Correlation Between Amputation of Diabetic Foot and Nephropathy

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Introduction. A diabetic foot lesion remains a major cause of morbidity in diabetic patients with chronic kidney disease. We studied the relation between kidney function and the risk of amputation in patients with diabetic foot.

Materials and Methods. We reviewed retrospectively the charts of 244 patients admitted to Imam Khomeini Hospital of Sari, Iran, for diabetic foot from 1996 to 2005. Their clinical characteristics and kidney function indicators, including urine protein excretion and serum creatinine were analyzed and compared between amputees and nonamputees.

Results. There were 244 patients with diabetic foot who were admitted to our center during the studied period. The duration of being affected by DM was between 3 months and 34 years (mean, 11.80 ± 6.81 years). Sixty-six patients (27.0%) underwent amputation. The amputees were older than the nonamputees (61.1 ± 11.5 years versus 55.6 ± 12.5 years, $P < .001$). There were 20 patients (30.3%) in the amputee group and 44 (24.7%) in the nonamputee group who had proteinuria ($P = .38$). The mean creatinine level was significantly higher in the amputees compared to the nonamputees (1.78 ± 1.36 mg/dL versus 1.28 ± 1.23 mg/dL, $P = .03$).

Conclusions. Lower extremity amputations in our patients with diabetic foot were strongly associated with elevated serum creatinine levels. The presence of this complication necessitates intensifying actions in order to prevent amputations.

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INTRODUCTION

Diabetes mellitus (DM) is one of the most common chronic diseases with high costs worldwide. It is expected that by 2025, the prevalence of diabetic patients older than 20 years old will reach 300 000 000 in the world.[1] Diabetic foot is one of the chronic complications of DM, which is one of the main causes of morbidity and mortality that leads to nontraumatic amputations.[2] The risk of limb amputation in diabetic patients has been reported to be 15 to 20 times more than that in nondiabetic individuals, reaching 15% during their lives.[3-5] Amputation rate in different studies was reported from 5.2% to 39.4 % in diabetic patients.[6-13] These differences are due to different factors contributing to amputation of the diabetic foot. Recognizing and controlling these factors could be effective in decreasing amputation rate and its side effects.

Diabetic nephropathy is a major vascular complication of DM, as well.[14] A diabetic foot lesion remains a major cause of morbidity in patients with kidney failure. Foot complications are encountered more than twofold in diabetic patients with kidney failure, and the rate of amputation is 6.5 to 10 times higher in comparison to the general diabetic population.[15,16] On the other hand, while foot ulcers

are more likely to develop in patients with diabetic nephropathy, they are no less likely to heal than are those in diabetic patients with intact kidney function.[16] The pathogenesis of foot ulceration in the context of chronic kidney disease and DM is primarily due to peripheral neuropathy. Loss of protective sensation due to sensory neuropathy combined with motor and autonomic neuropathy and macrovascular compromise result in increased risk of foot complications.[16]

There is little research on the relation between lower extremity morbidity in diabetic patients and diabetic nephropathy in Iranian patients. Thus, we decided to investigate about the frequency of amputation and its relationship with diabetic nephropathy in our center in the north of Iran.

MATERIALS AND METHODS

This descriptive-analytic study was done on the patients admitted to Imam Khomeini Hospital in Sari, Iran, presenting with diabetic foot between 1998 and 2005. We collected data on age, sex, duration of DM, treatment modalities (diet change, oral hypoglycemic drugs, and insulin), cigarette smoking, kidney function tests, blood glucose level test at presentation, history of previous amputation, history of nephropathy, history of hypertension, site of the diabetic ulcer, extension of the ulcer in centimeters, and amputation surface.

Overt proteinuria was defined as 24-hour a urine protein excretion greater than 500 mg. For all of the patients, urine analysis and urine culture had been checked. In patients with a positive urine culture for microorganisms treatment was done. After normalization of urine culture and controlling diabetic foot infection, 24-hour urine was collected and protein and creatinine levels were measured. Blood urea nitrogen and creatinine level were measured in all patients, using a Biosystems kit (Madrid, Spain) and an automated analyzer (Hitachi Model 717, Tokyo, Japan), respectively. The coefficient of variation for blood urea nitrogen was 1.9% and it was 1.3% for serum creatinine. The 24-hour urine protein was measured with the chemical method (sulfosalicylate) spectrophotometry. The Student *t* test and the chi-square test were used for comparisons of variables between groups, where appropriate. A *P* value less than .05 was considered significant.

RESULTS

There were 244 patients with diabetic foot who were admitted to our center during the studied period. They were 129 men (52.9%) and 115 women (47.1%) with a mean age of 57.0 ± 12.4 years (range, 43 to 72 years). The duration of being affected by DM was between 3 months and 34 years (mean, 11.80 ± 6.81 years). Twenty-seven patients (11.1%) were smokers. The therapies for DM were insulin in 75 patients (30.7%), oral medication in 146 (59.8%), diet change in 13 (5.3%). The most common ulcer site was the right foot's fingers in

Demographic and Clinical Parameters in Diabetic Patients with and Without Amputation*

Parameter	Patients With Diabetic Foot		*P*
	Amputee	Nonamputee	
Age, y	61.1 ± 11.5	55.6 ± 12.5	.001
Duration of DM, y	12.90 ± 6.72	11.40 ± 6.96	.15
Blood glucose, mg/dL	260 ± 135	269 ± 122	.68
Body mass index, kg/m^2	36.6 ± 31.5	33.4 ± 22.0	.86
Smoker	12 (6.7)	4 (6.1)	.30
Treatment			
Insulin	60 (33.7)	15 (22.7)	
Oral medication	100 (56.2)	46 (69.7)	
Diabetic diet	12 (6.7)	1 (1.5)	
Insulin and oral medication	6 (3.4)	4 (6.0)	.26
Previous amputations	34 (19.1)	18 (27.3)	.20
Hypertension	30 (16.8)	20 (30.3)	.13
Ulcer's duration, d	40.2 ± 43.5	24.6 ± 38.7	.01
Size of ulcer, cm^2	12.4 ± 23.1	13.2 ± 32.9	.84
Proteinuria	20 (30.3)	44 (24.7)	.38
Serum creatinine, mg/dL	1.78 ± 1.36	1.28 ± 1.23	.03

*Values for continuous variables are demonstrated as mean ± standard deviation. Values in parentheses are percents.

79 patients (32.4%). The minimum extension of the wound was 0.5 × 0.5 cm^2 and the maximum was 10 ×10 cm^2.

The mean blood urea level was 48.5 ± 12.2 mg/dL (range, 13 mg/dL to 247 mg/dL), and the mean serum creatinine level was 1.43 ± 1.30 mg/dl (range, 0.3 mg/dL to 10.3 mg/dL). Accordingly, 61 patients (25%) had kidney dysfunction. Proteinuria was documented in 64 patients (26.2%).

Sixty-six patients (27.0%) underwent amputation (Table). The most common amputation site was the right foot at the fingers level in 21 patients (8.6%). The patients of the amputee group were older than those of the other group (61.1 ± 11.5 years versus 55.6 ± 12.5 years, $P < .001$). Although the extensions of the ulcers were comparable between the two groups, patients with amputation had a longer history of diabetic foot. Duration of DM and the first fasting blood glucose level at diagnosis were not different between the two groups (Table). There were 20 patients (30.3%) in the amputees group and 44 (24.7%) in the nonamputees group who had proteinuria ($P = .38$). The mean creatinine level was significantly higher in the amputees compared to the other patients with diabetic foot (1.78 ± 1.36 mg/dL versus 1.28 ± 1.23 mg/dL, $P = .03$).

DISCUSSION

Of our 244 patients admitted due to diabetic foot, 27.3% were amputees. Aksoy and colleagues studied 66 patients with the diabetic foot in Turkey (2000 to 2002) of whom 39.4% were amputees.[13] In our study, influential factors such as age and the first fasting blood sugar were not significantly different between amputees and nonamputees. In a research on patients with diabetic foot from 1979 to 1993 in Shariati and Imam Khomeini hospitals in Tehran, amputation rate was reported to be 34.7% .[11] A cause of lower amputation rate in our study could be the lower frequency of cigarette smoking (11.1% versus 27.7%), and also the sooner hospitalization in our patients. The average age of the patients and also the average duration of being a diabetic patient in both reports were almost the same. Lower rates of amputation (5.2% to 9.4%) have been reported elsewhere.[6,7] Training of the patients is a crucial to reduce amputation rate. The study sample and the indications of amputation can be other factors of the discrepancy in the above reports. In our study, we had not recorded the detail information about osteomyelitis and gangrene.

In our cohort of patients with diabetic foot, we did not find any significant difference between the amputees and nonamputees in terms of DM duration, blood glucose level at diagnosis, the ulcer extension, sex, cigarette smoking, the type of DM treatment, previous amputation background, blood glucose control, and hypertension background. However, duration of the foot ulcer before seeing a doctor was longer and the patients were older in the amputee group. Aksoy and colleagues did not find such differences between their groups of patients.[13] In a study of Karakoc and colleagues,[7] the age was greater and the duration of being affected by DM and hospital stay were longer in the amputees than nonamputees. Considering the role of the age, duration of ulcer before going to a physician, and lower extremity's vascular involvement in amputation rate, it is necessary to give more training to the diabetic patients to prevent the sore and how to take care of it at home, and also to inform the doctor as early as possible.

In McIntyre and associates' study, lower extremity complications were significantly more frequent in diabetic patients with end-stage renal disease. Financial cost and knowledge deficit were barriers to adequate foot care and footwear.[17] Locking-Cusolito and coworkers evaluated the prevalence of risk factors predisposing to foot problems in patients on hemodialysis. They showed that the most common comorbidities were hypertension (75%), coronary artery disease (50%), DM (42.2%), hyperlipidemia (34.9%), and peripheral vascular disease (27.2%), which were all established risk factors of peripheral arterial occlusive disease.[18]

Xiao and coworkers studied the relationship between kidney function and the therapeutic effect and prognosis of foot ulcers in the patients with DM. They divided 126 patients with diabetic foot ulcers, classes I to V into 1 to 5 classes (according to Mogenson standard) and provided with systemic treatment and local debridement, with astragulus for topical application. The time of growth of granulation tissue, the time of healing, the amputation rate, and mortality were observed. Granulation tissue and healing time of ulcer prolonged with worsening of diabetic nephropathy regardless of the disease phase of foot ulcers. Especially the granulation tissue and healing time of foot ulcers were significantly longer

in IV and V phases of diabetic nephropathy than those of III phase diabetic nephropathy though the conditions of their foot ulcers were about the same. Granulation tissue and healing time in all the patients with the foot ulcers in the similar condition exhibited significantly positive linear correlation with the severity of diabetic nephropathy. The mortality of I to III phase diabetic nephropathy was significantly lower than that of IV and V phase diabetic nephropathy when the foot ulcers of these patients were of the same extent. The authors concluded a worsening of kidney function would affect the treatment effect and prognosis of foot ulcers in patients with diabetic foot ulcers, implicating that it is very important to improve the kidney function in the treatment of patients with diabetic foot ulcers.[19] Nather and colleagues found that nephropathy was a significant predictive factor for limb loss.[20] Some other studies have also found nephropathy to be a significant prognostic factor.[21-23] However, some investigators have disputed the predictive role of nephropathy.[24,25]

Current literature indicates poor survival and limb salvage rates in patients with DM and kidney failure who present with ulcerated or gangrenous lower extremities.[26] Three major pathogenesis, neuropathy, ischemia, and infection, are the main contributory factors. Nephropathy appears to be an important predictor of long-term outcome of the treatment of diabetic foot ulcer.[27] Increasing awareness of the condition and careful clinical examination are indispensable to avoid serious complication. Evaluation of the foot includes a history and a focused examination of skin integrity, presence of sensory neuropathy or vascular insufficiency, and biomechanical and footwear inspection. Effective treatment of diabetic foot complications include appropriate antibiotics (if indicated), meticulous wound care, off-loading, vascular surgery (if indicated), and selective/elective or prophylactic nonvascular surgery. The multidisciplinary diabetic foot clinic model provides an ideal setting for early intervention, treatment, and assistance with preventive strategies.

CONCLUSIONS

Lower extremity amputations are strongly associated with retinopathy, nephropathy, and neuropathy. In our patients with DM, those with higher serum creatinine were more likely to undergo amputation. The presence of such complications should lead to intensified actions in order to prevent amputations.

CONFLICT OF INTEREST

None declared.

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