutaneous	94(58.0)	-	-
osteomyelitis	20(12.3)	-	-
Amputation	46(28.3)	-	-

Data are mean ± sd or n(%) unless otherwise indicated. WBC: White Blood Cells; Hb: Haemoglobulin; LDL-C: Low Density Lipoprotein Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; SGOT/AST: Serum Glutamic Oxaloacetic Transaminase/Aspartate Transaminase; SGPT/AST: Serum Glutamate-Pyruvate Transaminase/Aspartate Transaminase; TSP: Total Serum Protein; SA: Serum Albumin; SG: Serum Globulin.

Table 1: General and demographic variables in cases and controls.

association in predicting the foot ulcer by One way analysis were BMI (>23 kg/m^2), HDL-C (<40 mg/dl), LDL-C (>100 mg/dl), Total cholesterol (>150 mg/dl), Triglycerides (>200 mg/dl), Neuropathy, Retinopathy, Hypertension, Nephropathy and smoking habit (Table 3). Using multiple linear regression analysis, factors that predict the ulcer were BMI (>23 kg/m^2), HDL-C (<40 mg/dl), Neuropathy, Retinopathy, Hypertension, Nephropathy and smoking habit. In last analysis of multivariate analysis, the factors which show a positive risk factors by forward stepwise regression were Neuropathy, Retinopathy, Hypertension, Nephropathy and smoking habit.

Correlation analysis

There was a perfectly positive correlation corrected for age between HbA1c and Foot ulcer were BMI (>23 kg/sqmt) (r=0.154, p=0.050), Retinopathy (r=0.167, p =0.037), hypertension (r=0.207, p=0.007), and smoking habit (r=0.164, p=0.034). While week correlation were neuropathy (r=-0.007, p=0.048), and nephroathy (r=-0.165, p=0.036) Table 4.

Discussion

In this study, we have demonstrated diabetic individuals WITH/WITHOUT foot ulcer seen at the RGCDE, AMU, Aligarh, only elevated HbA1c was significantly independently associated with duration of diabetes, BMI, cholesterol status, diabetic complication like neuropathy, nephropathy & retinopathy, and those on OHA therapy of management. This relationship was stronger for the wounds located on the foot, which were insensate neuropathic wounds (approximately 60% of all wounds), when our analysis was restricted to these foot wounds, this association of HbA1c remained significant.

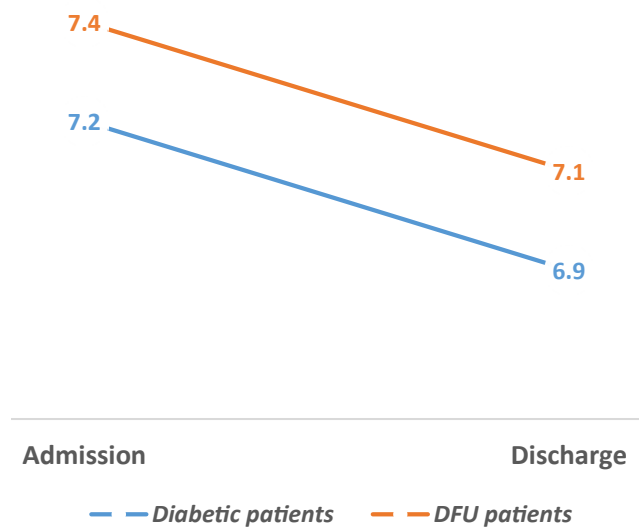

Figure 1: HbA1c % among diabetic patients with and without ulcer in foot at the time of admission and discharge.

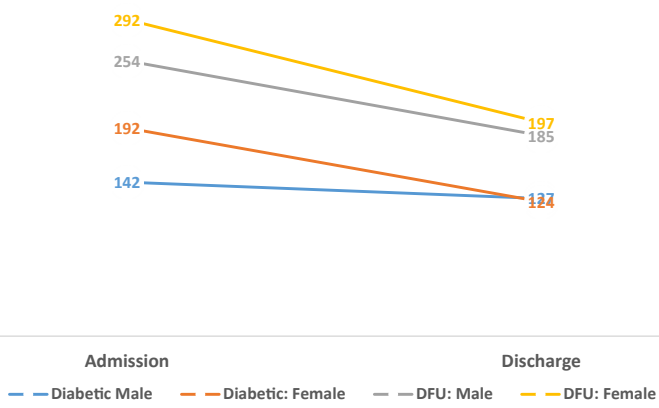

Figure 2: Fasting and Postprandial blood glucose levels (mg/dl) among diabetic patients with and without ulcer in foot at the time of admission and discharge.

INDEPENDENT VARIABLE	ODDS RATIO	RISK RATIO	P- value	CHI SQUARE TEST	
	OR(95%CI)	*RR(95%CI)*		*YATES*	*P*
AGE [>40 YRS]	0.77(0.49-1.20)	0.90(0.74-1.08)	0.309	1.27	0.259
MALE/FEMALE	1.02(0.65-1.61)	1.00(0.85-1.19)	0.99	0.01	0.92
BMI (>25kg/mt^2)	1.34(0.87-2.09)	1.16(0.93-1.44)	0.219	1.8	0.179
Total cholesterol (>150 mg/dl)	1.43(0.88-2.32)	1.29(0.91-1.82)	0.179	2.16	0.14
Triglycerides (>200 mg/dl)	1.86(1.12-3.10)	1.59(1.08-2.34)	0.021	5.86	0.015
HDL-C (<40 mg/dl)	1.88(1.12-3.15)	1.61(1.09-2.38)	0.020	5.94	0.014
LDL-C (>100 mg/dl)	1.96(1.26-3.04)	1.40(1.11-1.75)	0.003	9.0	0.007
Neuropathy	2.50(1.58-3.90)	1.74(1.31-2.31)	0.0001	15.78	<0.0001
Retinopathy	3.34(2.07-5.38)	2.15(1.57-2.96)	6.129	25.62	<0.0001
Hypertension	1.86(1.19-2.86)	1.37(1.09-1.72)	0.007	7.72	0.005
Nephropathy	1.13(0.73-1.76)	1.07(0.83-1.38)	0.55	0.31	0.57
THERAPY					
Insulin only	0.46(0.24-0.71)	0.66(0.52-0.84)	0.0008	11.89	0.0005
OHA only	3.31(2.07-5.29)	2.07(1.53-2.78)	0.006	26.08	<0.0001
Both	0.43(0.21-0.87)	0.48(0.25-0.89)	0.027	5.59	0.01
SGPT (IU/L)	1.90(1.17-3.07)	1.56(1.11-2.19)	0.011	7.0	0.008
SGOT (IU/L	1.72(1.11-2.68)	1.30(1.05-1.61)	0.019	5.98	0.014
TSP (gm %)	1.32(0.87-2.11)	1.19(0.92-1.55)	0.214	1.86	0.17
SA (gm %)	1.91(0.76-1.84)	1.08(0.88-1.31)	0.502	0.61	0.434
Smoking	2.57(1.64-4.05)	1.50(1.23-1.84)	0.001	4.39	0.001

The following independent variable were considered for the model: HbA1c (>6.9 %), Total cholesterol (>150 mg/dl), Triglycerides (>200 mg/dl), HDL-C (<40 mg/dl), LDL-C (>100 mg/dl), Neuropathy, Retinopathy, Hypertension, Smoking, SGOT/AST, serum glutamic oxaloacetic transaminase/aspartate transaminase; SGPT/AST, serum glutamate-pyruvate transaminase/aspartate transaminase, TSP, total serum protein. Only the variable that had a p value <0.05 were considered in the final fitted model.

Table 2: Odds Ratio, Risk Ratio, To Study the Independent Variable Predicting Foot Ulcer In Diabetic Patients.

Independent variable	One way analysis			Multiple linear regression			Forward step wise regression		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
	p	p-	p	p	p	p	p	p	p
Hospital stay >1 month	0.05	NS	NS	0.029	NS	NS	0.022	NS	NS
Age (yrs)	0.05	0.05	0.05	NS	NS	NS	NS	NS	NS
Wagner Grades	0.05	0.05	0.05	<0.001	<0.001	0.001	<0.001	0.001	0.001
UTG	0.05	0.05	0.05	0.025	0.05	0.045	0.025	0.032	0.045
Ulcer duration	0.05	0.05	0.05	NS	NS	NS	NS	NS	NS
Size of ulcer (sq CM)	0.05	NS	NS	NS	NS	NS	NS	NS	NS
BMI (>25kg/mt^2)	0.05	NS	NS	0.018	0.039	NS	NS	NS	0.05
S creat	0.05	0.05	0.05	NS	NS	NS	NS	NS	NS
ESR	0.05	0.05	0.05	NS	NS	0.013	NS	NS	NS
SGPT (IU/L)	NS	NS	NS	<0.001	0.018	0.007	NS	NS	NS
SGOT (IU/L	NS	NS	NS	<0.001	0.013	0.045	NS	NS	NS
Alk Phosphate (IU/L)	0.05	0.05	0.05	<0.001	0.017	0.010	NS	NS	NS
TSP (gm %)	NS	NS	NS	0.003	NS	0.023	NS	NS	NS
SA (gm %)	0.05	0.05	NS	0.031	NS	NS	NS	NS	NS
SG (gm %)	0.05	NS	NS	0.016	NS	NS	NS	NS	NS
T-cholesterol (mg/dl)	0.05	0.05	0.05	NS	NS	NS	NS	NS	NS
Triglycerides (mg/dl)	0.05	0.05	0.05	NS	NS	NS	NS	NS	NS
HDL-C (mg/dl)	0.05	0.05	0.05	0.029	NS	NS	NS	NS	NS
LDL-C (mg/dl)	0.05	0.05	0.05	NS	NS	NS	NS	NS	NS
Neuropathy	0.05	0.05	0.05	<0.001	0.002	<0.001	0.018	0.007	<0.001
Retinopathy	0.05	0.05	0.05	0.05	0.05	0.042	0.013	0.045	0.05
Hypertension	0.05	0.05	0.05	0.025	0.045	0.028	0.045	0.028	0.025
Nephropathy	0.05	0.05	0.05	0.035	0.001	0.050	<0.05	0.012	0.035
Smoking	0.05	0.05	0.05	<0.05	0.012	0.016	0.024	0.05	<0.05

The following independent variable was considered for the model: HbA1c (>6.5 %), Total cholesterol (>150 mg/dl), Triglycerides (>200 mg/dl), HDL-C (<40 mg/dl), LDL-C (>100 mg/dl), Neuropathy, Retinopathy, Hypertension, SGOT/AST, serum glutamic oxaloacetic transaminase/aspartate transaminase; SGPT/AST, serum glutamate-pyruvate transaminase/aspartate transaminase, TSP, total serum protein, and Smoking. Only the variable that had a p value <0.05 were considered in the final fitted model, NS; non-significant.

Table 3: Multiple Linear Regression Analysis, Forward Stepwise Regression Analysis and One Way Anova Analysis to study the Independent Variable Predicting Foot Ulcer in Diabetic Patients.

Independent Variable	Total		Male Patients		Female Patients	
	r	*p*	*r*	*p*	*r*	*p*
Hospital stay >1 month	-0.033	0.677	0.031	0.749	0.116	0.397
Wagner Grades	0.079	0.315	-0.353	0.002	-0.053	0.695
UTG	-0.219	0.005	0.150	0.126	0.300	0.024
Ulcer duration	-0.233	0.002	-0.082	0.406	0.0003	0.998
Size of ulcer	-0.0375	0.636	-0.026	0.789	-0.045	0.742
BMI (>25kg/mt^2)	0.154	0.050	0.150	0.126	0.300	0.024
WBC	-0.145	0.067	-0.153	0.122	-0.165	0.222
S creat	-0.098	0.214	0.003	0.971	0.002	0.988
ESR	-0.169	0.031	-0.188	0.055	-0.095	0.485
Alk Phos	0.090	0.256	0.042	0.663	0.323	0.015
Triglycerides	-0.018	0.814	-0.076	0.441	0.294	0.027
HDL-C	0.009	0.904	-0.050	0.613	0.088	0.516
LDL-C	0.013	0.864	0.035	0.719	-0.216	0.109
Neuropathy	-0.007	0.048	0.234	0.002	0.207	0.007
Retinopathy	0.167	0.037	0.155	0.048	0.141	0.072
Hypertension	0.207	0.007	0.250	0.001	0.174	0.026
Nephropathy	-0.165	0.036	0.118	0.035	0.155	0.049
Smoking	0.164	0.034	0.036	0.005	0.161	0.040

The following independent variable was considered for the model: HbA1c (>6.5 %), Total cholesterol (>150 mg/dl), Triglycerides (>200 mg/dl), HDL-C (<40 mg/dl), LDL-C (>100 mg/dl), Neuropathy, Retinopathy, Hypertension and Smoking. Only the variable that had a p value <0.05 were considered in the final fitted model.

Table 4: Correlation analysis between HbA1c and laboratory and clinical variables in patients with diabetic foot.

The literature on age is also mixed, Apelqvist and Agardh [14] reported a higher risk of amputation with increasing age, but Ince et al. [15], Golinko et al. [16] and Margolis et al. [17] reported no association with age and the same was also reported in our previous study [18]. This study results are similar to [14] and our previous study [18] where positive association with cholesterol or white blood cell count between foot amputee patients and non-amputee patients. In addition, according to the obtained results, it is clear that as HbA1c levels are increasing and hence, there is a progressive loss of vibration sensations. For those patients in whom HbA1c levels are higher, they definitely have loss of vibration sensations. This reflects their poor glycaemic control at the time of examination or presentation. Further, it is clear that those patients, in whom high HbA1c levels have developed neuropathy, shows again reflecting poor glycaemic control. The associations between demographic, clinical, laboratory variables and healing in the literature are not consistent, our study is largely in agreement with existing reports where the majority of clinical data are not associated with wound healing per day. These findings can be correlated to the fact that diabetes mellitus being a metabolic disorder causes the altered protein and lipid metabolism and thereby abnormal granulation tissue formation. It can also be significantly supported by the findings of Goldin et al. [19] who indicated that increased glucose levels in the body end up in uncontrolled covalent bonding of aldose sugars to a protein or lipid without any normal glycosylation enzymes. The accumulation of these products called advanced glycation end product (AGEs) over the surface of cell membranes occurs on extracellular matrix proteins and alter the properties of matrix proteins such as collagen, vitronectin and laminin results in increased stiffness and increased synthesis of granulation tissue [19-22].

This relationship was also stronger among participants with peripheral artery disease. Our results suggest that HbA1c is an important clinical predictor of wound, particularly in those with neuropathic foot wounds and in those with peripheral artery disease. To our knowledge, a strong association between HbA1c and diabetic complications including biochemical parameters over time in a large clinic population of diabetic individuals is previously unreported. Previous studies have found either no association [14,17] or have reported a trend, but have had small sample size and did not statistically analyze data [23]. Previous studies have used need for amputation [14,18] or total time to complete healing [17,23] as the outcome of interest.

The most important aspect of this study was to determine the association between the diabetic complications i.e., the high risk foot and the development of the progressive retinopathy. According to Table 2, Odds ratio, Risk ration and Pearson chi square statistics, this association was found to be highly significant at the level of p-value of <0.001. Similar results were also observed for hypertension, neuropathy, and patients on oral antidiabetic medications, LDL-C, HDL-C and smoking cessation except in a study reported from Bangladesh where the cholesterol, LDL and TG were higher in diabetic patients compared with DFU [24]. One of the important assessments from the present study is that, diabetic patients cannot well examine their feet daily because of the occurrence of retinopathy or visual loss, and need assistance of other persons at home. It should also be noted that visual impairment is one of the risk factors for the development of diabetic foot ulcers, because of associations and their coincidence in diabetes.

Accordingly, rise in HbA1c, patients have developed non-proliferative and proliferative retinopathy, indicating severity of retinopathy with uncontrolled diabetes. But, those patients who were having average HbA1c levels under controlled or less; they are within normal limits or have not yet developed retinopathy, when examined in the current study. In other words, diabetic complications will occur if blood sugars remain high for long time, and may occur at any level of the disease process, but those patients whose HbA1c was higher, have definitely developed the chronic complications as has been shown by the results in the present study. In addition, by identifying high-risk patient and tailoring a total foot care prevention program accordingly, the incidences of ulceration and lower extremity amputations can be reduced [25,26]. The results of the present study clearly indicate the most important complications of diabetes (nephropathy, retinopathy, hypertension and neuropathy) finally leads to the Diabetic Foot Syndrome, which occur together as glycemic control worsens [27,28]. In other words, to prevent the complications, the blood sugars should be controlled to the target levels as recommended by American Diabetes Association and other associations and others as well. Lowering HbA1C to below or around 7% has been shown to reduce microvascular and neuropathic complications. Therefore, for micro-vascular disease prevention, the HbA1C goal for non-pregnant adults in general is 7% [12].

Further, HbA1c is now considered also a diagnostic tool, as has been recommended by American Diabetes Association in 2010 [10] because now its methodology is standardized. Nevertheless in the past and still now it has been a good tool for monitoring diabetes and its complications. It is easy to measure and gives reliable evidence for the past control of diabetes. In our study and data, we have used this tool and have related its association with other complications reported by others [28-30].

Summary, in this study, keeping HbA1c in acceptable range (by intensifying treatment, education and counselling) will prevent the complications and will have greater impact on reducing the burden and health cost at National as well as International levels. The patients with foot ulcers exhibit a specific and nonrandom upregulation of

HbA1c % in diabetic foot compared with patients without ulcer. These associations were independent of multiple potential confounders and were mainly associated with severity of ulceration (different grades of ulcer using University of Texas system). Diabetic patients at risk for foot lesions must be educated about risk factors and the importance of foot care, including the need for self-inspection and surveillance, monitoring foot temperatures, appropriate daily foot hygiene, use of proper footwear, good diabetes control, and prompt recognition and optimal evidence based treatment of newly discovered lesions. This emphasizes the importance of diabetic educator and the foot care specialist nurse. Also there is a need for multidisciplinary team including the diabetologist, the podiatrist, the vascular surgeon, the radiologist, ophthalmologist and the infectious disease specialist for better management and care for diabetic patients.

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