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Determination of risk factors for the development of diabetic foot disease

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ABSTRACT

Aim: The aim of this study was to analyze risk factors involved in the development of diabetic foot disease.

Methods: Eighty-five diabetic foot patients and 109 diabetes mellitus diagnosed patients without diabetic foot disease (as the control group) were involved in this study. This was an analytic, case-control study. A questionnaire interrogating the patients' socio-demographic characteristics, general information about their diseases and Morisky Medication Adherence Scale-8 were used in this research.

Results: According to this study, diabetic foot disease is more frequently observed in male patients, in smokers, in those with an education level lower than high school and in those with a low income level. The rate of insulin users was higher in the group with diabetic foot disease. A history of retinopathy has been identified as a risk factor for diabetic foot disease. Each 1 unit of decline in e-GFR level increases the risk of diabetic foot development by 2%. Regular exercise is five times protective against diabetic foot disease.

Conclusions: A decline in e-GFR values was a risk for diabetic foot disease; regular blood glucose monitoring and regular exercise were protective against diabetic foot disease. These factors should be considered in the management of diabetes mellitus.

Keywords: Diabetic foot disease, medication adherence, retinopathy, exercise, e-GFR

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Introduction

40-60% of all non-traumatic lower limb amputations are related to Diabetes Mellitus (DM). (1). In DM, the prevalence of ulcer is approximately 4-10% and its incidence 2.2 - 5.9% (2). Diabetic foot complications, which may present with concomitant skin changes, ulceration, infection and gangrene, are unfortunately an annoying health problem caused by diabetes. In diabetes, vascular disease, neuropathy and relative immune suppression coexist (3). There are two main mechanisms in diabetic foot pathogenesis. These are angiopathy and neuropathy. Arterial plaque stenosis caused by micro-angiopathy and macro-angiopathy leads in time to malnutrition of bones and joints. Moreover, sensory, autonomic and motor neuropathy develops as a result of malnutrition of the foot muscle and nerve tissues. This situation leads to hot-cold sensation loss, limitation in joint mobility, reduced pain sensation, reduced perspiration and postural disorders. Foot ulcers, chronic wounds and even osteomyelitis caused by various microorganisms penetrating through fissures due to dry skin may develop in the foot, which is prone to trauma due to deformity (4). This situation leads in time to gangrene, and extremity losses resulting in amputation may occur.

Adherence can be described as the patient's acceptance of health-related recommendations and compliance with them, briefly, applying all of the clinician's recommendations in the behavioral aspect (5) Medication adherence is generally the extent to which patients take medication as prescribed by their doctors (6). In medication adherence, the patients are expected to take their medications with respect to the timing, dosage and frequency as recommended and not to stop their medications before the recommended time, assuming that they recover, and to behave in accordance with the behaviors recommended, what to do and what not to do (7-9). Medication non-adherence can occur by not using the prescribed medications, by irregular usage of medications, not complying with the recommended dosage or recommended frequency, using non-prescribed medications, missing appointments or follow-ups or abandoning treatment (10).

Diabetes can be asymptomatic for years but severe complications can occur after many years. It is difficult to encourage treatment with the patient during an asymptomatic period. In diabetic patients, medication adherence affects glycemic control, avoids acute complication development and delays chronic complication occurrences (11). The relationships between morbidity, mortality, health expenses and medication adherence rates have been emphasized several times in recent studies (12-14). The aim of this study was to analyze the risk factors involved in the development of diabetic foot disease.

Methods

This study involved patients with diabetic foot disease who were admitted to the UHS Bursa Yuksek Ihtisas Training and Research Hospital, Orthopedics, Endocrinology, Hyperbaric Medicine Outpatient clinics between July 2018- December 2018 and diabetes patients who were hospitalized for various indications. Ethics committee approval was received from the UHS Bursa Training and Research Hospital, dated; 14.02.2018, no; 2011-KAEK-25 2018/01-07.

Eighty-five diabetic foot patients and 109 diabetes mellitus diagnosed patients without diabetic foot disease (as a control group) were involved in the study. This was an analytic, case-control study. A face-to-face survey method was used. The patients were informed prior to the survey and their consent was received. Patient confidentiality was maintained.

A questionnaire interrogating the patients' socio-demographic characteristics and general information

about their diseases was used. The Morisky Medication Adherence Scale-8, for which the Turkish validity and reliability have been shown for diabetes mellitus, was used to evaluate the medication adherence of the volunteers. The questionnaire interrogated the following: protocol number, gender, age, marital status, education status, height, weight, body mass index, smoking status, alcohol usage, profession, income status, chronic diseases, and medications used. In addition to these, diabetes mellitus diagnosis time, medications still used for DM, subcutaneous injection usage time (if used), number of admissions to the emergency service in the recent year due to diabetes, reason for admissions, number of hospitalizations and diagnosis in the recent year, HbA1c values of the patients for the last 3 months from the hospital laboratory archive records, fasting and postprandial blood glucose levels, frequency of doctor visits for diabetes monitoring, health institutions where medical check-ups are frequently performed, whether the patient regularly measures their blood glucose or not, whether they obey the diet recommended for diabetes and their exercising status were also interrogated.

Among the anthropometric measurements, height and weight was measured using standard measuring instruments. Patients were asked to take off their shoes during height measurement. It was also assured that the patients wore light clothes during weight measurement. BMI: Body mass index was calculated by dividing the patient's weight by the square of his/her height (kg/m²).

The scale used in the study is comprised of 7 two-choice (yes/no) close-ended questions and one 5-choice close-ended question. In the first 4 questions No is rated as 1, Yes is rated as 0; in the 5th question Yes is rated as 1 and No is rated as 0; in the 6th and 7th questions No is rated as 1 and Yes is rated as 0 and in the 8th question never is rated as 1 and the other 4 choices are rated as 0. Adherence to medication increases as the score increases. Patients with a Morisky score of <6 are classified as low adherence, a score of 6-7 reflects medium adherence and a score of 8 reflects high adherence. In our study, those with a score <6 were classified as non-adherent (low adherence), those with a score 6-8 were classified as adherent (medium-high adherence). The scale was translated into Turkish by Sayiner in 2006 and its validity and reliability were validated with its adaptation to Turkish society (15).

Statistical analysis

Compatibility of variables to normal distribution was analyzed with Shapiro Wilk test. Continuous variables are expressed with mean ± standard deviation and median (minimum: maximum) values. Categorical variables are expressed with n (%). Mann Whitney U test or independent sample t test was used in the comparisons performed between the two groups according to the normality test results. Pearson chi-square, Fisher's exact chi-square test or Fisher Freeman-Halton tests were used in the inter-group comparisons of categorical variables. SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program was used for statistical analysis and $p<0.05$ was accepted as statistically significant.

Results

85 DM patients with diabetic foot disease and 109 DM patients without diabetic foot disease volunteered for the study (Table 1). A difference was detected between diabetic foot groups in terms of gender distribution. The rate of male patients was higher in the group with diabetic foot ($p=0.027$). There was a difference between diabetic foot groups in terms of smoking status ($p<0.001$). There was a difference

between diabetic foot groups in terms of alcohol usage (p=0.003). There was a difference between diabetic foot groups in terms of education status (p=0.010). There was a difference between diabetic foot groups in terms of income status (p=0.002).

Table 1: Sociodemographic characteristics of the participants and diabetic foot disease

	n	Diabetic Foot (+)	n	Diabetic Foot (-)	p-value
Age (year)	85	61(29:80) *60.95±10.39*	109	62(21:85) *60.61±13.90*	0.652[a]
Gender					
Female	85	25(29.41%)	109	49(44.95%)	**0.027[b]**
Male		60(70.59%)		60(55.05%)	
Height	83	168(150:190) *168.46±7.82*	105	165(70:182) *164.95±12.82*	0.067[a]
Weight	82	76.50(55:140) *79.89±15.48*	107	80(45:118) *79.83±13.88*	0.517[a]
BMI	82	26.98(17.96:56.08) *28.25±5.58*	105	28.40(17.58:185.71) *30.53±16.13*	0.101[a]
Smoking					
Never smoked	85	29(34.12%)	109	63(57.80%)	**<0.001[b]**
Still smoking		11(12.94%)		24(22.02%)	
Quit smoking		45(52.94%)		22(20.18%)	
Alcohol					
Never used	84	54(64.29%)	109	93(85.32%)	**0.003[b]**
Still using		6(7.14%)		3(2.75%)	
Quit		24(28.57%)		13(11.93%)	
Education Status	**n**	**Diabetic Foot (+)**	**n**	**Diabetic Foot (-)**	**p-value**
Lower than high school	85	74(87.06%)	109	78(71.56%)	**0.010[b]**
High school		9(10.59%)		16(14.68%)	
Higher education		2(2.35%)		15(13.76%)	
Profession					
Unemployed	85	1(1.18%)	108	1(0.93%)	0.079[c]
Housewife		21(24.71%)		40(37.04%)	
Officer		1(1.18%)		7(6.48%)	
Retired		43(50.59%)		48(44.44%)	
Driver		1(1.18%)		1(0.93%)	
Farmer		4(4.71%)		1(0.93%)	
Worker		5(5.88%)		6(5.56%)	
Craft		8(9.41%)		3(2.78%)	
Other		1(1.18%)		1(0.93%)	
Marital Status					
Married	85	72(84.71%)	109	93(85.32%)	0.070[c]
Single		1(1.18%)		3(2.75%)	
Widow		12(14.12%)		13(11.93%)	
Income Status					
Low	84	17(20.24%)	107	7(6.54%)	**0.002[b]**
Medium		61(72.62%)		79(73.83%)	
High		6(7.14%)		21(19.63%)	

Data given as n (%), median (minimum: maximum) and mean ± standard deviation.
[a]: Mann-Whitney U test, [b]: Chi-Square Test, [c]: Fisher-Freeman Halton Test

Comparisons between the groups with and without diabetic foot disease are given in Table 2. There was a difference between diabetic foot groups in terms of DM duration. The median DM duration was longer in the diabetic foot group (p<0.001). The rate of insulin users was higher in the diabetic foot group than those without diabetic foot (p<0.001). The rate of patients who administered self-treatment was higher in the group without diabetic foot presence (p=0.016).

Table 2. Comparisons between groups with and without diabetic foot disease

	n	Diabetic Foot (+)	n	Diabetic Foot (-)	p-value
Diabetes Mellitus Duration	85	15(0.30:37) *15.56±8.40*	107	8(0.02:40) *10.21±9.20*	**<0.001[a]**
Diabetes Mellitus Medication					
insulin	84	64(76.19%)	109	25(22.94%)	**<0.001[c]**
Oral antidiabetic drug		11(13.10%)		68(62.38%)	
Insulin+ oral antidiabetic drug		9(10.71%)		15(13.76%)	
Stopped taking medications		0		1(0.92%)	
Subcutaneous treatment (year)	75	5(0.05:37) *6.74±6.51*	39	5(0.02:30) *8.33±7.68*	0.369[a]
Administering					
Himself/Herself	75	54(72%)	37	34(91.89%)	**0.016[b]**
Relative		21(28%)		3(8.11%)	

Data given as n (%), median (minimum: maximum) and mean ± standard deviation. [a]: Mann-Whitney U test, [b]: Chi-Square Test, [c]: Fisher-Freeman Halton Test

Comparisons of emergency and hospital admissions of diabetic foot patients are given in Table 3. There was a difference between diabetic foot groups in terms of number of patients who were admitted to the emergency service due to DM. The number of patients admitted to the emergency service due to DM was higher in the diabetic foot group (p=0.042). There was a difference between diabetic foot groups in terms of number of hospitalizations. The median hospitalization number was higher in the group with diabetic foot (p=0.005).

Table 3. Hospital admissions and related factors and diabetic foot disease

	n	Diabetic Foot (+)	n	Diabetic Foot (-)	p-value
Number of admissions to emergency due to DM	20	2.50(1:10) *3.70±2.99*	14	1.50(1:10) *2.93±2.99*	**0.042[a]**
Reason of admission to emergency					
Ketoacidosis/hyperglycemia	20	18(90.00%)	14	11(78.57%)	0.627[e]
hypoglycemia		2(10.00%)		3(21.43%)	
Number of hospitalizations	64	2(1:8) *2.22±1.41*	35	1(1:4) *1.51±0.74*	**0.005[e]**
Reasons for hospitalization					
Blood glucose regulation	85	21(24.71%)	109	21(19.27%)	0.361[b]
Pneumonia	85	1(1.18%)	109	0	0.438[e]
Diabetic foot	85	33(38.82%)	109	0	**<0.001[b]**
Amputation	85	10(11.76%)	109	0	**<0.001[e]**
CAD	85	10(11.76%)	109	3(2.75%)	**0.013[b]**

Data given as n (%), median (minimum: maximum) and mean ± standard deviation.[a]: Mann-Whitney U test, [b]: Chi-Square Test, [e]: Fisher's Exact Test

There was no difference between diabetic foot groups in terms of HbA1c fasting and postprandial blood glucose levels (respectively, p=0.083, p=0.378 and p=0.191). The rate of patients who visited the doctor once every 6 months was higher in the group without diabetic foot compared to the diabetic foot group (p=0.004) (Table 4). The rate of those who visited university hospitals was higher in the group without diabetic foot than the diabetic foot group (p<0.001). The rate of patients who had regular blood glucose measurement was higher in the group with diabetic foot compared to the group without diabetic foot (p=0.003). There was a difference between diabetic foot groups in terms of regular exercising status (p=0.005)

Table 4. Blood glucose control, diet and exercise and diabetic foot disease

	n	Diabetic Foot (+)	n	Diabetic Foot (-)	p-value
HbA1c	53	8(5.20:15.40) *8.72±2.48*	47	7.30(5:13.80) *7.78±1.75*	0.083[a]
Fasting blood glucose	82	150(50:401) *155.90±62.72*	91	132(42:332) *145.37±47.54*	0.378[a]
Postprandial blood glucose	61	200(98:450) *209.98±82.90*	66	176.50(99:332) *188.14±60.71*	0.191[a]
Control frequency					
Once a month	85	7(8.24%)	109	4(3.67%)	**0.006[c]**
Once every 3 months		23(27.06%)		36(33.03%)	
Once every 6 months		3(3.53%)		18(16.51%)	
Once a year		2(2.35%)		6(5.50%)	
I don't visit the doctor regularly		50(58.82%)		45(41.28%)	
Control location					
University hospitals	82	27(32.93%)	103	63(61.17%)	**<0.001[b]**
State hospitals		32(39.02%)		15(14.56%)	
Family health center		17(20.73%)		22(21.36%)	
Private hospital		6(7.32%)		3(2.91%)	
Private practice		0		0	
Regular blood glucose measurement					
yes	85	58(68.24%)	109	51(46.79%)	**0.004[b]**
no		14(16.47%)		20(18.35%)	
sometimes		13(15.29%)		38(34.86%)	
Compliance with diet	**n**	**Diabetic Foot (+)**	**n**	**Diabetic Foot (-)**	**p-value**
yes	85	35(32.11%)	109	30(35.29%)	0.615[b]
no		29(26.61%)		26(30.59%)	
sometimes		45(41.28%)		29(34.12%)	
Regular exercise					
yes	85	10(11.76%)	109	33(30.28%)	**0.005[b]**
no		70(82.35%)		68(62.39%)	
sometimes		5(5.88%)		8(7.34%)	
Exercise frequency	85	4(1:4) *3.49±1.02*	94	3.5(1:4) *2.72±1.39*	**<0.001[a]**

Data given as n (%), median (minimum: maximum) and mean ± standard deviation.a: Mann-Whitney U test, b: Chi-Square Test, c: Fisher-Freeman Halton Test

Data achieved in the regression analysis performed to identify risk factors for diabetic foot disease is given in table 5. The risk of diabetic foot occurrence is 11 times higher in smokers compared to non-smokers. The risk of diabetic foot is 6.53 times higher in those who stated that they "gave up" smoking compared to non-smokers. Middle income status presents a protective effect on diabetic foot development compared to a low income level. Diabetic foot occurrence risk decreases by 84% in case of middle income status. High income status presents a protective effect from diabetic foot development compared to a low income level. Diabetic foot occurrence risk decreases by 95% in case of high income status. 1 unit of increase in e-GFR level decreases the risk of diabetic foot occurrence by 2%. The risk of diabetic foot is 4.52 times higher in the patients with retinopathy compared to those without retinopathy. Diabetic foot risk decreases by 95% in patients who have an examination once every 3 months compared to those who have an examination once a month. Diabetic foot risk decreases by 99% in patients who have an examination once every 6 months compared to those who have an examination once a month. Diabetic foot risk decreases by 841% in patients who declare their blood glucose measurement frequency as "sometimes" compared to those who regularly have their blood glucose measured. Risk of diabetic foot occurrence is 5.08 times higher for patients who do not exercise regularly compared to those who exercise. For cases where the control center is a state hospital, the diabetic foot occurrence risk is 8.13 times higher than cases for which controls are performed in a university hospital.

Table 5. Analysis of factors that may have an effect on diabetic foot disease

Risk Factor	Wald	OR(%95CI)	p-value
Gender *(Ref. Cat.: Female)*			
Male	1.60	2.76(0.57:13:31)	0.206
Smoking *(Ref. Cat.: No)*			
Yes	4.80	11(1.29:93.90)	**0.028**
Sometimes	4.53	6.53(1.16:36.80)	**0.033**
Education *(Ref. Cat.: Lower than high school)*			
High school	0.40	1.99(0.23:17.03)	0.528
Higher education	2.31	0.12(0.01:1.83)	0.128
Income *(Ref. Cat.: Low)*			
Medium	4.16	0.16(0.03:0.93)	**0.041**
High	4.64	0.05(0:0.76)	**0.031**
How many years of DM	1.10	1.04(0.97:1.12)	0.294
Retinopathy *(Ref. Cat.: No)*	4.95	4.52(1.20:17.09)	**0.026**
e-GFR	5.11	0.98(0.95:0.99)	**0.024**
Control frequency *(Ref. Cat.: Once a month)*			
Once every 3 months	4.24	0.05(0:0.86)	**0.039**
Once every 6 months	5.18	0.01(0:0.55)	**0.023**
Once a year	1.93	0.06(0:3.23)	0.165
I don't visit the doctor	1.34	0.19(0.01:3.14)	0.247
Bg regular measurement *(Ref.Cat.: Yes)*			
No	0.10	0.76(0.14:4.11)	0.752
Sometimes	4.73	0.19(0.04:0.85)	**0.030**
Regular exercise *(Ref.Cat.: Yes)*			
No	3.86	5.08(1:25.70)	**0.049**
Sometimes	0.42	0.30(0.01:11.65)	0.517
Hyperlipidemia *(Ref. Cat.:No)*			
Yes	0.03	1.13(0.30:4.32)	0.856
Hypertension *(Ref. Cat.: No)*			
Yes	0.16	1.29(0.37:4.49)	0.693
Morisky *(Ref. Cat.: High adherence)*			
Low adherence	2.18	3.01(0.70:13.02)	0.140
Control location *(Ref. Cat.: University Hospital)*			
State Hospital	7.74	8.13(1.86:35.55)	**0.005**
Family Health Center	1.61	2.93(0.56:15.39)	0.205
Private Hospital	0.04	0.73(0.03:16.67)	0.842

Ref. Cat: Reference category, OR: Odds ratio, CI: Confidence Interval Logistic regression model found to be significant (p<0.001)

Discussion

From the results of the study, diabetic foot disease was more frequently observed in male patients, smokers, those with an education level lower than high school and those with a low income level. The rate of insulin users was higher in the group with diabetic foot disease. Retinopathy history was determined as a risk factor for diabetic foot disease. Each 1 unit of decrease in e-GFR levels increased diabetic foot development risk by 2%. Regular exercise gave 5 fold more protection against diabetic foot disease. The number of admissions to the emergency service and the number of hospitalizations in the group with diabetic foot disease was significantly higher than the control group. Although diabetes mellitus generally occurs in females, diabetic foot, which is one of the most common complications of this disease, is more prevalent in males (16, 17). In our study, we detected differences between diabetic foot groups in terms of gender distribution as well. The male ratio was higher in the group with diabetic foot disease. Longer time passed outside by male patients and wearing shoes may be the reason for this.

Rovner et al. have reported in their study that diabetes complications are more common among individuals with a low socio-cultural level (18). Health behaviors of individuals may be affected positively by an increase in

their education level (19). These results are similar to our findings.

The risk of diabetic foot development increases in smoking individuals because the speed of wound healing and circulation decreases with the effect of cigarettes, and the risk of amputation increases to a great extent as well (20). In our study, the proportion of "non-smokers" in the group without diabetic foot was higher than the group with diabetic foot and these results are consistent with the literature. The proportion of "ex-smokers" in the group with diabetic foot was higher than the group without diabetic foot. The results of our study showed that quitting smoking decreased the risk compared with continuing smoking. Based on this, the importance of quitting smoking comes to the front. Generally, long duration of disease in patients with diabetic foot wounds can be associated with the failure of OAD agent therapy due to poor glycemic control and usually the presence of co-morbid complications (21). We have obtained similar results in our study, and there was a difference between groups in terms of DM drug distribution. The insulin usage rate was higher in the group with diabetic foot disease.

Diabetic foot disease is the most common complication of diabetes for hospitalization (22). In our study, the number of admissions to the emergency service due to DM was interrogated and a difference was detected between diabetic foot groups in terms of the number of admissions to the emergency service due to DM. The number of admissions to emergency due to DM was higher in the group with diabetic foot. Complications in DM patients with frequent emergency admission must be revised and the necessary interventions must be performed as soon as possible.

In the present study, there was a difference between diabetic foot groups in terms of regular blood glucose measurement. The rate of those who regularly have blood glucose measurement was higher in the diabetic foot group compared to the group without diabetic foot (respectively, 68% and 46%). This situation can be explained by the positive effect of diabetic foot ulcer development on blood glucose measurement behavior. It was shown that patients with painful neuropathy had poor plasma glucose monitoring and possibly poorer diabetes control, compared with patients with painless neuropathy. (23). Harris et al. also stated the importance of the role of blood glucose self-monitoring in the prevention of diabetes complications. (24). 30-day readmission rate of patients with diabetic foot ulcer can be reduced when good blood glucose control is achieved. The practice of self-monitoring blood glucose enables optimal blood glucose control. (25).

In diabetes, physical activity and exercise have positive effects on blood glucose regulation, blood pressure control, dyslipidemia, and weight loss (26). In our study, there was a difference between diabetic foot groups in terms of regular exercising. The rate of those who did regular exercise was higher in the group without diabetic foot compared to the diabetic foot group. According to literature studies, the incidence of diabetic nephropathy is increased in diabetic foot patients (27-29). Kidney damage may contribute to foot lesion development and/or may slow down the recovery period. In the regression analysis performed in our study, we found that increase in e-GFR, increased the risk of diabetic foot development.

In conclusion, a decrease in e-GFR values is a risk for diabetic foot disease; regular blood glucose measurement and regular exercise are protective against diabetic foot disease. These factors must be considered in the management of diabetes mellitus.

Conflict of interest

The authors declare no conflicts of interest related to this article.

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