Long-Term Outcome and Disability of Diabetic Patients Hospitalized for Diabetic Foot Ulcers

A 6.5-year follow-up study

EDOUARD GHANASSIA, MD[1,2]
LAETITIA VILLON, MD[1,2]
JEAN-FRANÇOIS THUAN DIT DIEUDONNÉ, MD[1,2]
CATHERINE BOEGNER, MD[1]
ANTOINE AVIGNON, MD[1,2]
ARIANE SULTAN, MD[1,2]

OBJECTIVE — The long-term outcome and functional status of subjects hospitalized for diabetic foot ulcers have been poorly studied and thus are the topics of this study.

RESEARCH DESIGN AND METHODS — Ninety-four consecutive diabetic subjects hospitalized for diabetic foot ulcers between January 1998 and December 2000 were prospectively followed for mean ± SD 79.5 ± 13.3 months. We calculated rates of primary healing, new ulcers, amputations, mortality, and disability and evaluated the global therapeutic success (GTS) of foot care management as defined by the association of primary healing without recurrence or disability at the end of follow-up.

RESULTS — Follow-up was successful in 89 of 94 subjects (63 men and 31 women; age 63.7 ± 10.8 years). Of these, 69 (77.5%) experienced primary healing without major amputation, 39 (43.8%) underwent amputation (24 minor and 15 major), and 46 died (51.7%), including 23 from cardiovascular events. Forty-two of 69 patients who experienced primary healing (60.9%) had ulcer recurrence. At the end of the follow-up period, 25 patients (28.1%) were dependent and 40 subjects (44.9%) had achieved GTS. Multivariate analysis showed the role of age as an independent predictor of GTS ($P < 0.05$) and of impaired renal function/albuminuria as independent predictors of healing failure, first amputation, and mortality ($P < 0.01$).

CONCLUSIONS — Despite a satisfactory initial healing rate, the global long-term outcome of patients hospitalized for diabetic foot ulcers was poor. Nephropathy appears to be an important predictor of long-term outcome. Further studies are needed to establish recognized criteria for therapeutic success going beyond just the evaluation of healing rate in the management of diabetic foot ulcers.

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Diabetic foot ulcers represent a major public health concern (1) and are commonly viewed as a lower-extremity disease associated with a high amputation rate (2). They are generally associated with advanced micro- and macroangiopathy, resulting in excessively high morbidity and mortality (3).

Pathogenic mechanisms and therapeutic options for foot ulcers have been extensively studied, leading to an international consensus in 1999 (4). However, most studies have focused on ulcer-related outcomes over short periods of time (healing, change in area, or amputations), rather than evaluation of long-term patient-related outcomes (5–7). Recently, Jeffcoate et al. (8) used the association of survival, absence of any amputation, and freedom from ulcers as an estimate of patient-related outcomes, showing that ulcer-related outcomes may extensively underestimate the true morbidity and mortality associated with diabetic foot disease. However, these authors did not evaluate functional outcome, and their measurements were confined to the first year after initial registration in their clinic. The aim of the present study was to analyze the long-term outcome of diabetic patients after hospitalization for foot ulcers using a scale for disability (9) and to investigate possible prognostic factors.

RESEARCH DESIGN AND METHODS

— From January 1998 to December 2000, all patients hospitalized in our department for diabetic foot ulcers were included in a cohort. Admission for inpatient treatment was ordered if a limb-threatening infection and/or nonfavorable evolution of the wound despite standard outpatient care was observed, according to international recommendations (4). Limb-threatening infection was defined by the presence of full-thickness ulcer, >2 cm of cellulitis with or without lymphangitis, bone or joint involvement, or systemic toxicity. Standard outpatient care included pressure offloading, treatment of infection including debridement, local wound care, podiatric care, adapted footwear when needed, metabolic control, and treatment of comorbidities and associated risk factors including smoking, hypertension, and dyslipidemia. The evolution of the wound was considered nonfavorable in the case of an aggravation at two consecutive visits or in the absence of any improvement after 1 month of care. During that period of time, 94 patients were included in the cohort.

Each patient gave oral informed consent, in accordance with the European directives as edited in 2001 (available from http://europa.eu/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf), which require no approval from an ethics committee for a study design as described herein.

Participants were considered to have type 2 diabetes if they had no history of ketosis and if they did not commence in-

From [1]Le Centre Hospitalier Universitaire Montpellier, Montpellier, France; and the [2]Université Montpellier 1, Unités de Formation et de Recherche de Médecine, Montpellier, France.
Corresponding author: Antoine Avignon, a-avignon@chu-montpellier.fr.
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sulin treatment either in the 2 years after the diagnosis or before age 40 years. Otherwise, they were considered to have type 1 diabetes.

Past history of myocardial infarction was determined using medical records and/or when an electrocardiographic Q wave was present. Hypertension was diagnosed if one of the following conditions was present: systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥80 mmHg, or the presence of at least one antihypertensive medication. Patients were considered smokers if they were current smokers or if they stopped smoking <3 years before admittance.

Peripheral neuropathy was diagnosed when two criteria were met among the following: paresthesias, neuropathic pain, altered 10-g Semmes-Weinstein monofilament test, and diminished ankle reflexes. Peripheral arterial disease was diagnosed in the case of abolition of ≥2 peripheral pulses and/or ≥1 significant stenoses as shown by Doppler ultrasound or by a reduction of lumen diameter ≥50% or an occlusion of ≥1 artery as shown by angiogram.

Arterial stenoses diagnosed by Doppler ultrasound were deemed significant when occlusions, single or multiple stenoses, or diffuse stenotic disease in the femoropopliteal segments, individually or collectively, caused significant velocity change and flow disturbance locally and resulted in loss of reverse flow distally or in the presence of occlusions of arteries below the knee. Lesions were classified as ischemic wounds when peripheral arterial disease was diagnosed or as nonischemic wounds otherwise.

Wounds were graded using Wagner's classification (10). The lesions were then categorized into two main clinical groups: skin ulcers (Wagner 1 and 2) and critical ulcers, which included both deep tissue infections and suspected osteomyelitis (Wagner 3), and gangrenous lesions (Wagner 4 and 5).

We defined a foot infection by clinical criteria consistent with the International Working Group guidelines (4) (i.e., the presence of purulence or ≥2 other local signs of inflammation). We evaluated patients with an infection for the extent of soft tissue involvement and for evidence of bone involvement. Bone infection was suspected in the presence of positive bone probing (11) and was confirmed either by magnetic resonance imaging or by a standard ^{99m}Tc-hexamethylpropyleneamine oxime leukocyte scan.

The biological and bacteriological data considered were the first realized after admittance. In the presence of clinical infection, culture specimens were obtained using deep swabbing and/or surgical debridement.

A1C was measured using high-performance liquid chromatography with an automated analyzer (Menarini, Rungis Cedex, France). The instrument was calibrated according to Diabetes Control and Complications Trial standards (reference range 4.1–5.7%). The urinary albumin excretion rate was measured by radioimmunoassay on 24-h urine collections, and diabetic nephropathy was defined by urinary albumin excretion rate ≥30 mg/day. The serum creatinine level was measured, and creatinine clearance was calculated according to the Cockroft-Gault formula. Renal impairment was defined as creatinine clearance ≤60 ml/min.

Follow-up data were obtained during the month of July 2007 (which was 5.5 years after the last patient's inclusion) through a telephone interview of each patient's family physician or diabetologist, using a specifically designed questionnaire. The clinical outcomes considered were primary wound healing, ulcer recurrence, major amputation, death, disability, and global therapeutic success (GTS) for diabetic foot management, defined as the association of primary healing, absence of recurrence, and no disability. If death occurred during the follow-up period, GTS was considered if the three criteria were met at the time of death. Primary wound healing was considered to be achieved when total disappearance of the initial ulcer was reported without major amputation of the limb. Ulcer recurrence was reported when the subject developed a new ulcer after a successful primary healing. An amputation was considered as major if it was performed above the midtarsal level and as minor otherwise (4). Cardiovascular death was defined as death caused by ischemic heart disease, acute pulmonary edema, acute congestive heart failure, cardiogenic shock, stroke, or sudden death. Death was considered wound-related when it was caused by immobilization (pulmonary embolism) or sepsis due to wound infection or when it occurred during wound-related events such as vascular surgery.

Disability was assessed by Katz's Index of Activities of Daily Living (9). This index measures performance in six personal activities of daily living: bathing, dressing, toileting, transfer, continence, and feeding. It consists of six items with binary quotations of 1 or 0 based on the individual's ability to perform the corresponding activity without assistance by another individual. Patients living with a partner were considered independent if they were able to perform the activity when left alone. A subject whose score was <3 was regarded as very dependent (12). Hence, in the present study, we defined disability as a Katz's Index score <3.

Statistical analysis was performed using StatView (SAS Institute, Cary, NC) and StatBox Pro 6.0 (GrimmerSoft, Issy Les Moulineaux, France). The normality of the distribution of each quantitative parameter was assessed using the Kolmogorov-Smirnov test. If normality was established, results were given as mean ± SD, and comparisons were made using the Student's *t* test for unmatched series. Otherwise, the results were given as median (range), and comparisons were made using the nonparametric Mann-Whitney *U* test. Discontinuous parameters were calculated as a frequency and expressed as percentages. Univariate analyses between qualitative parameters were made using the χ^2 test with the Yates' test. We used logistic regression analyses to compute the relative risks (RRs) of an end point associated with different factors. Multivariate analysis to identify independent predictive factors was performed using Cox's logistic regression. The entry criterion was $P < 0.1$, and the permanence criterion was $P < 0.05$. Predictive value was expressed as RR with a 95% CI. Kaplan-Meier curves were used to compare survival between two groups, and significance was assessed by log-rank test. For all tests, significance was set at $P < 0.05$.

RESULTS — Follow-up data were obtained in 89 of 94 (95%) patients. The main characteristics of the patients at inclusion are given in Table 1. Mean ± SD follow-up was 79.4 ± 13.3 months (range 66.1–92.6).

Of the 89 patients, 82 (92.1%) had sensorimotor diabetic neuropathy and 41 (46.1%) had ischemic wounds; a total of 48 (53.9%) patients were considered purely neuropathic. Fifteen of the 89 patients in the cohort (16.9%) underwent vascular procedures.

Primary healing

Primary healing was achieved in 69 of 89 patients (77.5%) (Table 2). Univariate predictors of healing failure were smok-

Table 1—*Patients' baseline characteristics*

	Total
n	89
Male sex	62 (69.7)
Age (years)	63.8 ± 10.8
Diabetes duration (years)	24.0 ± 11.3
Type 1 diabetes	11 (12.4)
Past history of myocardial infarction	21 (23.6)
Past history of amputation	27 (30.4)
Minor	18 (20.3)
Major	9 (10.1)
BMI (kg/m²)	26.6 ± 4
Ischemic wounds	75 (84.3)
Critical wounds (Wagner ≥3)	41 (46.1)
A1C (%)	9.2 ± 1.7
Insulin therapy	60 (67.4)
Retinopathy	65 (75.3)
Nephropathy	52 (58.4)
Creatinine clearance (ml/min)	73.3 ± 30
High blood pressure	84 (94.4)
Dyslipidemia	74 (83.1)

Data are mean ± SD or *n* (%).

ing (RR 2.89 [95% CI 1.01–8.27]; $P < 0.05$), popliteal stenosis (3.6 [1.28–10.14]; $P < 0.02$), and renal impairment (6.45 [2.17–10.83]; $P < 0.0001$). All 14 patients (100%) with nonischemic wounds and 55 of 75 patients (73.3%) with ischemic wounds achieved primary healing ($P = 0.06$). After factors associated with healing failure at $P < 0.1$ in univariate analysis were introduced into a multivariate model, renal impairment (6.21 [1.28–31.05]; $P < 0.03$) and smoking (6.11 [1.42–26.30]; $P < 0.02$) were found to be independent predictors of healing failure.

Table 2—*Main outcomes*

	Total
n	89
Primary healing	69 (77.5)
Recurrent ulceration	42 (60.9)
Amputations	39 (43.8)
Minor	30 (33.7)
Major	9 (10.1)
All-cause mortality	46 (51.7)
Cardiovascular mortality	23 (25.8)
GTS for diabetic foot management	40 (44.9)

Data are *n* (%). Percentage is calculated in proportion to the 69 patients who reached primary healing.

Ulcer recurrence

Among the 69 patients who achieved primary healing, 42 (60.9%) developed a new ulcer during the follow-up period (Table 2). Insulin treatment before admission was the only predictor of ulcer recurrence, both in univariate analysis (RR 3.87 [95% CI 1.37–10.98]; $P < 0.006$) and after adjustment for factors associated at $P < 0.01$ in univariate analysis, i.e., ischemia and osteitis (4.61 [1.35–15.79]; $P = 0.015$).

Amputations

Thirty-nine of the 89 patients in the whole cohort (43.8%) underwent an amputation (30 minor and 9 major) (Table 2). Univariate predictors of amputation were critical ulcers (RR 3.01 [95% CI 1.26–7.21]; $P < 0.01$), ischemic wounds (6 [1.26–28.69]; $P < 0.003$), suprapopliteal stenosis (14.4 [1.73–119.48]; $P < 0.01$), and popliteal stenosis (4.03 [1.03–10.12]; $P < 0.003$). In multivariate analysis, popliteal stenosis was the only independent predictor of amputation (3.67 [1.34–10.07]; $P \leq 0.01$).

Regarding major amputations, past history of lower limb revascularization (RR 5.80 [95% CI 1.38–24.40]; $P < 0.02$), previous amputation (either minor or major) (5.52 [1.27–24.10]; $P < 0.02$), and critical ulcers (11.15 [1.33–93.52]; $P < 0.03$) were found to be univariate predictors, but none of these factors remained as independent predictors in multivariate analysis.

Even though the rate of amputation was higher in the group of patients with a previous history of amputation (15 of 27 patients, 55.6%) compared with those who did not have a previous history of amputation (23 of 62 patients, 37.1%), the difference between these two groups did not reach the level of statistical significance.

Among the 62 patients without previous amputation, univariate predictors of first amputation were diabetic nephropathy (RR 5.54 [95% CI 1.59–19.32]; $P < 0.008$) and ischemic wounds (8.54 [1.03–72.16]; $P < 0.05$). After multivariate analysis, only diabetic nephropathy remained as an independent predictor of first amputation (6 [1.62–22.21]; $P < 0.01$).

Disability

Twenty-five subjects (28.1%) were considered to have a disability (Katz's Index <3) at the end of the follow-up period or at the time of their death (Table 2). Patients with a disability were older at the time of entry into the study than those without (70.1 ± 8.3 vs. 61.5 ± 10.7 years, respectively; $P < 0.001$). Other univariate associates of disability were renal impairment (RR 3.76 [95% CI 1.26–11.24]; $P < 0.01$) and history of amputation (3.02 [1.14–7.99]; $P < 0.03$). None of these factors remained as independent predictors of disability after multivariate analysis.

GTS

GTS was achieved for 40 subjects (44.9%): 28 (31.5%) who were alive at the end of the follow-up period and 12 (13.4%) who had died (Table 2). In the subgroup of 43 patients still alive at the end of the follow-up period, the GTS rate was 65.1%. In the subgroup of 46 deceased patients, the GTS rate was 26.1% ($P < 0.001$).

In univariate analysis, failure to reach GTS was associated with advanced age (66.6 ± 9.3 vs. 59.8 ± 11.6 years, GTS vs. no GTS; $P < 0.01$), previous history of foot ulcers (RR 2.67 [95% CI 1.03–6.91]; $P < 0.05$), and insulin therapy before admission (2.63 [1.06–6.53]; $P < 0.04$). In multivariate analysis, age >70 years was the only independent predictive factor that persisted (2.8 [1.01–7.67]; $P < 0.05$).

Mortality

Forty-six patients (51.7%) died during the follow-up period, including 23 (25.8%) from a cardiovascular event, 9 (19.6%) from a wound-related event, 7 (15.2%) from malignancies, and 7 (15.2%) from other causes (Table 2). In univariate analysis, mortality was associated with advanced age (68 ± 9.1 vs. 57.5 ± 10.8 years, deceased vs. alive; $P < 0.001$), renal impairment (RR 6.93 [95% CI 2.67–18.04], $P < 0.0001$), and past history of amputation (3.08 [1.17–8.59]; $P < 0.03$). When disability, age, renal impairment, and history of myocardial infarction were considered in a multivariate analysis, only renal impairment (4.57 [1.1–19.4]; $P < 0.05$) was identified as an independent predictor of mortality (Fig. 1).

After both univariate and multivariate analyses with the introduction of insulin therapy, renal impairment, and history of myocardial infarction into the model, we found the independent predictive factors for cardiovascular mortality to be insulin therapy before admittance (RR 13.14 [95% CI 1.39–124.48]; $P < 0.05$) and

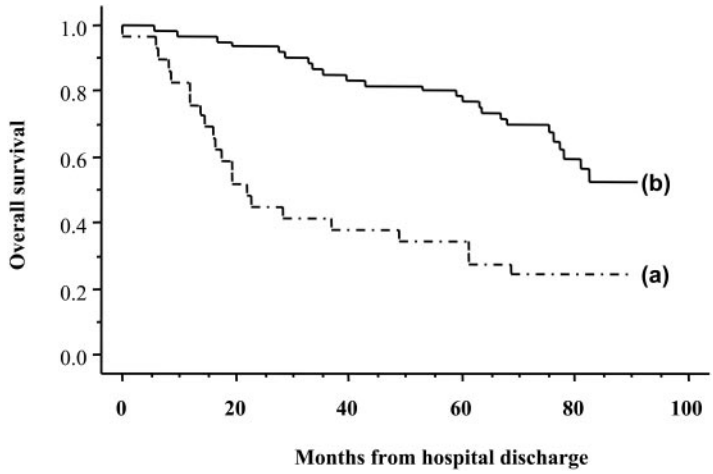

Figure 1—*Kaplan-Meier survival curves comparing survival rate in patients without (b) or with (a) impaired renal function.*

renal impairment (8.7 [1.6–48]; $P \leq 0.01$).

CONCLUSIONS — Most previous studies evaluating diabetic foot ulcer outcome were short-term studies (<5 years) and were limited to ulcer-related end points, such as healing and amputations. Thus, in the present report, we evaluated long-term outcome (6.5 years), including disability as an end point in a consecutive series of patients hospitalized at a single specialized center for foot ulcers. Predictors of long-term outcome were evaluated further.

The primary healing rate was 77.5%, but the years after the initial event were marked by high rates of ulcer recurrence (60.9%) and amputations (43.8%). At the end of the follow-up period or at the time of their death, 28.1% of the patients were considered to have a disability leading to dependency, which is one of the essential criteria used to evaluate functional status (13). To our knowledge, no data concerning prospective evaluation of disability or dependency in diabetic subjects with foot ulcers are available nor has it ever been considered as a therapeutic criterion in any previous study. Even though it was not specifically designed for diabetic subjects with foot ulcers, we chose Katz's Index to evaluate disability for several reasons: *1*) it is easy to use in routine clinical practice, *2*) the French version has been validated, and *3*) it is widely used in the literature (12).

Dependence is plurifactorial, and one of today's crucial issues is the identification of easily measurable predictive markers to undertake effective interventions for its prevention. In our study as well as in the literature, disability was associated with aging (13,14). Thus, even though the primary healing rate observed in our series might be considered satisfactory and is in agreement with those of published prospective studies with a similar follow-up duration (5,6,15), GTS for foot care, as defined by healing and absence of recurrence and disability, occurred in <50% of the patients (44.9%). The definition we used for GTS in the present study was based on a pragmatic basis because we wanted it to be simple enough to be used in everyday clinical practice, but other definitions, including more criteria, could have been used.

Vital status was not included as a success criterion for foot-ulcer management in the present study because in this population of diabetic patients, a number of deaths were unrelated to diabetic foot care. For example, only 9 of 46 deaths were directly related to a foot ulcer complication, whereas 7 deaths were related to malignancies. However, at the end of the follow-up period, 46 patients had died, with half of these deaths being due to a cardiovascular event. Thus, as few as 28 patients (31.5%) were both alive and considered to have achieved GTS at the end of the study.

Ulcer recurrence in the present study is also in agreement with the current literature (5,15), even though Faglia et al. (6) reported a much lower value (12.75%). These authors explained their particularly good results as resulting from the facts that all of their subjects had therapeutic shoes with an adapted sole and that their families were educated on foot care. Of course, all of our subjects were also directed to wear adapted shoes and soles and received education regarding foot care. However, patients in France are somewhat reluctant to buy devices that are not covered by the social security, as is the case for therapeutic shoes and soles, thus limiting their use. This could explain the difference in rate of ulcer recurrence between the study of Faglia et al. and ours.

Similarly, Moulik et al. (7) reported a limited rate (19%) of amputations for all levels after 5 years, contrasting with our amputation rate of 43.8%, which is nevertheless similar to that of other studies (5,6,15). The lower amputation rate in that latter study could be explained by the fact that Moulik et al. included only patients with new ulcerations.

Diabetic nephropathy appears to be an important marker of long-term prognosis, with impaired renal function being an independent predictor of healing failure, of all-cause mortality, and of cardiovascular death and with albuminuria being associated with amputations. This latter point is in agreement with a previous study by Apelqvist and Agardh (16). These results confirm the importance of diabetic nephropathy as a marker of extended angiopathy in patients with diabetic foot ulcers.

Ischemia, as defined in the present study, was a univariate associate of amputation but was not found to be an independent predictive factor after correction for confounding factors. However, other markers of macroangiopathy were associated with long-term outcomes, with popliteal stenosis as an independent predictor of amputation, confirming that vascular involvement in diabetic patients with foot ulcers is particularly important (17). Thus, our results do not deny the crucial role of macroangiopathy in the long-term global prognosis of these subjects (7).

Insulin therapy before admittance also appears as a central marker, as it is an independent predictive factor of ulcer recurrence and cardiovascular mortality. Insulin is generally needed after a long diabetes duration associated with poor glycemic control, with both being major risk factors for micro- and macroangiopathic complications (18). Insulin must thus be considered more as a marker of the severity of the disease rather than a risk factor per se.

One of the limitations of our study is that data were collected via a telephone interview and not face to face. However, we do not feel that this limits the validity or importance of these results.

In summary, we found that despite a satisfactory initial healing rate, the global long-term outcome of patients hospitalized for diabetic foot ulcers was poor. These observations confirm the need to establish recognized criteria, going beyond just healing rate, for the long-term evaluation of diabetic foot ulcers. Multicenter trials are needed in this respect. Our results also stress the importance of impaired renal function as a predictor of diabetic foot ulcer outcome and the need to pay particular attention to patients with this condition.

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