Endocr (2010) 38:87–92
DOI 10.1007/s12020-010-9355-z

ORIGINAL ARTICLE

Change in amputation predictors in diabetic foot disease: effect of multidisciplinary approach

Kadriye Aydin · Mehlika Isildak · Jale Karakaya · Alper Gürlek

Received: 12 January 2010 / Accepted: 1 June 2010 / Published online: 20 June 2010

Abstract Diabetic foot disease causes important morbidity in diabetic population, and amputation due to diabetic foot disease occurs more often than in general population. We have been evaluating patients with diabetic foot disease in a multidisciplinary approach since year 2000. In the current study, we sought to investigate the change in amputation rate and its predictors in diabetic foot with a multidisciplinary team approach. Seventy-four patients (52 male, 22 female) hospitalised between January 2002 and December 2007 were retrospectively analysed. Sixteen out of 74 have undergone amputation. We found overall amputation rate as 21.6%, which is lower than previously reported from our institution (36.7 and 39.4%, respectively). Major amputations (syme, below-knee, above-knee) were applied to 11 patients (14.9%). A logistic regression model including osteomyelitis, peripheral neuropathy, peripheral vascular disease, hypertension, gangrene and age revealed that gangrene is now the only significant predictor for amputation. Our observations confirm that amputation rate has declined after implementation of a multidisciplinary team work, and risk factors apart from presence of gangrene are no longer amputation predictors in our centre.

Keywords Diabetic foot · Multidisciplinary approach · Amputation predictors

K. Aydin · M. Isildak · A. Gürlek (✉)
Department of Endocrinology and Metabolism, Hacettepe University Medical School, 06100 Ankara, Turkey
e-mail: agurlek2001@yahoo.com

J. Karakaya
Department of Biostatistics, Hacettepe University Medical School, 06100 Ankara, Turkey

Introduction

Diabetic foot disease is among the most feared complications of diabetes. Amputation is the most feared and costly complication of diabetic foot disease [1, 2]. The lifetime risk of a person with diabetes developing foot ulceration is reported to be as high as 25% [3], and amputation due to diabetic foot disease occurs 10–30 times more often in diabetic patients than in general population [1, 2]. Impairment of tissue perfusion due to peripheral arterial disease and loss of the protective mechanisms in the existence of diabetic neuropathy are the main risk factors for diabetic foot disease development. Infection plays a major role in morbidity, hospitalisation and amputation, but is not stated as a component for the development of diabetic foot disease. After St. Vince Declaration setting a 5-year target of decreasing by half the leg amputation rate in diabetic patients [4], several studies have established the importance of multidisciplinary approach to diabetic foot lesions [5, 6]. We have previously shown the effectiveness of team working in diabetic foot disease and reported the risk factors of amputation in hospitalised patients due to diabetic foot disease [7]. In the current study, we aimed to assess the risk factors and prevalence of amputation to compare with two previous data sets which have been reported for patients hospitalised between 1992–1996 and 2000–2002 in our institution.

Materials and methods

Medical records of 74 patients (52 men, 22 women) with diabetic foot disease who had been hospitalised in Hacettepe University Hospital between January 1, 2002 and December 31, 2007 were retrospectively analysed. Age,

type of treatment, fasting plasma glucose, smoking history, presence of hypertension, nephropathy, retinopathy, peripheral vascular disease, peripheral neuropathy, osteomyelitis, microorganisms proliferated in wound cultures, antibiotics and duration of hospitalisation were evaluated from medical records.

Smoking history was defined as smoking more than one pack-year. Hypertension was considered to be present if a patient was taking antihypertensive medicine or had elevated blood pressure measurements over systolic 140 or diastolic 90 mmHg. Retinopathy was defined as the presence of retinal hemorrhages, exudate or microaneurysms on fundoscopic examination. Nephropathy was defined as persistent albuminuria ($\geq$30 mg/day). Decrease or loss in sensations (vibration, light touch, pain, awareness of temperature differences) in a glove and stocking distribution, and depression or loss of deep tendon reflexes indicated peripheral neuropathy. Peripheral vascular disease was diagnosed in the presence of typical intermittant claudication in association with at least one non-palpable major lower limb arterial pulse and cold extremities. Peripheral vascular disease was confirmed by doppler studies in all patients, as well. All diabetic foot lesions were graded according to Wagner's classification system [8]. Microorganisms proliferated in the lesions were isolated from wound cultures. Osteomyelitis was defined based on magnetic resonance imaging.

All patients have been hospitalised and advised for bed rest for pressure relief of ulcers. All the non-amputees were given local wound care consisting of periodic sharp debridement of exudates, devitalized necrotic tissue and saline-wet dressing. Patients were evaluated by a multidisciplinary team consisting of endocrinologist, orthopaedic surgeon, cardiovascular surgeon, plastics and reconstructive surgeon, infectious disease specialist and diabetic foot nurse. Antibiotic therapy was given if infection was present.

Statistical analysis

Numerical variables were evaluated for normality of data distribution by using the Kolmogorov–Smirnov test. Descriptive statistics were expressed as mean $\pm$ standard deviation (SD). For continuous variables, independent samples *t* test was performed to compare the means of two groups. The difference of categorical variables between amputees and non-amputees were compared by Pearson χ^2 test or Fisher exact tests. Odds ratios with 95% confidence intervals (CIs) were calculated for potential predictors of amputation.

Multiple logistic regression analysis was performed to determine important risk factor for amputation. Asymptotic methods may be inadequate when sample sizes are small or the data are sparse, skewed [9]. Therefore, exact logistic regression method was performed using the SAS software package.

A $P < 0.05$ was accepted as statistically significant. Data analysis was performed by SPSS 15.0 (Statistical Package for Social Sciences, SPSS Inc. Chicago, IL, United States) and SAS 9.1 (SAS Institute Inc., Cary, NC, USA) software packages.

Results

Clinical features of the patients

All the patients included into the study were caucasians. The mean age of the patients was 62.4 $\pm$ 10.6 year (range 29–84). Fifteen patients had prior history of limb loss due to diabetic foot before admission to our clinic. Thirty patients had a previous history of diabetic foot disease which did not require amputation and surgical intervention. Two patients had type 1 diabetes and 72 patients had type 2 diabetes. Patients were treated with diet only ($n = 8$), oral hypoglycemic agents ($n = 28$), insulin regimes ($n = 30$) or combination of insulin and oral hypoglycemic agents ($n = 8$). Insulin regimes applied by the patients on admission were conventional insulin therapy (twice daily subcutaneous insulin injections either including a combination of intermediate-acting and short-acting human insulin or analogue insulin, $n = 29$), multiple insulin injections ($n = 6$) or single dose injection ($n = 3$).

In this admission, 16 patients (21.6%) have undergone amputation due to diabetic foot disease (amputees) and 58 patients (78.4%) have been treated conservatively (non-amputees). Five patients in the amputee group and ten patients in the non-amputee group had amputation previously due diabetic foot disease. Both groups had poorly controlled diabetes in respect to fasting plasma glucose levels and HbA1c levels on admission (Table 1). In order to achieve glycemic control, patients on diet or hypoglycemic agents have been changed to insulin regimes, either conventional insulin regime with short and intermediate-acting human or analogue insulin, or multiple injections when appropriate.

Twenty patients (27.0%) were active smokers on admission. Nephropathy was present in 45 patients (60.8%) and retinopathy was present in 49 patients (66.2%). Forty-nine patients (66.2%) showed signs of peripheral neuropathy. Peripheral vascular disease was demonstrated in 34 patients (45.9%) by invasive or non-invasive methods.

The comparison of the clinical characteristics of the amputees and non-amputees are shown in Table 1. Age, sex, FPG, HbA1c, duration of diabetes, duration of hospitalisation, smoking, previous history of diabetic foot,

Table 1 Comparison of the clinical characteristics of the patients in the amputees and non-amputees groups

	Amputees $n = 16$	Non-amputees $n = 58$	P value	OR (%95 CI)
Age (year)	60.6 ± 7.9	62.9 ± 11.3	0.87	
Sex			0.76	1.35 (0.38–4.76)
Female, *n* (%)	4 (25)	18 (31)		
Male, *n* (%)	12 (75)	40 (69)		
Type of diabetes			1.00	0.90 (0.09–9.17)
Type 1, *n* (%)	–	2 (3.4)		
Type 2, *n* (%)	16 (100)	56 (96.6)		
Diabetes duration (year)	12.8 ± 7.6	14.7 ± 8.1	1.00	
FPG (mg/dl)	155.6 ± 86	148.3 ± 50	0.49	
HbA1c (%)	9.7 ± 2.7	8.8 ± 2.3	0.23	
Hospitalisation duration (day)	35.2 ± 29.6	25.5 ± 20.4	0.20	
Previous diabetic foot history, *n* (%)	10 (62.5)	35 (60.3)	1.00	1.10 (0.35–3.43)
Smoking, *n* (%)	5 (38.5)	15 (31.3)	0.74	1.37 (0.39–4.91)
Hypertension, *n* (%)	12 (75)	32 (60.3)	0.25	2.43 (0.70–8.46)
Nephropathy, *n* (%)	10 (62.5)	35 (60.3)	1.00	1.09 (0.35–3.42)
Retinopathy, *n* (%)	11 (68.8)	38 (65.5)	1.00	1.16 (0.35–3.80)
Peripheral neuropathy, *n* (%)	13 (92.9)	36 (70.6)	0.16	5.42 (0.65–45)
Peripheral vascular disease, *n* (%)	10 (62.5)	24 (41.4)	0.22	2.36 (0.76–7.37)
Gangrene, *n* (%)	8 (50)	2 (3.4)	<0.001	28 (5.02–155)
Osteomyelitis, *n* (%)	8 (50)	19 (32.8)	0.33	2.05 (0.67–6.31)

Data are expressed as mean ± standard deviation

FPG fasting plasma glucose, *OR* odds ratio, *CI* confidence interval

nephropathy, retinopathy, peripheric neuropathy, peripheric vascular disease, osteomyelitis were similar between two groups. Presence of gangrene was higher in the amputees (50 vs. 3.4%). Data from our previous two studies represented peripheral vascular disease and osteomyelitis higher in amputee group [7, 10]. But there were no difference in osteomyelitis and peripheral vascular disease rates between both groups in current study.

When evaluated according to Wagner classification system, 15 patients (20.3%) had grade 1, 27 (36.5%) patients had grade 2, 21 (28.4%) patients had grade 3, 11 (14.9%) patients had grade 4 lesions. None of the patients had grade 5 lesion. During the course of hospitalisation none of the patients developed gangrene. Number of the patients in the current study and the previous two studies in the Wagner classes are shown in Table 2. It is notable that more patients have low grade foot ulcers in the current study compared with the previous studies from our institution.

Table 2 Number of patients in Wagner classes in the current and previous studies from our center [7, 10]

Wagner class	1992–1996 [7] $n = 147$ (%)	2000–2002 [10] $n = 66$ (%)	Current study $n = 74$ (%)
1	–	3 (4.5)	15 (20.3)
2	23 (15.6)	13 (19.7)	27 (36.5)
3	71 (48.2)	22 (33.3)	21 (28.4)
4	36 (24.4)	20 (30.3)	11 (14.9)
5	17 (11.5)	8 (12.1)	–

Predictors of amputation

To understand the changing factors influencing amputation, some of which had been demonstrated to be a predictor previously, an exact logistic regression analysis was performed. The clinical parameters osteomyelitis, neuropathy, peripheral vascular disease, hypertension, gangrene and age were included into the logistic regression analysis (Table 3). Presence of gangrene was now found to be the only significant predictor in determining the amputation risk.

Graft and revascularisation procedures

All the hospitalised patients were evaluated by a cardiovascular surgeon. Two patients had coronary artery revascularisation and one patient had femoropopliteal by-pass grafting during hospitalisation for diabetic foot disease. Six patients had grafting procedure for extended diabetic foot lesions, but one of them failed to heal.

Level of amputation

The distribution of the amputation levels in comparison with our previous studies is shown in Table 4. The most frequent amputation was below-knee (56.3%). Above-knee

Table 3 Risk factor analysis for lower extremity amputation by logistic regression

Parameter	OR	%95 CI	*P* value
Osteomyelitis	1.36	0.18–8.59	0.99
Neuropathy	18.46	0.57–>999.99	0.17
Peripheral vascular disease	3.20	0.62–24.10	0.22
Hypertension	3.23	0.55–36.27	0.28
Gangrene	48.85	4.11–>999.99	0.0002
Age	0.95	0.88–1.01	0.10

OR:Odds ratio

CI:confidence interval

Table 4 Distribution of the amputation levels and mortality rates in amputees in the current and previous two studies [7, 10] from our institution

Level	1992–1996 [7] $n = 4$ (%)	2000–2002 [10] $n = 26$ (%)	Current study $n = 16$ (%)
Ray	–	9 (34.6)	2 (12.5)
Transmetatarsal	2 (3.7)	–	3 (18.8)
Syme	4 (7.4)	2 (7.7)	2 (12.5)
Below-knee	28 (51.9)	8 (30.7)	9 (56.3)
Above-knee	6 (11.1)	2 (7.7)	–
Others (transphalangeal, boyd, calcaneal)	14 (25.9)	5 (19.3)	–
Mortality	7 (13.2)	7 (26.7)	1 (6.3)

amputation was not performed anyway. Ray-type amputation was performed in two patients (12.5%), transmetatarsal amputation in three patients (18.8%) and Syme-type amputation in two patients (12.5%).

Wound cultures and antimicrobial therapy

Out of 45 patients in whom wound cultures were performed, culture results were negative in 12 patients. Most frequent culture technique was deep curettage of the ulcer base. Tissue culture and aspirate cultures have also been carried out. Although the most frequent microorganism in wound cultures was coagulase positive staphylococci previously, we came across with pseudomonas as the most frequent microorganism. Enterobacteriaceae family was also frequent. Twelve cultures (26.6%) yielded gram positive cocci, 14 cultures (31.1%) yielded gram negative bacilli, and 7 cultures (15.5%) yielded both species.

Mortality and outcome

Only one patient (6.3%) who had undergone amputation died at the postoperative period. He passed away due to cardiovascular problems. Three patients in the non-amputees died, two of them due to cardiovascular problems and one of them due to sepsis. Complete wound healing, or improved healing process was noted in 49 (84.5%) of the non-amputees and in all of the surviving amputees.

Discussion

Patients with diabetes have a 12–25% lifetime risk of developing a foot ulcer [11, 12]. The most feared and costly complication of diabetic foot disease is amputation, since it carries a significantly elevated mortality risk [3]. It is estimated that more than a million people with diabetes require limb amputation annually [13].

In this series, we found that 16 out of 74 patients (21.6%) had undergone lower limb amputation. First of all, this rate was lower than the amputation rates previously declared by our center (amputations rates were 36.7 and 39.4% between 1992–1996 and between 2000–2002, respectively). A multidisciplinary approach was initiated in the year 2000 in our center. In the current study, the primary and the unique predictor of amputation was found to be gangrene. Contrary to our previous observations [7, 10], all other potential risk factors like osteomyelitis and peripheral arterial disease were now found not related to having an amputation.

Diabetic neuropathy increases the risk of foot ulceration by sevenfold [14], and it is a risk factor for amputation [15, 16]. However, the amputees and non-amputees in our current study had similar neuropathy and peripheral arterial disease rates as well as other clinical features. Disappearance of some of the risk factors' efficacy on amputation rate would be as a consequence of the loss of statistical significance due to smaller sample size. Diabetic patients in our current series had lower Wagner grades than previously reported by us [7, 10] so that lower amputation rates may, at least in part, be attributable to these lower grades.

In a previous study, the incidence of new foot ulcer has been reported to be 2.2% and there was an ethnic difference in the incidence which was attributable to peripheral arterial disease, neuropathy, insulin use and foot deformities [17]. It is plausible to assume that the amputation profiles must differ from one nation to another. A nationwide diabetic foot disease or diabetic foot amputation profile has not been published in the Turkish population so far.

We examined the published studies regarding diabetic foot disease from different centers in Turkey, which have different designs and purposes to examine. Although not all studies have been designed to evaluate amputation rates, the amputation rates from these various studies range from 9.4 to 64.5% [18–22]. Since these studies were looking for

Table 5 Amputation profiles before and after multidisciplinary approach

	Before multidisciplinary approach	After multidisciplinary approach	*P* value
Gürlek et al.			
Total amputation, *n* (%)	54 (36.7)	42 (30.0)	0.227
Major amputation, *n* (%)	38 (25.9)	23** (16.4)	0.051
Karakoc et al [21]			
Total amputation, *n* (%)	17 (20.7)	11 (9.4)	0.023
Major amputation, *n* (%)	*	7 (5.9)	*
Yesil et al [22]			
Total amputation, *n* (%)	55 (40.1)	158 (36.2)	0.418
Major amputation, *n* (%)	28 (20.4)	55 (12.6)	0.026

* Data not provided

** Sum of the patients in 2000–2002 study ($n = 12$) and in the current study ($n = 11$)

different issues other than rate of amputation, gathering standard information is impossible related to amputation risks, hospitalisation, microorganisms grown in cultures, osteomyelitis rates and Wagner grades.

In the published literature, we find reports of three distinct centers in Turkey approaching to diabetic foot disease in a multidisciplinary way [10, 19, 21]. The one conducted by Kandemir et al. [19] has determined the diagnosis of osteomyelitis, but have mentioned neither about risk factors of amputation nor efficacy of multidisciplinary diabetic foot team. They have reported that the most frequent etiologic agent for diabetic foot infection was staphylocci, being inconsistent with our current study which defined pseudomonas as the most frequent etiologic agent.

The other studies conducted by Yesil et al. [22] and Karakoc et al. [21] had primarily examined the efficacy of multidisciplinary approach to diabetic foot disease and had made a comparison between amputation rates before and after multidisciplinary approach is realized. We also set the data of the patients after diabetic team's beginning. We represented the number of the patients having amputations and major amputations in our series after adjusting to the diabetic foot team's beginning and two other studies in Table 5. Heel protective amputations (Ray, metatarsal) were considered as minor; syme, below-knee, above-knee were considered as major amputations.

Two other studies from Turkey also had consisted outpatients and admissions. As seen in Table 5, the percentages of total amputations decreased in all centers, being most prominent in major amputations. Although our data exhibits borderline statistical significance ($P = 0.051$), major amputations decreased from 25.9 to 16.4%. In our data, decrease in total amputation rate could not reach to statistical level of significance. Formerly, various reports from developed countries have demonstrated the effectivity of multidisciplinary approach to diabetic foot disease. The greatest reduction in the amputation rate was reported to be 50% from United Kingdom [23]. To the best of our knowledge, developing world, except some countries, could not have reported the progress in diabetic foot outcome after implementation of such multidisciplinary teams.

In summary, the lower rates of mortality and amputation in the current study were thought to be resulted from a multidisciplinary approach which ensured careful preoperative assessment, earlier hospitalisation, suitable antibiotic choice and a surgical approach aiming at limb salvage. Our data clearly show that this approach progressively improves the overall outcome of patients with diabetic foot, with greater rates of limb salvage. In a nationwide perspective, multidisciplinary teams for diabetic foot disease must be widely available so to reduce the risk for major amputations. Multidisciplinary team enables earlier attempts for the treatment of comorbidities to reduce major amputations. It should be advised to hospitalise the patients earlier because amputation is more costly than hospitalisation.

References

1. O.I. Siitonen, L.K. Niskanen, M. Laakso, J.T. Siitonen, K. Pyorala, Diabetes Care **16**, 16–20 (1993)
2. C. Trautner, B. Haastert, G. Giani, M. Berger, Diabetes Care **19**, 1006–1009 (1996)
3. N. Singh, D.G. Armstrong, B.A. Lipsky, JAMA **293**, 217–228 (2005)
4. American Diabetes Association, Diabetes Care **21**, 5–19 (1998)
5. J. Apelqvist, J. Larsson, Diabetes Metab. Res. Rev. **16**(Suppl 1), S75–S83 (2000)
6. R.S. Berardi, Y. Keonin, Am. J. Surg. **135**, 231–234 (1978)
7. A. Gurlek, M. Bayraktar, C. Savas, O. Gedik, Exp. Clin. Endocrinol. Diabetes **106**, 404–409 (1998)
8. D.E. Bild, J.V. Selby, P. Sinnock, W.S. Browner, P. Braveman, J.A. Showstack, Diabetes Care **12**, 24–31 (1989)
9. Performing exact logistic regression with the SAS system. http://www.ats.ucla.edu/stat/sas/library/exactlogistic.pdf
10. D.Y. Aksoy, A. Gurlek, Y. Cetinkaya, A. Oznur, M. Yazici, F. Ozgur, U. Aydingoz, O. Gedik, Exp. Clin. Endocrinol. Diabetes **112**, 526–530 (2004)
11. C.A. Abbott, A.P. Garrow, A.L. Carrington, J. Morris, E.R. Van Ross, A.J. Boulton, Diabetes Care **28**, 1869–1875 (2005)
12. S.D. Ramsey, K. Newton, D. Blough, D.K. McCulloch, N. Sandhu, G.E. Reiber, E.H. Wagner, Diabetes Care **22**, 382–387 (1999)

13. W. Jeffcoate, K. Bakker, Lancet **365**, 1527 (2005)
14. M.J. Young, J.L. Breddy, A. Veves, A.J. Boulton, Diabetes Care **17**, 557–560 (1994)
15. G.E. Reiber, R.E. Pecoraro, T.D. Koepsell, Ann. Intern. Med. **117**, 97–105 (1992)
16. C.L. Saltzman, M.L. Hagy, B. Zimmerman, M. Estin, R. Cooper, Clin. Orthop. Relat. Res. **435**, 185–90 (2005)
17. C.A. Abbott, A.L. Carrington, H. Ashe, S. Bath, L.C. Every, J. Griffiths, A.W. Hann, A. Hussein, N. Jackson, K.E. Johnson, C.H. Ryder, R. Torkington, E.R. Van Ross, A.M. Whalley, P. Widdows, S. Williamson, A.J. Boulton, Diabet. Med. **19**, 377–384 (2002)
18. N. Saltoglu, A. Dalkiran, T. Tetiker, H. Bayram, Y. Tasova, C. Dalay, M. Sert, Clin. Microbiol. Infect. (2009). doi:10.1111/j.1469-0691.2009.03067
19. B.M. Ertugrul, O. Savk, B. Ozturk, M. Cobanoglu, S. Oncu, S. Sakarya, Med. Sci. Monit. **15**, CR307–CR312 (2009)
20. A. Kaya, F. Aydin, T. Altay, L. Karapinar, H. Ozturk, C. Karakuzu, Int. Orthop. **33**, 441–446 (2009)
21. A. Karakoc, R.U. Ersoy, M. Arslan, F.B. Toruner, I. Yetkin, J. Diabetes Complicat. **18**, 169–172 (2004)
22. S. Yesil, B. Akinci, F. Bayraktar, H. Havitcioglu, O. Karabay, N. Yapar, C. Demirdover, S. Yener, M. Yalcin, A. Comlekci, S. Eraslan, Exp. Clin. Endocrinol. Diabetes **117**, 345–349 (2009)
23. M. Edmonds, Int. J. Low. Extrem. Wounds **7**, 66–67 (2008)