Factors Affecting Mortality in Rapidly Progressive Diabetic Foot Ulcer Patients

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Abstract

Objective: A diabetic foot ulcer with progressive infection is a life-threatening condition that requires urgent surgical intervention. Because of the severity of this condition, it is important to understand its epidemiological and prognostic background. This study aims to evaluate the epidemiology of the diabetic foot ulcer and describe the etiology and the surgical procedures performed to treat it.

Methods: A retrospective review of 35 diabetic patients with foot ulcers was performed. These individuals were admitted to the emergency department and were subsequently hospitalized between April 2006 and April 2011. Factors affecting their mortality were statistically assessed.

Results: The long duration of ulcer treatment and need for intensive care were found significantly related to mortality ($p<0.05$). There was a trend toward higher mortality in the patient group with cardiac comorbidity (24% versus 20%), but this was not found to be statistically significant.

Conclusion: Infective diabetic foot ulcers may have a highly mortal course. Having knowledge of how to discriminate between the acute infection and the factors affecting patient mortality may lead us to making better prognoses and delivering more effective treatment.

Keywords: Diabetic foot wound, infection, mortality, sepsis

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Hızlı ilerleyici diyabetik ayak yarası hastalarında mortaliteyi etkileyen faktörler

Öz

Amaç: Hızlı ilerleyici septik enfeksiyonla seyreden diyabetik ayak yaraları son derece ölümcül durumlardır. Bu nedenle hızlı bir cerrahi müdahale gerektirirler. Bu durumların ciddiyetinden ötürü hastalığın epidemiyolojik ve prognostik altyapısının bilinmesi önemlidir. Bu çalışmanın amacı; bu hasta grubunda epidemiyoloji, etiyoloji ve uygulanan cerrahi prosedürlerin mortalite üzerine etkisini araştırmaktır.

Yöntemler: Nisan 2006 ile Nisan 2011 arasında acil polikliniğine başvuran ve acil yatış gerektiren 35 diyabetik ayak yarası hastasının kayıtları retrospektif olarak tarandı. Hastaların yaş, cinsiyet, eşlik eden hastalık, diyabet süresi, yara süresi, yara etiyolojisi, mikrobiyolojik inceleme sonuçları, uygulanan cerrahi girişimler, operasyon sonrası yoğun bakım ihtiyacı ve mortaliteleri incelendi. İstatistiksel olarak diğer tüm parametrelerin mortalite ile korelasyonu araştırıldı.

Bulgular: Yara süresinin uzun olması ve postoperatif yoğun bakım ihtiyacı istatistiksel olarak anlamlı şekilde mortalite ile korale bulundu ($p<0,05$). Kardiyak ek hastalık öyküsü bulunan hasta grubunda mortalitenin daha yüksek olduğu görüldü ancak bu fark istatistiksel olarak anlamlı bulunmadı (%24'e %20).

Sonuç: Enfekte diyabetik ayak yaraları son derece ölümcül bir seyre sahip olabilir. Akut enfeksiyon ayrımını yapabilmek ve mortalite üzerine etki eden faktörleri bilmek daha iyi bir prognoza ulaşmak için yol gösterici olacaktır.

Anahtar Sözcükler: Diyabetik ayak yarası, enfeksiyon, mortalite, sepsis

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Diabetes mellitus is a metabolic disease that is characterized by its tendency to harbor concomitant infections. Foot ulcers are one of the most important complications of diabetes mellitus occurring in a chronic phase as a consequence of neuropathy and angiopathy [1]. But the tendency to infection turns this chronic condition into a progressive acute disease that requires urgent surgical intervention. Limb- and life-threatening foot infections in diabetic patients are caused by necrotizing fasciitis, any type of gangrene, or infections with systemic toxicity or metabolic instability [2]. Therefore, the mortality rates in this patient group and the factors affecting mortality

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should be well defined. The current studies about diabetic foot wounds mainly focus on the management of mild-to-moderate diabetic foot infections, whereas information related to severe foot infections, namely, limb and life-threatening infections, is conspicuously less. For this reason, we aimed to explore the effect of variables on mortality in patients with life-threatening septic diabetic foot ulcers requiring urgent surgical intervention, by assessing the epidemiology, etiology and the surgical procedures performed.

Material and Methods

Patients hospitalized in the emergency department because of life-threatening septic diabetic foot wound between April 2006 and April 2011 were assessed retrospectively. The study was approved by the Local Ethics Committee and conducted in accordance with the 2008 Declaration of Helsinki.

All patients were classified as suffering from severe diabetic foot infection according to the Infectious Disease Society of America (IDSA) [3] and the International Working Group on Diabetic Foot [4]. In addition, a foot that required immediate and emergent surgery was considered life-threatening septic foot in our clinic when the following clinical signs were evident: gaseous or wet gangrene (acutely purulent without gas observed in the subcutaneous tissues); necrotizing fasciitis; necrotizing cellulitis; acute extensive osteomyelitis with either a clinical or a biological marker of systemic toxicity, such as an oral temperature higher than 38.5°C, chills, tachycardia (heart rate> 100 beats per minute), systolic hypotension (<100 mmHg), mental confusion, leukocytosis (>15.000 white blood cells/mL). We excluded normoglycemic patients with skin infections, necrosis or gangrene of the foot, and diabetic patients with superficial or local (present in the toes) infection without systemic involvement. Surgery was performed in all patients within 6 hours of hospitalization. In all cases, a purulent or necrotic tissue specimen was taken during surgery and tested for bacteria and antibiotic sensitivity. Patient records were reviewed for information about sex, age, duration of diabetes, duration of the wound, etiology of the wound, microbiological examination results, operations performed, need for postoperative intensive care, and mortality rate.

Statistical Analysis

Statistical analysis was performed with Statistical Package for the Social Sciences Windows software version 21.0 (IBM Corp.; Armonk, NY, USA). Qualitative variables were analyzed by the χ^2 test and non-normally distributed quantitative variables by using the non-parametric Mann-Whitney U test. The patients were successively divided into groups consisting of survivors and fatalities. Univariate analysis was performed between both the groups. Variables with a p value <0.05 in the univariate analysis were subsequently included in a multivariate analysis to identify independent predictors of mortality using a Cox regression analysis.

Results

Out of a total of 35 patients, 22 were male (62.9%) and 13 were female (37.1%). The mean age of the patients was 58.5 years (range: 42–72 years). The mean duration of diabetes mellitus was 14.4 years (range: 3–35 years). The mean duration of foot wound was 2 months (range: 1–6 months). Thirteen patients (37.1%) did not know the reason for the wound. Out of the remaining 22 patients, 9 (25.7%) had ischemic ulcers, 7 (20%) had an acute infection along with the chronic neurotrophic ulcer base, 3 (8.5%) wounds were due to a burn, 2 (5.7%) were posttraumatic, and 1 (2.8%) was due to a dog bite.

Microbiological investigation revealed that 19 patients (54.2%) had bacterial isolation. About 63.1% of the positive samples (n=12) were polymicrobial. *Pseudomonas* was the most frequently isolated agent (n=8), followed by methicillin-resistant *Staphylococcus aureus* (MRSA) (n=6), *Enterococcus* spp. (n=5), and *Acinetobacter* (n=4).

A total of 26 patients (74.3%) suffered from a combined infection: osteomyelitis as well as necrotizing fasciitis and 9 patients (25.7%) from necrotizing cellulitis.

Twenty-six patients (74.2%) had one or more comorbid diseases, with 25 patients having cardiac comorbidity and 8 patients having chronic kidney disease, 6 of whom were hemodialysis-dependent.

A history of previous revascularization was found in 19 patients. All patients were examined by a vascular surgeon but did not meet the criteria for vascular surgery bypass during our study. Thirty-five patients underwent 59 surgical operations (bedside debridements were not included). Two-staged major amputation (tibiotalar joint disarticulation and drainage through vertical incisions in the first stage; transtibial amputation and closure of the stump in the second stage) was planned for 23 patients (65.7%) but 2 patients were lost after the first stage operation and the second stage operation could not be applied for them. In 3 of the 21 patients who underwent both stages, transfemoral amputation was needed because of wound healing problems. Figure 1, 2, and 3 reveal case examples for two-staged major amputations.

Transmetatarsal amputation was performed in 9 patients (25%). During the follow-up of these 9 pa-

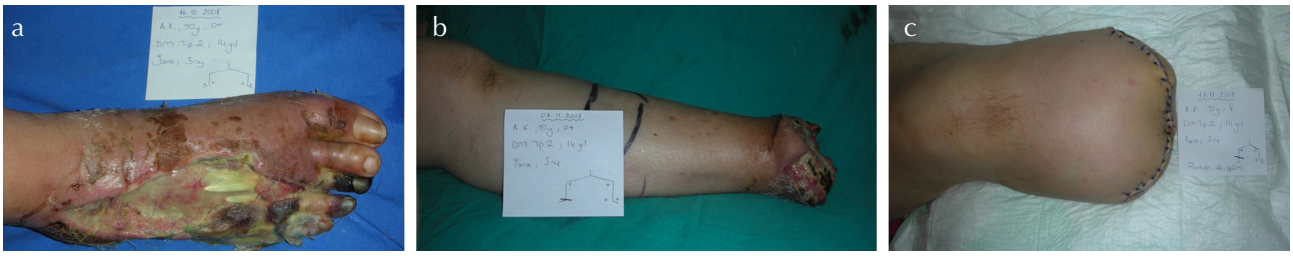

Figure 1. a-c. A 50-year-old female, 14-year history of diabetes, admitted to our hospital with an ischemic ulcer of 3 months and subsequent progressive, severe infection of the right foot (a). At the 1st day of hospitalization, we have performed tibiotalar disarticulation and adequate vertical incisions. 21 days after the first operation (b) we performed transtibial amputation and closed the stump. Postoperative surgical site 4 days after a successful secondary transtibial amputation (c)

Figure 2. a-c. A 52-year-old male, 10-year history of diabetes, admitted to our hospital with an ischemic ulcer of 2 months (a). Tibiotalar disarticulation and appropriate vertical incisions along the pathway of infection were performed for drainage. After 20 days second stage transtibial amputation was performed (b). Postoperative surgical site 10 days after transtibial amputation (c)

Figure 3. a-c. A 54-year-old male, 18-year history of diabetes, admitted to our hospital with an acute progressive infection spreading to the dorsum and ankle region of the right foot and distal cruris occurred within 10 days (a). Tibiotalar disarticulation and appropriate vertical incisions along the pathway of infection were performed for drainage. After 39 days (b) second stage transtibial amputation was performed. Postoperative surgical site 9 days after transtibial amputation (c)

tients, one transtibial, and one transfemoral amputation was performed because of persistent infection and wound healing problems. Two patients underwent single-staged transtibial amputation, 1 patient underwent transfemoral amputation.

Need for postoperative intensive care was identified in 13 patients (37.1%), 7 of whom are now deceased (%20).

Statistical analysis showed no significant effect of sex, age, duration of diabetes, wound etiology, and the operation performed on mortality. The long duration of the wound had a significant effect on mortality (p=0.025). The need for intensive care was also significantly relevant to mortality (p=0.0002). There was a trend toward higher mortality in the patient group with cardiac comorbidity, but this was not found to be sta-

tistically significant (p=0.06). Considering the previous studies supporting the effect of cardiac comorbidity on mortality, the reason for the statistical insignificance was thought to be the low patient count.

Discussion

Although amputation for diabetic foot ulcers is not a favored type of treatment by the patients, it might be life-saving, especially in cases of rapidly progressive foot infections. Therefore, it is crucial to diagnose such patients and to be able to differentiate the diabetic ulcer from other frequently seen chronic ulcers.

Certain infection types and necrosis depths should be considered as criteria for severity of foot infections as well as gangrene [3, 4]. Although gangrene is mostly associated with arterial insufficiency, it may also occur due to serious infection even in a completely vascularized foot [5]. The reason for gangrene in such cases is mainly the necrosis of vessels. With the spread of infection to deeper layers of the foot, the compartmental pressure increases and further necrosis takes place when the compartmental pressure exceeds the perfusion pressure [6]. Early diagnosis and precise treatment of necrotizing soft tissue infections are crucial since these ulcers may easily become not only limb-threatening but also life-threatening in diabetic patients [7, 8]. The aim of this study was to evaluate the epidemiological factors and surgical results of necrotizing foot infections and to detect a correlation of these criteria with mortality.

The diabetic foot ulcer is one of the most important reasons for hospitalization in diabetic patients, as it is a common complication seen in 15% of diabetic patients, 14%–24% of whom eventually require amputations [9, 10]. Diabetic foot ulcer has slow chronic progress along with neuropathy, angiopathy, and tendency to infection. In acute infection cases, late or inadequate treatment may result in necrotizing soft tissue infections, extremity amputations, and even death [2, 7]. About 21%–64% of patients presenting with multiple-site necrotizing soft tissue infections are diagnosed as diabetic [2]. However, there are only a few reports that have evaluated the impact of necrotizing soft tissue infections exclusively in cases involving the feet of diabetic patients. Many authors agree with the concept that urgent major amputation is an appropriate course of action for the treatment of life- and limb-threatening septic diabetic foot characterized by deep necrotic infections with bone and joint involvement [6, 8].

All of the patients in our cohort study had a septic diabetic foot with either a clinical or a biological marker of systemic toxicity. In 25 patients, the entire foot up to the ankle was involved with deep tissue infections and necrosis. Therefore, the two-staged amputation method was decided in 23 patients [8]. Tibiotalar disarticulation was performed in the first stage. It is a reasonably fast procedure and provides quick disposal of the septic and necrotic tissue while keeping the patient away from the systemic disadvantages of extensive surgery, such as major amputation. The septic state disappears rapidly and dramatically even on the same day after the removal of the infected foot. After managing the wound with daily wet-absorbing dressings and serial debridements, transtibial amputation and closure of stump were performed at the second stage. By this method, the transmission of infection proximally to the stump closure site and potential wound healing problems were prevented. One-staged major amputation was the initial procedure in 3 patients (2 transtibial, 1 transfemoral). Overall major amputation was performed for 28 patients (80%). Transmetatarsal amputation was performed in 9 patients in whom only the forefoot and midfoot were involved.

In our study, 35 patients who admitted to the emergency department with life-threatening septic diabetic foot requiring urgent surgical intervention were assessed. Major amputation was performed for 28 patients (80%). Compared to the major amputation rates in previous studies (8%–29%), our rate of major amputation was excessively high [5, 6, 11]. The reason for this result was due to the life-threatening condition of our patients, which required urgent surgical intervention. For most of the patients who admitted in septic condition (66%), tibiotalar disarticulation to remove the source of infection and vertical incisions for purulent material drainage were performed. After managing the wound with daily wet-absorbing dressings and serial debridements, transtibial amputation and closure of the stump were performed at the second stage. By this method, the transmission of infection proximally to stump closure site and potential wound healing problems were prevented [8].

High rates of need for intensive care (40%) and mortality (20%) are thought to be associated with retarded admission and presence of systemic disorders at the time of admission. Both the major amputation rate (80%) and the mortality rate (20%) are high compared to the previous studies. However, the information is recorded from an overall group of diabetic foot ulcer patients in these studies. Thus, the high mortality rate and the high number of major amputations are an expected consequence in our patient group.

The long duration of the ulcer is surprisingly has a significant effect on mortality. Although chronic ulcers were thought to be more benign than acute ulcers, patients with chronic ulcers had a higher mortality rate. This is thought to be because the patients become familiar with and tend to live with their ulcers in the

chronic phase and can neglect the new onset of acute infection. These patients usually present the at emergency rooms with general disorders, such as sepsis.

Although all the patients had infectious wounds on admission, only 54% of the microbiological samples revealed bacterial isolation. This was due to the previous antibiotic therapy supporting the inappropriate or insufficient treatment that may have led to late admission. The most frequently isolated agents also support the deduction of previous antibiotic therapy application. Usual agents such as *S. aureus* or *Streptococci*, which are susceptible to common antibiotic agents, were not isolated [12].

Although a statistically significant effect on mortality could not be determined, cardiac comorbidity and accompanying chronic kidney disease are found high in the patients who needed intensive care and in deceased patients. Previous studies support the observation that accompanying cardiac and renal disease has an effect on mortality [10, 13-16].

The small sample size was an important limitation of the study. Although our institution has been an important reference center for diabetic wound care, the number of such progressive septic wound patients remains low. This low patient count might be the reason for the insignificant correlation between cardiac and renal diseases and mortality. The retrospective nature of the study is also a limitation as parameters might be enhanced with more variables in a prospective study.

In conclusion, invasive necrotizing foot infection in the diabetic population is a life-threatening condition that requires urgent surgical intervention. Removing the source of infection as soon as possible is vital. The mortality rate was high in this patient group even though major surgery was performed. Low major amputation rates and low mortality rates in overall diabetic foot ulcer patient groups in the previous studies may mislead the inexperienced surgeon to act conservatively. It is important to discriminate between the chronic wound and the signs of progressive acute infection in diabetic patients. Our study may lead to a better understanding of the epidemiology and prognosis of diabetic foot ulcer in patients requiring urgent surgical intervention.

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References

1. American Diabetes Association. Foot wound care consensus conference. Diabetes Care 1999; 22: 1354-60. **[CrossRef]**
2. Wallace GF. Debridment of invasive diabetic foot infections. Clin Plastic Surg 2007; 34: 731-4. **[CrossRef]**
3. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012; 54: e132-73. **[CrossRef]**
4. Peters EJ, Lipsky BA, Aragón-Sánchez J, Boyko EJ, Diggle M, Embil JM, et al. Interventions in the management of infection in the foot in diabetes: a systematic review. Diabetes Metab Res Rev 2016; 32 (Suppl 1): 145-53. **[CrossRef]**
5. Moulik PK, Mtonga R, Gill GV. Amputation and Mortality in New-Onset Diabetic Foot Ulcers Stratified by Etiology. Diabetes Care 2003; 26: 491-4. **[CrossRef]**
6. Taylor LM Jr, Porter JM. The clinical course of diabetics who require emergent foot surgery because of infection or ischemia. J Vasc Surg 1987; 6: 454-9. **[CrossRef]**
7. Capobianco CM, Stapleton JJ, Zgonis T. Surgical management of diabetic foot and ankle infections. Foot Ankle Spec 2010; 3: 223-30. **[CrossRef]**
8. Altındaş M, Kılıç A, Çınar C. A reliable surgical approach for the two-staged amputation in unsalvageable limb and life threatening acute progressive diabetic foot infections: Tibiotalar disarticulation with vertical crural incisions and secondary transtibial amputation. Foot Ankle Surg 2011; 17: 13-8. **[CrossRef]**

9. Lipsky BA. A report from the international consensus on diagnosing and treating the infected diabetic foot. Diabetes Metab Res Rev 2004; 20 (Suppl 1): S68-77. **[CrossRef]**
10. Robbins JM, Strauss G, Aron D, Long J, Kuba J, Kaplan Y. Mortality Rates and Diabetic Foot Ulcers: Is it Time to Communicate Mortality Risk to Patients with Diabetic Foot Ulceration?. J Am Podiatr Med Assoc 2008; 98: 489-93. **[CrossRef]**
11. Altindas M, Kilic A, Cinar C, Bingol UA, Ozturk G. The epidemiology of foot wounds in patients with diabetes: a description of 600 consecutive patients in Turkey. J Foot Ankle Surg 2011; 50: 146-52. **[CrossRef]**
12. Tascini C, Piaggesi A, Tagliaferri E, Iacopi E, Fondelli S, Tedeschi A, et al. Microbiology at first visit of moderate-to-severe diabetic foot infection with antimicrobial activity and a survey of quinolone monotherapy. Diabetes Res Clin Pract 2011; 94: 133-9. **[CrossRef]**
13. Aragón-Sánchez J, Hernández-Herrero MJ, Lázaro-Martínez JL, Quintana-Marrero Y, Maynar-Moliner M, Rabellino M, et al. In-hospital complications and mortality following major lower extremity amputations in a series of predominantly diabetic patients. Int J Low Extrem Wounds 2010; 9: 16-23. **[CrossRef]**
14. Hambleton IR, Jonnalagadda R, Davis CR, Fraser HS, Chaturvedi N, Hennis AJ. All-cause mortality after diabetes-related amputation in Barbados: a prospective case-control study. Diabetes Care 2009; 32: 306-307. **[CrossRef]**
15. Izumi Y, Satterfield K, Lee S, Harkless LB, Lavery LA. Mortality of first-time amputees in diabetics: a 10-year observation. Diabetes Res Clin Pract 2009; 83: 126-31. **[CrossRef]**
16. Faglia E, Clerici G, Clerissi J, Gabrielli L, Losa S, Mantero M, et al. Early and five-year amputation and survival rate of diabetic patients with critical limb ischemia: data of a cohort study of 564 patients. Eur J Vasc Endovasc Surg 2006; 32: 484-90. **[CrossRef]**