Diabetic Foot Infections and the Role of Doppler USG in Prognosis

Diyabetik Ayak Enfeksiyonları ve Doppler USG'nin Prognozdaki Rolü

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ABSTRACT Objective: To determine the value of patient characteristics, laboratory parameters, and imaging procedures in the assessment of the severity and prognosis of diabetic foot infections (DFIs). **Material and Methods:** Demographic and clinical characteristics of 71 patients with DFI were evaluated retrospectively. Patient characteristics and clinical data including diabetes status and wound related information, laboratory and radiologic findings, and outcomes were recorded. **Results:** In patients between 35 and 60 years old, the frequency of recurrent diabetic foot infections were four and half-times higher than in those over 60 years (OR 4.55, 95% CI 1.50-13.83, p= 0.007). The white blood cell count was significantly higher in severe infections (p<0.05). Gram negative microorganisms were predominantly isolated from the wound cultures of patients aged between 35 and 65 years (p= 0.04). Pathological findings in Doppler Ultrasonography (dUSG) was correlated with smoking (p= 0.004). There was no significant association between the severity of the wound and pathological findings in dUSG. However, presence of a pathological finding in dUSG was correlated with amputation (p=0.001). Moreover, the probability of poor outcome was four-fold higher in patients with a pathology in dUSG in the logistic regression analysis (OR 4.32, 95% CI, 1.24-14.97, p= 0.025). **Conclusion:** In the management of empirical therapy, gram negative microorganisms should be considered, especially in patients of 35-65 years of age. Pathological findings in dUSG were found to be related to poor outcome such as amputation. Therefore, all patients with diabetic foot should be screened with dUSG to identify those at risk for amputation.

Key Words: Diabetic foot; risk factors; prognosis; ultrasonography, doppler

ÖZET Amaç: Bu çalışmada, diyabetik ayak enfeksiyonlarında klinik, laboratuvar ve radyolojik bulguların enfeksiyon şiddetine ve prognozuna etkisi değerlendirilmiştir. **Gereç ve Yöntemler:** Diyabetik ayak enfeksiyonu olan 71 hasta retrospektif olarak incelenmiştir. Hastaların özellikleri, diyabet ve diyabetik ayak yarası ile ilgili bilgileri, laboratuvar ve radyolojik bulguları ve prognozları değerlendirilmiştir. **Bulgular:** Hastalarda tekrarlayan lezyon gelişme sıklığının, 35-60 yaş arası hasta grubunda, >60 yaş hasta grubuna göre yaklaşık 4.5 kat fazla olduğu saptanmıştır [Odds Oranı (OO) 4.55, %95 GA 1,50- 13,83, p= 0,007]. Şiddetli enfeksiyon ile lökositoz arasında anlamlı bir ilişki saptanmıştır (p< 0,05). Yaşları 35-65 arasında olan hastaların yara yeri kültürlerinde gram negatif mikroorganizlar daha sık izole edilmiştir (p=0,04). Sigara kullanma ile Doppler ultrasonografi (USG) incelemesinde patoloji olması arasında anlamlı bir ilişki bulunmuştur (p= 0,004). Doppler USG'de patoloji ile yaranın ciddiyeti arasında herhangi bir ilişki gözlenmemiştir. Ancak Doppler USG'de patoloji varlığı ile ampütasyon arasında anlamlı bir ilişki saptanmıştır (p= 0,001). Ayrıca, lojistik regresyon analizinde, Doppler USG'de patoloji saptanan hastalarda komplikasyonlu prognoz olasılığı dört kat fazla bulunmuştur (OO 4,31, %95 GA 1,24-14,97, p= 0,025). **Sonuç:** Diyabetik ayak enfeksiyonu olan hastaların ampirik tedavisinde, 35-65 yaş arası hastalarda özellikle gram negatif mikroorganizmalar dikkate alınmalıdır. Doppler USG'de patolojisi olan hastalarda, ampütasyon gibi komplikasyonlu bir prognoz gelişme olasılığının artmış olduğu saptanmıştır. Bu nedenle, diyabetik ayak enfeksiyonu olan tüm hastaların ampütasyon riskini saptamak için Doppler USG ile tarama yapılması yararlı olacaktır.

Anahtar Kelimeler: Diyabetik ayak; risk faktörleri; prognoz; ultrasonografi, Doppler

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Diabetic patients are particularly susceptible to foot diseases such as ulceration and infection. Foot ulcers are associated with increased mortality, the development of morbidity and reduced quality of life.[1,2] Among diabetic patients, the lifetime risk of developing an ulcer is as high as 25% and it remains one of the most common causes for hospital admission.[3] The main causes for foot disease are peripheral neuropathy, foot deformities and peripheral arterial disease. Arterial disease is the main factor accounting for this increased risk. Of greater clinical significance is the 3-fold increased risk of mortality in people with ischaemia or peripheral arterial disease.[4]

An infected foot wound precedes about two-thirds of lower extremity amputations.[5] The risk factors for amputation are multifactorial and are distinguished by general or systemic considerations versus those localized to the foot and its pathology. The risk factors for major amputation were neuropathy, peripheral arterial disease, infection, history of prior foot ulcer or amputation, structural foot deformity, trauma, charcot foot, poor glycemic control, older age, male sex, ascending lymphangitis, calcaneal lesions, Wagner grade 5 lesions, duration of diabetes and Gram-positive microorganisms in cultures.[2,6]

Although early diagnosis and control of risk factors are essential to prevent complications, the poor outcomes of the diabetic foot infections cannot be easily predicted. Therefore, we conducted a retrospective study to determine the value of patient characteristics, laboratory parameters and imaging procedures in the assessment of the severity and prognosis of diabetic foot infections.

MATERIAL AND METHODS

STUDY POPULATION

Diabetic patients with foot ulcers who were admitted to the Department of Infectious Diseases and Clinical Microbiology Gazi University Faculty of Medicine between 2001-2006 were included in this study. Clinical and laboratory findings of 71 patients with diabetic foot infection were evaluated retrospectively. Patient characteristics [age, gender, body mass index (BMI), and smoking history], diabetes specific information (medication and duration of diabetes), wound related information (first or recurrent ulceration, presence of osteomyelitis, and mild, moderate and severe infection), laboratory findings [complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and wound culture], radiologic findings [Doppler ultrasonography (dUSG) examination of lower extremity arteries including femoral, popliteal, tibial, posterior tibial, and dorsalis pedis arteries, and magnetic resonance imaging for osteomyelitis], and poor outcomes (debridement, amputation, and death) were recorded. To avoid the isolation of colonizing (rather than pathogenic) flora, we instructed to first clean and debride all foot wounds and to obtain specimens by tissue biopsy, wound curettage, or aspiration rather than swab techniques. Isolates were identified by standard methods. Doppler USG was performed to assess arterial blood circulation. Vascular examination was carried out by palpation of dorsal pedal and posterior tibial pulses, and evaluation of cyanosis and edema. The PEDIS system, which was recommended in the Infectious Disease Society of America (IDSA) guideline in 2004, was preferred for the clinical classification of diabetic foot infections.[7]

DATA ANALYSIS

SPSS for Windows v10.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. The chi-square test was used to compare age groups, gender, body mass index, and smoking history, duration of diabetes primary or recurrent ulceration, presence of osteomyelitis, the severity of infection, laboratory and radiologic findings, and poor outcomes. $P < 0.05$ was considered statistically significant. Logistic regression analyses were performed for confounding effects of age groups, gender, duration of diabetes, laboratory parameters and poor outcome upon both pathological findings in dUSG and primary or recurrent ulceration modeled as a dichotomous variable.

RESULTS

All patients were over 35 years old. Mean age was 60.6 ± 9.1 (range 35-80) years. Of the 71 patients,

46 (64.8%) were females and 25 (35.2%) were males. According to the PEDIS classification, 29 patients (40.8%) had mild infection, 36 (50.7%) had moderate infection and 6 (8.5%) had severe infection. Outcome was poor in 20 (28.16%) patients; seven (35%) were managed only with debridement, 12 patients (60%) had amputation of which five had both debridement and amputation. Only one patient died. Median time for hospitalization was 18 days. The demographic and clinical characteristics of the patients were shown in Table 1.

The frequency of amputation in patients with severe disease was statistically higher than in patients with mild or moderate disease (p= 0.001). There was no correlation between amputation and osteomyelitis. The frequency of recurrent diabetic foot infections was four and half-times higher in patients between 35 and 60 years old than those over 60 years (OR 4.55, 95% CI 1.50-13.83, p= 0.007). Although it was not statistically significant, recurrent infections were also more common in overweight patients (BMI>25 kg/m^2) than in those with lower BMI as well as in patients with DM of at least 10-years duration than in those with a shorter duration (p> 0.05).

Regarding the laboratory test results, there was no difference between the severity of illness and ESR or CRP levels. However, white blood cell

TABLE 1: Demographic and clinical findings of 71 patients with diabetic foot infection, n (%).

Characteristic	Male	Female	Value n= 71	p
Sex, male/female	46	25	46/25 (1.8 4)	
Age, mean+SD (year)	60.96 (±9)	59.96 (±9.1)	60.61 (±9)	
Age group				
35-60 years	22 (47.8)	13 (52)	35 (49.3)	0.737
>60 years	24 (52.2)	12 (48)	36 (50.7)	
Body Mass Index				
≤25	23 (50)	8 (32)	31 (43.6)	0.144
>25	23 (50)	17 (68)	40 (56.4)	
Duration of diabetes				
0-10 years	25 (54.3)	9 (36)	34 (47.9)	0.139
>10 years	21 (45.7)	16 (64)	37 (52.1)	
Current smoking status				
Non-smoker	20 (43.5)	23 (92)	43 (60.5)	0.000
Smoker or ex-smoker	26 (56.5)	2 (8)	28 (39.5)	
Wound profile				
Primary	19 (41.3)	9 (36)	28 (39.5)	0.662
Recurrent ulceration	27 (58.7)	16 (64)	43 (60.5)	
Pathology in Doppler USG				
Absent	26 (56.5)	17 (68)	43 (60.5)	0.345
Present	20 (43.5)	8 (32)	28 (39.5)	
Osteomyelitis				
Absent	17 (37)	13 (52)	30 (43.6)	0.220
Present	29 (63)	12 (48)	41 (56.4)	
Debridement				
Absent	39 (84.8)	20 (80)	59 (83)	0.608
Present	7 (15.2)	5 (20)	12 (17)	
Amputation				
Absent	36 (78.3)	23 (92)	59 (83)	0.140
Present	10 (21.7)	2 (8)	12 (17)	

SD: Standard deviation; USG: Ultrasonography.

count was significantly higher in severe infections (p< 0.05).

Microbiological data of 71 patients showed that gram-positive microorganisms were isolated in 34 (47.8%) patients, whereas gram negatives were isolated from 13 (18.3%) cases. Polymicrobial growth was detected in 8 (11.2%) cases. No bacteria was recovered in 16 (22.5%) of the wound cultures. Gram-negative microorganisms were predominantly isolated from the wound cultures of the patients aged between 35 and 65 years (p= 0.04). The type of predominantly isolated microorganism was not correlated with poor outcome, the severity of infection, or presence of a pathology in dUSG.

As shown in Table 2, dUSG examination revealed pathologic findings in 46.4% of non-smoker patients, and in 53.6% of smokers or ex-smokers (p=0.04). Although it was not significant, the frequency of a pathologic finding with dUSG was higher in males, the elderly and patients with recurrent DFI.

There was no significant correlation between the severity of the wound and pathological findings in dUSG. However, existence of a pathological finding in dUSG was correlated with amputation (p=0.001) and the necessity for wound debridement (p=0.006). Moreover, the probability of poor outcome was four-fold higher in patients with a pathology in dUSG in the logistic regression analysis (OR 4.32, 95% CI, 1.24-14.97, p=0.025). Independent risk factors for foot infection were shown in Table 3.

DISCUSSION

Foot ulcer is a major cause for hospitalization for diabetes patients and its prevalence differs from 2% to 10%.[2,8,9] The major poor outcome for diabetic foot disorders is lower leg amputation. Diabetic patients have a 30-fold higher lifetime risk of undergoing a lower-extremity amputation compared with non-

TABLE 2: Evaluation of patient characteristics according to the pathology in dUSG, n (%).

	Pathology in dUSG*			
	Absent n= 43 (60.5)	Presence n= 28 (39.5)	Total n= 71 (100)	p
Age				
35-60 years	30 (69.7)	16 (57.2)	46 (64.8)	0.924
>60 years	13 (30.3)	12 (42.8)	25 (35.2)	
Gender				
Male	26 (60.5)	20 (71.4)	46 (64.8)	0.345
Female	17 (39.5)	8 (28.6)	25 (35.2)	
Presence smoking history**				
Non-smoker	30 (69.7)	13 (46.4)	43 (60.5)	0.049
Smoker/Ex-Smoker	13 (30.3)	15 (53.6)	28 (39.5)	
Infection				
Mild	19 (44.2)	10 (35.7)	29 (40.8)	0.721
Moderate	21 (48.8)	15 (53.6)	36 (50.7)	
Severe	3 (7)	3 (10.7)	6 (8.5)	
Osteomyelitis				
Absent	22 (51.2)	8 (28.6)	30 (43.6)	0.060
Present	21 (48.8)	20 (71.4)	41 (56.4)	
Amputation**				
Absent	40 (93)	19 (67.9)	59 (83)	0.006
Present	3 (7)	9 (32.2)	12 (17)	

*Column percent

** p< 0.05

dUSG: Doppler ultrasonography.

TABLE 3: Variables achieving independent statistical significance as risk factors for foot infection by multivariate analysis and the chi-square test.

Variable	Risk ratio (95% CI)	p value
Recurrent DFI >60 years old	4.55 (1.50–13.83)	0.007
Pathology in dUSG with poor outcome	4.32 (1.24–14.97)	0.025
Pathology in dUSG with smoking*		0.004
Pathological in dUSG with amputation*		0.001

DFI: Diabetic foot infection; dUSG: Doppler ultrasonography.

* Chi-square test.

diabetics.[5,10] In the literature, the reported risk of lower extremity amputations ranges from 2% to 39.4%, up to 70-90% depending on study design and the populations studied.[2,4,9,11-14] Amputation rate in patients with DFI was 17% in our study. Approximately 60% of our patients had a moderate or severe infection and amputation rate was higher in these groups. When considering the severity of infection among our patients, the amputation rate was comparable with other studies.

Peripheral arterial disease is one of the most common foot problems and develops frequently in diabetic patients. The prevalence of peripheral vascular disease is about 10% in diabetics and 2.6% in non-diabetics; peripheral vascular disease was associated with an approximately two-fold increased risk of foot infection in a multivariate model.[5,6] Arterial insufficiency will result in prolonged healing, indicating an elevated risk of amputation.[2] The studies have shown that amputation rate can be reduced more than 50% by early diagnosis of peripheral vascular disease and vascular intervention.[9,10] Aksoy et al. reported that lower extremity amputation was mainly required in the presence of a peripheral vascular disease, as well as in osteomyelitis and gangrene.[13] History and physical examination combined with dUSG are tools to detect peripheral vascular disease in diabetics.[15] Reports indicate that 31% of the diabetic patients have peripheral arterial disease in lower extremity arteries by dUSG even in asymptomatic patients.[16] Annual screening for peripheral arterial disease is recommended for patients with diabetes mellitus and for those older than 40 years.[17] In our study, dUSG revealed a pathological finding in 39.5% of the patients. Although half of the patients with severe disease had a pathological finding in dUSG, there was no significant difference between the groups with mild, moderate and severe diseases. Nevertheless, a poor outcome, especially amputation, was four-fold higher in patients with pathology in dUSG. Therefore, a Doppler ultrasonographic examination is recommended in patients with diabetic foot infection to assess the prognosis even though it may not be available for all diabetic patients. There is limited data to show clearly the role of dUSG in diabetic foot infections to assess the prognosis and evalute the patients. Edelman et al. reported that the vascular components of the clinical examination were the best predictors of healing in patients with a diabetic foot ulcer. They also concluded that dUSG should be carried out to assess posterior tibial pulse because the absence of a pulse confers an extremely high risk of nonhealing wound, amputation, or death.[18]

The prevalence of neuropathy, foot deformities and peripheral arterial disease, as well as the risk of amputation increase with age. Elderly patients tend to have recurrent diabetic foot infections due to increased frequency of vascular, neurological and visual pathologies.[19] However, individual characteristics of the patients such as foot care, life-long adherence to glycaemic control, treatment of hypertension and dyslipidemia, and smoking cessation are also very influential in the development of foot infections. Therefore, the rate of recurrent infection can be varied between the populations studied. Indeed, the frequency of recurrent diabetic foot infections in our study was four and half-times higher in patients between 35 and 60 years old than in those over 60 years in the logistic regression analysis. Peripheral arterial disease was also higher in the

younger group. It was concluded that a tendency to poor glycemic control, inelaborate foot care, and irregular clinical visits for diabetes related complications, among younger patients, contributed to poorer prognosis.[20,21]

Serum inflammatory markers such as leukocytosis, C-reactive protein, and erythrocyte sedimentation rate may predict severity of foot infection in diabetic patients.[22] In a study, erythrocyte sedimentation rate greater than 60 mm/h or C-reactive protein greater than 3.2 mg/dL and ulcer depth greater than 3 mm were reported to be useful markers to determine concomitant bone infection in diabetic foot patients.[23] In another study, white blood cell count was associated with an unfavourable clinical outcome.[22] However, several reports have documented the absence of leukocytosis in the presence of severe foot infections.[2] In our study, white blood cell count was significantly higher in severe infections ($p<0.05$), whereas there was no correlation between the severity of illness and ESR and CRP levels. Therefore, clinical and laboratory findings should be evaluated together to assess the severity of infection.

The most common pathogens in acute, previously untreated, superficial infected foot wounds in patients with diabetes are aerobic gram-positive bacteria, whereas deep limb-threatening infection or chronic wounds are usually caused by a mixture of aerobic gram-positive, aerobic gram-negative, and anaerobic organisms.[2,24] Anaerobic bacteria are usually part of mixed infections in patients with foot ischemia or gangrene.[24] Aerobic gram-positive microorganisms, as expected, were predominatly isolated from wound cultures of the patients with diabetic foot infection in our study. Interestingly, gram-negative microorganisms were isolated significantly higher in patients aged between 35 and 65 years ($p= 0.04$). However, there was no correlation between the gram-positive or -negative microorganisms with regard to poor outcome, severity of infection or presence of pathology in dUSG. The lack of anaerobic culture results is a limitation of our study.

In conclusion, the severity of infection and presence of pathology in dUSG were related to poor outcome such as amputation. Therefore, all patients with diabetic foot should be screened with dUSG to identify those at risk for amputation. In the absence of discriminatory laboratory tests for evaluating amputation risk, dUSG seems to provide a good clinical approach for the estimation of poor outcome in those patients. Young patients are at higher risk than elderly patients to develope recurrent infections. Even though gram positive microorganisms are predominantly isolated from wound cultures, gram negative microorganisms should be considered in the empirical treatment in 35-65 year old patients.

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