CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2551141

Available online at: http://www.iajps.com ***Research Article***

ASSOCIATION AND RELATION BETWEEN DIABETIC FOOT ULCER AND DIABETIC RETINOPATHY AMONG KAUH DIABETIC PATIENTS, JEDDAH, KSA

Diyaa Hassan Bokhary[1], Rabaa Hashim Alhibshi[1], Anas Yahya Khyatt[1], Iyad sameer kinsarah[1], Alfaisal Hashim Neyazi[1], Nizar Mohammed Alhibshi[2]

[1] Faculty of Medicine, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia., [2] Department of Ophthalmology, King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia.

Abstract:

Background:

Diabetes mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia. Twenty years after diagnosis of type 2 DM, 60% of those patients will develop retinopathy. As diabetic retinopathy (DR) minimizes visual acuity along with overlapping pathogenesis between diabetic foot ulcer (DFU) and DR, we assume that DFU is associated with DR. The aim was to calculate the prevalence of DR among DFU patients and to study the association between DFU and DR.

Methods:

A retrospective review was used to gather information from all patients with type 2 DM with foot ulcer who undergo fundoscopic examination; 199 patients with DFU vs. 200 diabetic patients without DFU as a control group compared regarding each clinical variable and retinopathy status. Data sheet consists of (sociodemographic, biochemical and medications) along with SPSS statistics v21 implemented in our study.

Results:

Among 199 patients with DFU, 71.4% were males, with a mean age of 63.4±12.5 and an average level of HbA1c was 9 ± 2.48. We compared among patients with DFU and diabetic patients without DFU; the DFU group was older, predominantly males and mostly smokers. We divided DFU patients into two groups: 1) 45 patients with DR, among them 15% had PDR while 7.5% had NPDR. 2) 154 without DR patients. The prevalence of DR was 22.5%. Using chi-square, DR significantly associated with DFU ($p < 0.001$).

Conclusions:

We found that 22.6% of patients with DFU had DR, and there was a significant association between DFU and DR. Among the results, we found a significant association between low hematocrit, gender, and HbA1c with DFU. Moreover, history of hypertension significantly associated with both DR and DFU. So, any patient with DFU, particularly those with hypertension, should be referred to an ophthalmologist to examine the retina.

Key words: *Diabetes; Retinopathy; Diabetic foot; Diabetic retinopathy; Foot ulcer*

Corresponding author:

Diyaa Hassan Bokhary,
Faculty of Medicine,
King Abdulaziz University,
Jeddah, Kingdom of Saudi Arabia.

QR code

Please cite this article in press Diyaa Hassan Bokhary et al., ***Association and Relation Between Diabetic Foot Ulcer And Diabetic Retinopathy Among Kauh Diabetic Patients, Jeddah, Ksa..,*** *Indo Am. J. P. Sci, 2019; 06(01).*

INTRODUCTION:

The prevalence of diabetes mellitus (DM) outweighs the prevalence of all cancers combines by four times [1], by a prevalence of 8.3% (382 million patients) worldwide in 2013. Saudi Arabia occupies the 7th place among the top 10 countries with a prevalence of 23.9%, and the 2nd among middle east [2,3].

DM is a metabolic disease characterized by chronic hyperglycemia [4]. Its complications are well known including diabetic foot ulcer (DFU), diabetic retinopathy (DR), angiopathy, neuropathy, and others [5]. In spite of the substantial advancement in medicine and the stress on the importance of early detection and management of the disease, people with diabetes in general and DFU patients still suffering from a miserable quality of life along with depression, which results in a 5-years mortality rate around 74% [6]. Because of poor application of prevention practices, underestimation of follow up and noncompliance to management plan [7,8]. Furthermore, the awareness of diabetes complications namely diabetic foot is insufficient for the patients as well as doctors and healthcare personnel resulting in dramatic increase in new cases and developing complications in those who already have the disease [9,10]. DFU will develop in 15–25% of diabetic patients during their life [11]. Yearly, about 2-3% of diabetic patients have a foot ulcer and need to be prolonged hospitalization to treat its complications like infection and gangrene [12,13].

DR is a microvascular complication of diabetes, ranked as the leading cause of blindness worldwide in middle-aged patients, which accounts for 4.8% (37 million) of the total number of blindness according to the World Health Organization [14]. Twenty years after diagnosis of type 2 DM, 60% of those patients will develop retinopathy [15].

A previous study conducted in Oman, 2003, noted that DR correlated with diabetic neuropathy and microvascular complications [16]. Also, another study published in Japan, 2016, showed that a decrease in visual acuity is a risk factor for DFU [9]. As DR minimizes the visual acuity along with the overlapping pathogenesis between DFU and DR, we assume that DFU associated with DR.

Despite the striking fact that neuropathy and angiopathy are risk factors for DFU, few studies are conducted to illustrate the relation between DFU and DR [17]. Up to our knowledge, there are no recent studies published in Saudi Arabia about the association between them. Our aim is to calculate the prevalence of DR among patients with DFU, to find if there is a possible association between DFU and DR at KAUH.

METHODOLOGY:

Our study was approved by research ethics committee (unit of biomedical ethics) at King Abdulaziz University. A retrospective review of medical records was used to gather information from all diabetic patients with DFU from 2010 to 2017 at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. The sample size includes 200 patients. Inclusion criteria were as follow: Patients with type 2 DM with foot ulcer who underwent fundoscopic examination. A control sample of 200 out of 1680 type 2 diabetic patients without foot ulcer from 2010 to 2017 were obtained using stratified random sampling in which the total population divided into eight strata according to the year of admission and each year represent one stratum. We used the following equation [(X / 1680) *200] to calculate the number of patients taken from each stratum (X stands for all diabetic patients in each stratum). A representative proportion was taken randomly from each stratum to avoid selection bias, and eventually, the control group became equal to the case group.

The data sheet composed of three main elements 1- sociodemographic such as age, gender, smoking and the presence of DF. 2-biochemical such as lipid profile, LDL, HDL, HbA1C, BUN, blood creatinine, and the hematocrit value. 3- if there are any medications like insulin, oral hypoglycemic agents or both. According to the international clinical DR severity scales, we classify the presence or absence of DR into a diabetic patient with proliferative DR, none- proliferative DR and without DR [18].

Google forms along with Microsoft Excel sheets (2016) used for data entry. A widely prevalent software of statistical package for the social sciences (IBM SPSS statistics) v21 used for data analysis. P-values > 0.05 were considered significant. Frequency and percentage were calculated for qualitative variables, while mean and standard deviation measured for quantitative variables. To assess the presence of significant association of each independent variable, chi square test ($\chi 2$), independent t-test and one-way ANOVA used. Multivariate logistic regression with 95% confidence interval (CI), which adjust for possible confounders, was implemented to predict the association of all independent variables with a dependent variable [19].

RESULTS:

In this study, we aimed to see the association between (DFU) and (DR). Our sample size was 402 patients with type 2 DM, 153 (38.1%) were males.

The mean age was 62 ± 14.05 years. Among 199 patients with DFU (cases), males were 142 (71.4%), Saudis were 76 (38.2%), and the mean of ages was 63.4±12.5. The average level of HbA1c was 9 ± 2.48. In [Table 1], we compared between patients with DFU and diabetic patients without DFU (control). The DFU group was older, males were predominant and mostly were smokers. There were significant relationship between male gender (p = 0.005), cholesterol (p = 0.705), HbA1C (p = 0.001), hematocrit value (p = 0.003) and DFU, as demonstrated in [Table 3].

Additionally, we divided DFU patients (n = 199) into two groups as demonstrated in [Table 2]: 1) with DR (n = 45), and they were separated into two sub-groups PDR 30 (15%) patients and NPDR 15 (7.5%) patients. 2) without DR 154 (77.5%) patients [figure 1]. By using univariate analysis, the prevalence of DR among DFUs is 45 (22.5 %) patients. A chi square test conducted, and we found that it significantly related with the nationality (p = 0.029). Moreover, there wasn't an association between DR and high creatinine level (p = 0.325) [Table3].

A multivariable logistic regression test was conducted to compare between DFU and none- DFU patients as shown in [Table 4]. The DFU group has higher HbA1c (OR, 0.758 P , 0.001 , 95% CI ; 0.647- 0.888), more males (OR; 0.365, P, = 0.005 95% CI ; 0.180- 0.737) than the control group. Moreover, DFU with DR and DFU without DR were compared to each other using the same test. The results showed that the Saudi nationality (OR; 0.704, P, 0.409 95% CI; 0.306 -1.619) is not significantly associated with DR.

history of hypertension (OR; 4.136, P, 0.017 95% CI; 1.287 -13.287) and DFU
(OR; 4.165, P, 0.001 95% CI; 1.826 -9.501) significantly associated with DR [Table 5].

By using bivariate analysis (chi square test), we found a significant association between DFUs and DR (p = < 0.001) [Table 6].

Table 1. univariate analysis of all patients classified according to DFU

	All diabetic patients	
	Sample size = 402	
	Cases	**Control**
	Sample size = 199	**Sample size = 203**
Demographic characteristics		
Age (years)	63.4±12.5	60.7±15.3
Gender (male)	142 (71.4%)	107 (52.7%)
Diabetes duration (years)	16.9±8.8	16.5±11.1
Nationality (Saudi)	76 (38.2%)	77 (37.9%)
History of HTN	133 (66.8%)	144 (70.9%)
Systolic BP (mmHg)	140.5±26.6	136.2±24.1
Diastolic BP (mmHg)	72.9±16.8	73.9±16.4
History of Smoking	40 (20.1%)	31 (15.3%)
Underweight BMI (kg/m2)	6 (3%)	6 (3%)
normal BMI (kg/m2)	57 (28.6%)	51 (25.1%)
Overweight BMI (kg/m2)	44 (22.1%)	55 (27.1%)
Obese class 1 (kg/m2)	28 (14.1%)	33 (16.3%)
Obese class 2 (kg/m2)	18 (9%)	13 (6.4%)
Obese class 3 (kg/m2)	8 (4%)	16 (7.9%)
Biochemical characteristics		
HbA1c (%, mmol/mol)	9±2.48	8.2±2.4
Random glucose (mg/dL)	201.68±92.3	190.8±101.2
Cholesterol (mg/dL)	140.54±50.2	150.5±53.3
Triglyceride (mg/dL)	136.28±97.3	150.44±115.04
LDL (mg/dL)	129.3±444	96.5±38.6
HDL (mg/dL)	37.4±11.58	38.6±11.58
Hematocrit (%)	32.1±6.4	34±7.7
BUN (mg/dL)	12±12.6	11.8±11.6
Creatinine	2.37±2.63	2.12±2.2
No retinopathy	154 (77.4%)	185 (91.1%)
Both types of retinopathy	45 (22.6%)	18 (8.9%)
PDR	30 (15.1%)	7 (3.4%)
NPDR	15 (7.5%)	11 (5.4%)
Methods of glycemic control		
No medication	36 (18.1%)	61 (30%)
Insulin	64 (32.2%)	45 (22.2%)
Oral hypoglycemic only	35 (17.6%)	49 (24.1%)
Both	57 (28.6%)	41 (20.2%)

*Missing data not written in patient's profiles in cases and controls, 38(19.2%) and 29(14.2%) respectively. *
* There was missing data not written in patient's profiles in cases and controls, 7(3.5%) and 7(3.5%) respectively. -
Underweight (> 18.5), normal (18.5-24.9), overweight(25.0-29.9), obesity class 1 (30,0-34.9), obesity class2 (35.0-39.9), obesity class 3 (< 40)

Table 2. Univariate analysis of patient with DFU, classified according to DR

	DFU Sample size = 199		
	With PDR	**With NPDR**	**Without DR**
	e size = 30 (15%)	**le size = 15 (7.5%)**	**le size = 154 (77.5%)**
Demographic characteristics			
Age (years)	64±8.26	62.7±15.14	63.3±13.01
Gender (male)	23 (76.7%)	12(80%)	107 (69.5%)
Diabetes duration (years)	19±6.44	15.6±9.88	15.87±9.50
Nationality (Saudi)	11 (36.7%)	1 (6.7%)	64 (41.6%)
History of HTN	24 (80%)	12 (80%)	97 (63%)
Systolic BP (mmHg)	146.5±25.61	135.3±18.26	139.8±27.56
Diastolic BP (mmHg)	72.7±14.89	71.6±12.59	73.1±17.69
History of Smoking	7 (23.3%)	5 (33.3%)	28 (18.2%)
Underweight BMI (kg/m2)	1 (3.3%)	0 (0%)	5 (3.2%)
normal BMI (kg/m2)	7 (23.3%)	5 (33.3%)	45 (29.2%)
Overweight BMI (kg/m2)	6 (20%)	4 (26.7%)	34 (22.1%)
Obese class 1 (kg/m2)	4 (13.3%)	1 (6.7%)	23 (14.9%)
Obese class 2 (kg/m2)	6 (20%)	2 (13.3%)	10 (6.5%)
Obese class 3 (kg/m2)	1 (3.3)	2 (13.3%)	5 (3.2%)
Biochemical characteristics			
HbA1c (%)	8.4±2.04	9.7±2.04	9.1±2.60
Random glucose (mg/dL)	210.5±92.75	249.9±93.93	159.3±91.12
Cholesterol (mg/dL)	150.5±48.64	135.1±42.47	138.9±52.5
Triglyceride (mg/dL)	132.74±73.45	120.35±66.37	141.6±106.19
LDL (mg/dL)	328.1±1040.9	96.5±32.4	92.6±44.78
HDL (mg/dL)	38.6±10	38.6±10.8	34.7±13.12
Hematocrit (%)	33.7±6.05	33.5±6.48	31.8±6.49
BUN (mg/dL)	13.3±12.96	10.4±8.15	12±12.91
Creatinine (mg/dL)	2.79±2.45	1.53±0.9	2.37±2.77
No retinopathy	-	-	154 (100%)
Retinopathy	30 (66.7%)	15 (33.3%)	-
Methods of glycemic control			
No medication	3 (10%)	1 (6.7%)	32 (20.8%)
Insulin	13 (43.3%)	2 (13.3%)	49 (31.8%)
Oral hypoglycemic only	4 (13.3%)	3 (20%)	28 (18.2%)
Both	10 (33.3%)	9 (60%)	38 (24.7%)

Table 3. bivariate analysis of all independent variable with each dependent variable

	P value	**P value**
	DFU	**DR**
Demographic characteristics		
Age (years)	0.059	0.939
Gender (male)	<0.001	0.541
Diabetes duration (years)	0.870	0.331
Nationality (Saudi)	1.00	0.029
History of HTN	0.435	0.103
Systolic BP (mmHg)	0.120	0.365
Diastolic BP (mmHg)	0.573	0.954
History of Smoking	0.255	0.336
Underweight BMI (kg/m2)	0.359	0.428
normal BMI (kg/m2)		
Overweight BMI (kg/m2)		
Obese class 1 (kg/m2)		
Obese class 2 (kg/m2)		
Obese class 3 (kg/m2)		
Biochemical characteristics		
HbA1c (%)	0.002	0.247
Preprandial glucose (mg/dL)	0.274	0.079
Cholesterol (mg/dL)	0.045	0.380
Triglyceride (mg/dL)	0.101	0.793
LDL (mg/dL)	0.319	0.096
HDL (mg/dL)	0.283	0.481
Hematocrit (%)	0.010	0.246
BUN (mg/dL)	0.857	0.755
Creatinine	0.315	0.325
No retinopathy	-	-
Both types of retinopathy	<0.001	-
PDR	-	0.247
NPDR	-	0.079

Table 4. Multivariate logistic regression test between independent variables and DFU

	P value	OR	95% CI for OR	
			Lower	Upper
DFU group vs control group				
Gender (male)	0.005	0.365	0.180	0.737
Age	0.561	0.992	0.965	1.019
Nationality (Saudi)	0.065	1.930	0.961	3.877
Smoking	0.574	0.800	0.368	1.741
History of HTN	0.040	2.478	1.044	5.882
Systolic BP	0.075	0.986	0.970	1.001
Diastolic BP	0.433	1.010	0.985	1.036
HbA1c (%)	0.001	0.758	0.647	0.888
Random glucose (mg/dL)	0.066	0.997	0.993	1.000
Cholesterol (mg/dl)	0.705	1.056	0.796	1.401
Triglyceride (mg/dL)	0.933	1.014	0.731	1.407
BUN	0.127	1.030	0.992	1.069
Hematocrit (%)	0.003	1.078	1.026	1.132
Creatinine (mg/dL)	0.331	0.999	0.996	1.001
DR	0.003	-	-	-
No DR	0.265	1.821	0.635	5.217
PDR	0.092	0.287	0.067	1.227

Table 5. Multivariate logistic regression test between independent variables and DR

	P value	OR	95% CI for OR	
			Lower	Upper
DFU with DR DFU without DR				
Gender (male)	0.667	1.208	0.511	2.859
Age	0.330	1.018	0.982	1.057
Nationality (Saudi)	0.409	0.704	0.306	1.619
Smoking	0.669	0.822	0.335	2.016
History of HTN	0.017	4.136	1.287	13.287
Systolic BP	0.999	1.000	0.981	1.019
Diastolic BP	0.862	1.003	0.973	1.034
HbA1c (%)	0.667	1.037	0.878	1.225
Random glucose (mg/dL)	0.919	1.000	0.996	1.004
Cholesterol (mg/dl)	0.243	1.216	0.876	1.687
Triglyceride (mg/dL)	0.248	0.753	0.465	1.218
BUN	0.497	0.982	0.931	1.035
Hematocrit (%)	0.114	1.047	0.989	1.108
Creatinine (mg/dL)	0.771	1.000	0.997	1.004
DFU	0.001	4.165	1.826	9.501

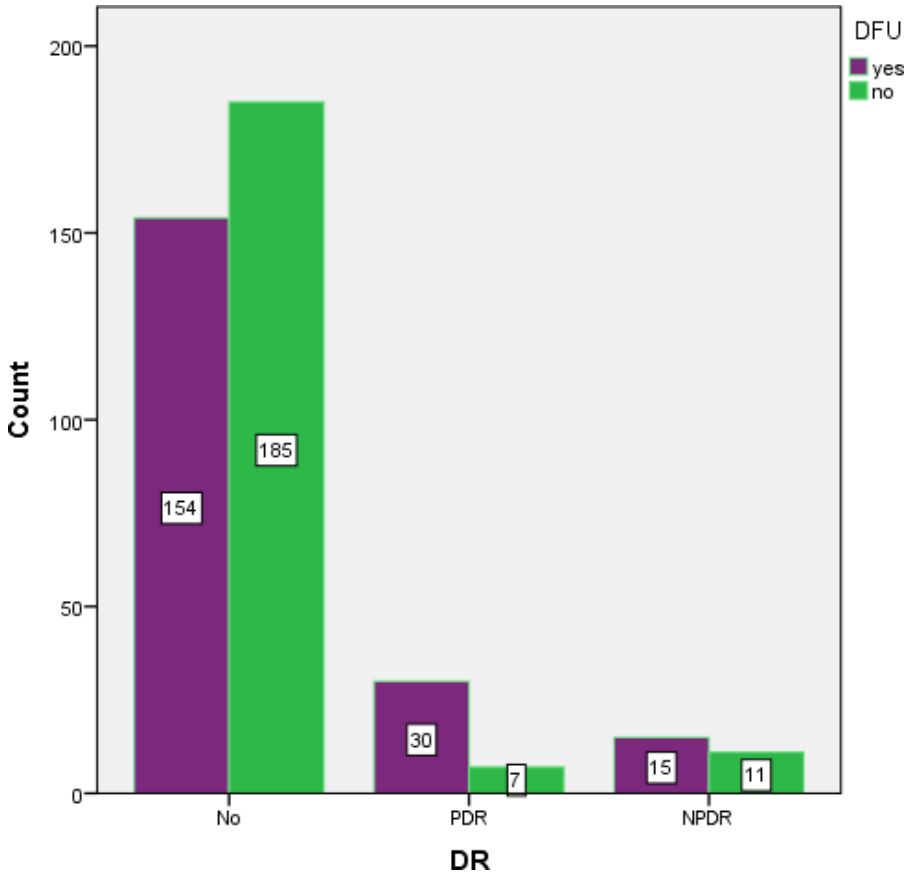

Figure 1: Bar chart showing the frequency of DR among patients with and without DFU

Table 6. chi-square test, showing a significant association between DFU and DR

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	17.709[a]	2	.000
Likelihood Ratio	18.816	2	.000
N of Valid Cases	402		

DISCUSSION:

In this study we found that 22.6% of patients with DFU had DR. During comparing diabetic patients with DFU and those group without DFU, we found a significant association between low hematocrit value, gender, and HbA1c and DFU. Also, we found that history of hypertension significantly associated with both DR and DFU.

In our study, the prevalence of DR among diabetic patients without DFU was 8.9%; meanwhile, its prevalence among DFU was 22.6%. Furthermore, 15.1% of patients with DFU had PDR. Liu et al [20] reported that DR was present in 21.2% of DFU patients which is consistent with our study most probably due to similar mean ages (64.6 vs. 63.4 years) and duration of diabetes (14.7 vs. 16.9 years). On the other hand, Lavery et al [21] showed that 66% of patients with DFU had DR, among them 22% had PDR. This difference can cause by the poorer diabetes control (HbA1c 9.9±2.4 vs. 9±2.48) which considered to be a risk factor to develop foot ulceration. Also, more males (74 vs. 71.4%) who have related to several lower limb complications in diabetes, while women seem to have a better prognosis and fewer complications than men. Besides, McNeely et al [22] revealed that (60.5%) of diabetic subjects with a documented foot ulcer present also with DR, their higher prevalence might be attributed to the majority of men in their study (93.5 vs. 71.4%).

A multivariate logistic regression demonstrated a significant correlation between DFU and DR with a p-value of 0.003. Similarly, Walters et al [23] also confirm a significant association between them (p>0.001). Lavery et al [21] showed that diabetic patients with DR were at a significantly higher risk for foot ulcer (p>0.001). Furthermore, Walsh et al [24] found a relation between DFU and DR which had been considered a risk factor for amputation [25]. Additionally, Hwang et al [5] further support this relationship. No wonder because the natural history of diabetes comprises both complications (DFU and DR) which compromise the patient's quality of life QOL [26-30] putting a heavy burden on them and their families and if left untreated DR will eventually lead to blindness.

We found that DFU (cases) and diabetes in general (control) occurs more frequently in males 142 (71.4%) and 107 (52.7%) respectively, with a p value <0.001. Similarly to a result conducted in Korea by Hwang et al [5], reported that DFU higher among males 74 (74%) and those with DM alone, 1789 (72%) of them were males but their result about gender was not significant (p= 0.583). Correspondingly Nongmaithem et al [31], gender was not significantly associated with the risk of DFU (P > 0.05) which is inconsistent with our study. The reasons behind that can be attributed to the younger age and larger sample size in the control group of Hwang et al [5], small number of cases (DFU) and the relative difference in ages of Nongmaithem et al [31]

In addition, HbA1c showed to be higher in DFU patients (9±2.48%) than the control group (8.2±2.4%) with a p value equal to 0.002 in our study. The same goes with Hwang et al [5], record a HbA1c of 8.0±1.8 and 7.4±1.3 of the DFU and the control groups respectively with a p-value equal to (0.003), also in Nongmaithem et al [31], DFU patients had HbA1c > 7.5% (P < 0.001). Jiang et al [32]and Al-Rubeaan et al [19] reported the same results with different numbers. Not surprisingly that the higher HbA1c level the patient had, the poorer outcome and complications he will develop. Contradictory to the previous studies, a study carried in Iran [33], had a different point of view about HbA1c, the number of DFU patients who had hbA1c ≥7% was 51(94.4) and controls 66(88) with (p=0.21). This result could be due to their small sample size DFU (n=54) and control (n=78).

Additionally, we found a significant association between DFU and low hematocrit value. Hwang et al [5] also support our result (P < 0.001). That may be due to anemia that caused by malnutrition and decrease of erythropoietin which is one of the consequences of diabetic kidney injury [5, 34]. Meanwhile, a study was established in Australia [35] about (Anemia in Diabetes: An Emerging Complication of Microvascular Disease) showed that decreased level of hemoglobin could affect the wound healing. Also, the compensated mechanisms for anemia in nondiabetic patients (increased peripheral perfusion, increased vasoreactivity and elevated erythropoietin) impaired in patients with diabetes especially in those with microvascular complication.

Hypertension is a risk factor of DFU. Hwang et al [5] showed a significant association between DFU and history of high blood pressure (P <0.001). The primary causes of these ulcers are due to neurologic abnormalities and peripheral arterial disease (PAD) [36]. Also, the diabetic patients with PAD are also at a higher risk of gangrene, ischemic ulceration, and lower limb amputation than diabetic patients without PAD [37]. Moreover, one of the complications of hypertension is PAD. Increase blood pressure leading

to thickening of the arterial wall and atheroma plaque formation. Subsequently, decrease blood flow to the tissues [38].

History of hypertension significantly associated with diabetic retinopathy. Both hypertension and diabetes cause retinopathy but the mechanism is different [39]. A study conducted in Brazil about "Hypertension Increases Inflammation in Diabetic Retina" [40] said that the presence of hypertension in diabetic patient exacerbate retinopathy through increasing inflammatory mediators. This may be explaining the relationship between DR and present history of hypertension. Our study has several limitations, may be due to retrospective nature. Therefore, this type of research needs to collect the data from patient's file. So, there were missing data like BMI and lipid profile. Also in our university, we don't use a particular classification for the severity of DFU. This defect may interfere with other studies that need to see any relationship the severity of ulcer and other variables.

Because we found a significant association between DFU and patients with DR, we recommend for any patients come to the clinic with DFU to examine their eyes using ophthalmoscopy and annual assessment by an ophthalmologist for any patient with diabetes in general which is crucial for their management and to stop further deterioration. Also, we need a particular protocol for any patient with DFU containing the classification of ulcer, a group of laboratory tests such as (lipid profile, fasting blood glucose and glycosylated hemoglobin) should be done for them and a report from the ophthalmologist about the condition of patient's eyes.

We also encourage some screening tools for early diabetics and those who have been suspected to become diabetic beside other clinics or specialties to manage other devastating complications of this catastrophe. Also, health education has its own effect on the patients and enhances their compliant to medication besides diet and exercise which is beneficial for any disease not only diabetes.

ACKNOWLEDGMENT:

We would like to thank Maha Yousef Baabdullah and Aseelah Ahmad AlRasheedi for their hard efforts in completion of our study and involvement in the data collection.

REFERENCES:

1 A. D. McInnes, “Diabetic foot disease in the United Kingdom: about time to put feet first,” Journal of Foot and Ankle Research, vol. 5, no. 1, article 26, 2012.
2 Naeem, Zahid. "Burden of Diabetes Mellitus in Saudi Arabia." International journal of health sciences 9.3 (2015): V.
3 Alwin Robert, Asirvatham, Abdulaziz Al Dawish, Mohamed, Braham, Rim, Ali Musallam, Maha, Abdullah Al Hayek, Ayman & Hazza Al Kahtany, Nasser. 2017. Type 2 Diabetes Mellitus in Saudi Arabia: Major Challenges and Possible Solutions. Current diabetes reviews 13: 59-64.
4 Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005; 293 (2):217–28. https://doi.org/10.1001/jama.293.2.217 PMID: 15644549
5 Hwang, Duck Jin, et al. "Association between diabetic foot ulcer and diabetic retinopathy." PloS one 12.4 (2017): e0175270
6 V. Fejfarov´a, A. Jirkovsk´a, E. Dragomireck´a et al., “Does the diabetic foot have a significant impact on selected psychological or social characteristics of patients with diabetes mellitus?”Journal of Diabetes Research, vol. 2014, Article ID 371938, seven pages, 2014.
7 J. J. vanNetten, P. E. Price, L. A. Lavery et al., “Prevention of foot ulcers in the at-risk patient with diabetes: a systematic review,”Diabetes/Metabolism Research and Reviews, vol. 32, supplement 1, pp. 84–98, 2016.
8 W.Clayton Jr. and T. A. Elasy, “A review of the pathophysiology, classification, and treatment of foot ulcers in diabetic patients,”Clinical Diabetes, vol. 27, no. 2, pp. 52–58, 2009.
9 Tomita, Masuomi, et al. "Diabetic microangiopathy is an independent predictor of incident diabetic foot ulcer." Journal of diabetes research 2016 (2016).
10 A. J. Boulton, L. Vileikyte, G. Ragnarson-Tennvall, and J. Apel-qvist, “Te global burden of diabetic foot disease,” Te Lancet, vol. 366, no. 9498, pp. 1719–1724, 2005.
11 Sargen MR, Hoffstad O, Margolis DJ. Geographic variation in Medicare spending and mortality for diabetic patients with foot ulcers and amputations. J Diabetes Complicat. 2013; 27: 128–133. doi: 10.1016/j.jdiacomp.2012.09.003 PMID: 23062327
12 Moss SE, Klein R, Klein BE. The prevalence and incidence of lower extremity amputation in a diabetic population. Arch Intern Med. 1992; 152(3):610±6. PMID: 1546925.Borssen B, Bergenheim T, Lithner F. The epidemiology of foot lesions in diabetic patients aged 15±50 years. Diabet Med. 1990; 7(5):438±44. PMID:

2142042.
13 Ting, Daniel Shu Wei, Gemmy Chui Ming Cheung, and Tien Yin Wong. "Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review." Clinical & experimental ophthalmology44.4 (2016): 260-277.
14 Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy.
III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30or more years. Arch Ophthalmol 1984;102:527±32.
15 Khandekar R, Al Lawatii J, Mohammed AJ, Al Raisi A. Diabetic retinopathy in Oman: a hospital based study. Br J Ophthalmol. 2003; 87(9):1061–4. PMID: 12928265.
16 Sriussadaporn, S., et al. "Factors Associated with Diabetic Foot Ulceration in Thailand: a Case-control Study." Diabetic medicine 14.1 (1997): 50-56.
17 Wilkinson CP, Ferris FL 3rd, Klein RE, Lee PP, Agardh CD, Davis M, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology. 2003;110(9):1677–82. https://doi.org/10.1016/S0161-6420(03)00475-5 PMID: 13129861
18 Al-Rubeaan, Khalid, et al. "Diabetic foot complications and their risk factors from a large retrospective cohort study." *PLoS One* 10.5 (2015): e0124446.
19 Liu C, Xu L, Gao H, Ye J, Huang Y, Wu M, et al. The association between skin autofluorescence and vascular complications in Chinese patients with diabetic foot ulcer: an observational study done in Shanghai. Int J Low Extrem Wounds. 2015; 14(1):28±36. https://doi.org/10.1177/1534734614568375PMID: 25694437
20 Lavery, Lawrence A., et al. "Practical criteria for screening patients at high risk for diabetic foot ulceration." Archives of internal medicine 158.2 (1998): 157-162.
21 McNeely, Marguerite J., et al. "The Independent Contributions of Diabetic Neuropathy and vasculopathy in Foot Ulceration: How great are the risks?." Diabetes care 18.2 (1995): 216-219.
22 Walters, D. P., et al. "The Distribution and Severity of Diabetic Foot Disease: a Community Study with Comparison to a Non-diabetic Group." Diabetic Medicine9.4 (1992): 354-358.
23 Walsh, C.H., Soler. N.G., FitzGerald, M.G. and Malins, J.M. (1975) Association of foot lesions with retinopathy in patients with newly diagnosed diabetes. Lancet i: 878-880.
24 Nelson, R.G. Gohdes, M.D., and Everhart, J.E. (1988) Lower extremity amputation in NIDDM: 12-year follow up study in Pima Indians. Diabetes Care 11. 8-16.
25 Brod M. Quality of life issues in patients with diabetes and lower extremity ulcers: patients and care givers. Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation.1998; 7(4):365±72.
26 Carrington AL, Mawdsley SK, Morley M, Kincey J, Boulton AJ. Psychological status of diabetic people with or without lower limb disability. Diabetes research and clinical practice. 1996; 32(1±2):19±25. PMID: 8803478
27 Sharma S, Oliver-Fernandez A, Liu W, Buchholz P, Walt J. The impact of diabetic retinopathy on health-related quality of life. Current opinion in ophthalmology. 2005; 16(3):155±9. PMID: 15870571
28 Sampson CJ, Tosh JC, Cheyne CP, Broadbent D, James M. Health state utility values for diabetic retinopathy: protocol for a systematic review and meta-analysis. Systematic reviews. 2015; 4:15. https://doi.org/10.1186/s13643-015-0006-6 PMID: 25875206
29 Coyne KS, Margolis MK, Kennedy-Martin T, Baker TM, Klein R, Paul MD, et al. The impact of diabetic retinopathy: perspectives from patient focus groups. Family practice. 2004; 21(4):447±53.https://doi.org/10.1093/fampra/cmh417 PMID: 15249536
30 Nongmaithem, Mackson, et al. "A study of risk factors and foot care behavior among diabetics." Journal of family medicine and primary care 5.2 (2016): 399.
31 Jiang, Yufeng, et al. "A cohort study of diabetic patients and diabetic foot ulceration patients in China." Wound Repair and Regeneration 23.2 (2015): 222-230.
32 Sanjari, Mojgan, et al. "A cross-sectional study in Kerman, Iran, on the effect of diabetic foot ulcer on health-related quality of life." The international journal of lower extremity wounds 10.4 (2011): 200-206.
33 Sahay M, Kalra S, Badani R, Bantwal G, Bhoraskar A, Das AK, Dhorepatil B, Ghosh S, Jeloka T, Khandelwal D, Latif ZA. Diabetes and Anemia: International Diabetes Federation (IDF)– Southeast Asian Region (SEAR) position statement. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2017 Apr 28.
34 Thomas M, Tsalamandris C, MacIsaac R, Jerums G. Anaemia in diabetes: an emerging complication of microvascular disease. Current diabetes reviews. 2005 Jan 1;1(1):107-26.

35 Apelqvist J, Larsson J. What is the most effective way to reduce incidence of amputation in the diabetic foot?. Diabetes/metabolism research and reviews. 2000 Sep 1;16(S1).
36 Schaper N, Andros G, Apelqvist J, et al. Diagnosis and treatment of peripheral arterial disease in diabetic patients with a foot ulcer. A progress report of the International Working Group on the Diabetic Foot. Diabetes Metab Res Rev 2012; 28: 218–224.
37 Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiological reviews. 2013 Jan 1;93(1):137-88.
38 Harrold BP. Diabetic retinopathy and hypertension. The British journal of ophthalmology. 1971 Apr;55(4):225.
39 Silva KC, Pinto CC, Biswas SK, Lopes de Faria JB, Lopes de Faria JM. Hypertension increases retinal inflammation in experimental diabetes: a possible mechanism for aggravation of diabetic retinopathy by hypertension. Current eye research. 2007 Jan 1;32(6):533-41.

Footnote
DM: Diabetes Mellitus
DR: Diabetic Retinopathy
DFU: Diabetic Foot Ulcer
SPSS: Statistical Package for the Social sciences
PDR: Proliferative Diabetic Retinopathy
NPDR: Non-Proliferative Diabetic Retinopathy
KAUH: King Abdulaziz University Hospital
LDL: Low Density Lipoprotein
HDL: High Density Lipoprotein
HTN: Hypertension
BMI: Body Mass Index
BUN: Blood Urea Nitrogen
PAD: Peripheral Arterial Disease