Multicenter Study of the Incidence of and Predictive Risk Factors for Diabetic Neuropathic Foot Ulceration

CAROLINE A. ABBOTT, BSC, PHD
LORETTA VILEIKYTE, MSC, MD
SHEILA WILLIAMSON, BSC
ANNE L. CARRINGTON, BSC, PHD
ANDREW J.M. BOULTON, MD, FRCP

OBJECTIVE — To investigate longitudinally prognostic factors for foot ulceration in a large population of diabetic patients with established neuropathy.

RESEARCH DESIGN AND METHODS — A double-blind multicenter study of a potential new agent for diabetic neuropathy provided the opportunity for this 1-year investigation since intervention demonstrated no efficacy in the condition. A total of 1,035 patients with NIDDM and IDDM were included. Inclusion criteria were vibration perception threshold (VPT) at the great toe ≥25 V in at least one foot and ≤50 V in both feet, normal peripheral circulation, and no previous foot ulceration. VPT and clinical components of the Michigan diabetic polyneuropathy (DPN) score were assessed at baseline and subsequent visits.

RESULTS — After 1 year, the incidence of first foot ulcers for the total population was 7.2%. Neuropathy parameters were the same between the treatment and placebo groups at baseline and were unchanged at 1 year; therefore, baseline data were combined for multiple regression analysis. VPT, age, and Michigan DPN scores for muscle strength and reflexes were significant independent predictors for first foot ulceration ($P < 0.01$). For each 1-U increase in VPT values at baseline, the hazard of the first foot ulcer increased by 5.6%. Similarly, for each 1-U increase in muscle strength and reflex components of the Michigan DPN scores, the hazard of the first foot ulcer increased by 5.0%.

CONCLUSIONS — Tests of VPT and Michigan DPN scores for muscle strength and reflexes are useful clinical predictors for foot ulceration in diabetic patients with established neuropathy. The rate of subsequent ulceration in the following year was alarmingly high, however, despite standardized foot care education at baseline and regular follow-up visits.

Foot ulceration remains one of the most common causes for hospital admission among diabetic patients, despite increased awareness of this problem among health care professionals in recent years (1). Among a large survey of >6,000 randomly selected patients attending diabetic clinics, over 2% had active foot ulcers, and 2.5% were amputees (2). However, there are few reports of the incidence of foot ulceration in diabetic populations. The rate of lower limb amputation is 15 times higher in diabetic patients compared with nondiabetic patients (3). Furthermore, >50% of diabetic amputees need an amputation in the contralateral limb within 4 years after the loss of the first leg (4). Peripheral neuropathy has been demonstrated as a strong risk factor for foot ulceration in many cross-sectional studies and is present in >80% of affected patients (5–7). Furthermore, a single-center survey demonstrated that foot ulcers, primarily attributable to neuropathy, are the cause of 50% of all hospital admissions for diabetic foot complications (8). In prospective studies, the three main independent predictors for foot ulceration have been shown to be an absent Achilles tendon reflex, impaired monofilament pressure sensation, and impaired vibration sensation (9,10). However, there are no published data regarding independent predictors of foot ulceration in large, multicenter populations of diabetic patients with significant neuropathy.

RESEARCH DESIGN AND METHODS

Study design

The present study was originally designed as a double-blind randomized placebo-controlled 2-year prospective multicenter trial of the safety and efficacy of the study drug Ro44-7190 (a derivative of carnitine) in reducing the incidence of first foot ulceration in diabetic patients with peripheral neuropathy. Patients were randomized (2:1 ratio) to receive either two 500-mg tablets of Ro44–7190 or two placebo tablets, each three times daily. However, this trial was discontinued after the 1st year as a result of the failure of the pivotal studies to demonstrate the efficacy of the product (unpublished data). The present study therefore provided an opportunity to determine the annual incidence of first foot ulceration in a large population of diabetic patients with established neuropathy and also to investigate, longitudinally, important prognostic factors for foot ulceration in these patients.

Subjects

Patients were included in the study if they were diagnosed with IDDM or NIDDM according to World Health Organization criteria, were ages 18–70 years, were men or nonpregnant women, had a vibration perception threshold (VPT) ≥25 V on at least one foot and ≤50 V on both feet (determined at the hallux by neurothesiometer), and had at least one palpable pedal pulse on each foot. The main exclusion criteria were as follows: *1*) past or present foot ulcers, defined as any full-thickness skin lesion that required treatment in hospital, with a

From the Department of Medicine, Manchester Royal Infirmary, Manchester, U.K.

Address correspondence and reprint requests to Caroline Abbott, PhD, Diabetes Foot Clinic, Disablement Services Centre, Withington Hospital, Cavendish Road, Manchester M20 8LB, U.K. E-mail: caroline@footclinic.demon.co.uk.

Received for publication 17 December 1997 and accepted in revised form 7 April 1998.

Abbreviations: AGE, age at study entry; DPN, diabetic polyneuropathy; DPNBL, sum of muscle strength and reflex component of Michigan DPN scores at baseline; r_j, rate of first foot ulcer during interval; VPT, vibration perception threshold; VPTBL, sum of the VPT scores at baseline.

general practitioner or chiropodist, excluding minor abrasions or blisters; 2) lower limb amputation; 3) presence of any other cause of diffuse peripheral neuropathy (malignancy, alcohol abuse, drug abuse, peripheral ischemia, anemia, known vitamin B_{12} deficiency, or untreated hypothyroidism); 4) significant neurological disorder other than diabetic polyneuropathy (DPN) (e.g., stroke with significant neurological deficit, transient ischemic attacks, multiple sclerosis, epilepsy, and dementia); 5) alcohol abuse or other drug dependence; 6) previous or present treatment with cytotoxic drugs and/or radiotherapy; 7) uncontrolled hypertension (systolic blood pressure ≥175 mmHg or diastolic blood pressure ≥105 mmHg); 8) renal disease with serum creatinine >160 μmol/l.

This study was approved by the Manchester Health Commission Ethical Committee and ethical committees for all other participating centers, and informed consent was obtained from each of the subjects studied.

Clinical measurements

Time to onset of the first foot ulcer was defined as the number of days between starting the study and a patient's first foot ulcer being found. At baseline and at every subsequent visit (weeks 13, 26, 39, and 52), a thorough foot examination was performed to determine presence of a first or new ulcer. If the patients suspected that they had an ulcer between scheduled visits, they were instructed to contact their investigator and make an unscheduled visit to confirm the ulcer. Routine medical/surgical treatment for the ulcer was then subsequently performed, and the patient made as many visits as required for treatment. In addition, the total number of foot ulcers developing in each patient was determined, following foot examinations every 13 weeks.

To ensure that all patients had the same minimum level of understanding of foot care, each patient was provided with a standardized foot care education leaflet at baseline, and the details in it were discussed. At every subsequent visit, the subject of foot care was raised, and patients were reminded of its importance.

VPT was assessed at the great toe of both feet in triplicate using a neurothesiometer (Biomedical, Newbury, OH) at baseline and after 52 weeks. The severity of DPN was determined at baseline and after 52 weeks using the clinical part of the Michigan DPN score (11). This score has three components: sensory impairment (assessed by vibration perception at the great toe using a tuning fork, 10-g Semmes-Weinstein monofilament at the great toe, and a pinprick on the dorsum of the great toe); muscle strength testing (assessing finger spread, great toe extension, and ankle dorsiflexion); and reflexes (assessing biceps brachii, triceps brachii, quadriceps femoris, and Achilles tendon).

Statistical analysis

The annual incidence rate of first foot ulcers in the total population was determined by Life Table Analysis (12), which makes use of information from discontinued patients (i.e., patients withdrawn from the study because of adverse events, intercurrent illness, or lack of compliance) for the time during the study when they were at risk and under observation. The method assumes that discontinued patients would have had a first foot ulcer occurrence at the same rate as patients remaining on the trial.

First foot ulcer occurrence rates, which do not include recurrences of the same foot ulcer, were calculated at 13, 26, 39, and 52 weeks as follows:

$$r_j = \frac{\text{Number of patients with first foot ulcer between } j-1 \text{ and } j}{\text{Number of patients who neither had first foot ulcer nor withdrew from the study by the end of the period corresponding to } j-1}$$

where r_j is the rate of first ulcer occurrence during the interval between scheduled visits $j-1$ and j. Patients withdrawn from the study between the scheduled visits are considered to be at risk for the entire period between scheduled visits $j-1$ and j, yet are excluded from the determination of rate of first foot ulcer occurrence for subsequent visits.

Cumulative first foot ulcer occurrence rates were then calculated at 13, 26, 39, and 52 weeks as follows (12):

$$R_k = 1 - (1 - r_1)(1 - r_2)\ldots(1 - r_k)$$

where R_k is the cumulative recurrence rate for first foot ulcer rate by end of visit k. The Wald χ^2 statistic (13) was used to test the null hypothesis of no association between treatment and incidence of first foot ulcer.

The estimated incidence density of foot ulceration was calculated as the ratio of the number of new foot ulcers to the total time at risk for each patient. This analysis takes into account the recurrence of the same foot ulcer and is epidemiologically relevant for estimating the incidence of total number of foot ulcers in the diabetic population (14). The total number of new foot ulcers was obtained by summing the number of new foot ulcers for each patient documented at each visit. The total time at risk was obtained by summing the time elapsed between the various visits for each patient.

To identify prognostic factors for foot ulcer occurrence, multiple regression models were fit to the data for all patients in the intent-to-treat group. Time to first foot ulcer was analyzed using Cox proportional hazards model, and the number of new foot ulcers was modeled using log-linear Poisson regression. For both models of time to first foot ulcer and incidence of all foot ulcers, the following were considered potential explanatory variables: age at study entry, sum of muscle strength and reflex component of Michigan DPN scores at baseline, sum of the 10-g monofilament scores from the sensory component of the Michigan DPN scores at baseline, sum of the VPT scores at baseline, diabetes status, race, economic status (classified from the occupation of the main wage earner of the household), and duration of diabetes at study entry.

RESULTS — A total of 1,035 patients were recruited into the study from 44 centers (29 from U.K., 9 from U.S., 6 from Canada). The withdrawal rate was 20% (n = 206) for all patients over the 1-year study. The majority of patients discontinued following occurrence of adverse events or intercurrent illnesses during the clinical trial. Other causes were non-cooperation, failure to return to follow-up visit, and other nonsafety events.

After 1 year, the efficacy of Ro44-7190 for preventing foot ulceration was demonstrated to be negative (15). In addition, all neuropathy parameters were the same between treatment and placebo groups at baseline and were unchanged at 1 year; therefore, baseline data for all 1,035 patients were combined to investigate incidence of and predictive factors for first foot ulceration in a longitudinal analysis. The baseline demographic characteristics of the total diabetic population are given in Table 1. Although type 1 diabetic patients were overrepresented in this population, the distributions of age and diabetes duration for all patients stratified by diabetes type showed no evidence of bimodality.

Table 1—*Demographic characteristics at baseline*

n	1,035
Female	25.4%
Type 1	24.6%
Race	
Caucasian	94.8%
Black	2.0%
Oriental	3.9%
Other	2.8%
Age (years)	60 (23–70)
BMI (kg/m^2)	28.4 (16.9–84.7)

Data are *n*, %, or median (interquartile range).

Table 2—*First foot ulcer occurrence rates for overall treatment*

Interval (weeks)	Patients at risk for interval	First foot ulcers in interval	r_j	R_j
0–13	1,022	14	0.014	0.014
13–26	966	32	0.033	0.047
26–39	912	14	0.015	0.061
39–52	888	11	0.012	0.072

Total intent-to-treat patients is 1,035. r_j is calculated as the ratio of the number of patients who had a first foot ulcer to the number of patients at risk during the interval. R_j, cumulative rate of first foot ulcer by end of interval.

Incidence of foot ulcers

Overall cumulative first foot ulcer occurrence rates for each 13-week interval are shown in Table 2. The overall first foot ulcer occurrence rate for the total population after 1 year was 7.2%, and the greatest increase in first foot ulcer rates was seen between 13 and 26 weeks. The estimated incidence density of new foot ulcers (which includes recurrence of the same ulcer) in the total population was 11.9% (Table 3).

Regression analyses

The time to first foot ulcer was modeled using the Cox proportional hazards model, using all variables described in methods. Forward and backward proportional hazards regression was performed to determine a subset of variables with the most explanatory power. The final model for time to first ulcer consisted of the following form:

hazard of foot ulcer for patient *i*
= baseline hazard × exp(0.0547 × VPTBL)
+ (0.0490 × DPNBL) − (0.0442 × AGE)

where VPTBL is the sum of the VPT scores at baseline, DPNBL is the sum of the Michigan DPN scores for muscle strength and reflex at baseline, and AGE is age at study entry. All variables in the model were statistically significant ($P = 0.01$). The hazard of foot ulcer was found to increase with increasing VPT scores at baseline and increasing the Michigan DPN scores at baseline. For each 1-unit increase in VPT values at baseline, the hazard of first foot ulceration was found to increase by 5.6%. Similarly, for each 1-unit increase in the muscle strength and reflex components of the Michigan DPN scores at baseline, the hazard of foot ulcer was found to increase by 5.0%. In addition, age was found to have a negative relationship with time to first foot ulcer (i.e., with increasing age, the hazard of foot ulcer was found to decrease).

The number of new foot ulcers was modeled using Poisson regression, using all variables previously described. Variables were removed from the model if the *P* value from the Wald χ^2 test was >0.05. The final model for the incidence density of foot ulceration consisted of the sum of the VPT scores at baseline, the sum of the Michigan DPN scores for muscle strength and reflex at baseline, and age at study entry, with the following form:

log (number of first foot ulcers for patient *i*)
= log (total time at risk for patient *i*)
+ (0.0588 × VPTBL) + (0.0467
× DPNBL) − (0.0501 × AGE)

All variables in this model were statistically significant ($P = 0.001$). The log incidence density was found to increase with increasing baseline values for VPT and Michigan DPN scores. For each 1-unit increase in VPT values at baseline, the risk of foot ulcer was found to increase by 6.1%. Similarly, with each 1-unit increase in the muscle strength and reflex components of the Michigan DPN scores, the risk of foot ulcer was found to increase by 4.8%.

Mean ± SD values for the baseline VPT and DPN, plus correlations of the ranks of these neuropathy variables (Spearman's correlations) for time to first foot ulcer and total number of new foot ulcers, are given in Table 4.

CONCLUSIONS — We have presented a natural history study of foot ulceration in a large population of high-risk diabetic patients with significant peripheral neuropathy but without peripheral vascular disease or previous foot ulcers. There are only a limited number of reports, to date, of the incidence of foot ulceration in diabetic populations (1). However, we have demonstrated that the annual incidence of first foot ulceration for the population here is very high (7.2%), highlighting the enormous potential for foot problems in diabetic patients with neuropathy. Furthermore, we have also estimated a 12% incidence for all new foot ulcers in this population, using sample survey methodology (14). This high level of foot ulceration may be inevitable since peripheral neuropathy has been demonstrated as a strong risk factor for foot ulceration in many previous cross-sectional and longitudinal studies, with neuropathy present in >80% of diabetic foot ulcer patients (5–7). Nevertheless, the annual incidence of first foot ulcers shown here is substantially higher than the 4.9% demonstrated for a comparable population (*n* = 202) in a single-center study with similar age, duration of diabetes, and neurological status (VPT >25 V) (10). To our knowledge, this is the first report of a longitudinal, large multicenter study of the incidence of and predictors for foot ulcers in diabetic patients with neuropathy. The advantage of this multinational, multicenter study design is that it provides a generalized population

Table 3—*Incidence of new foot ulcers for overall treatment*

Person-years at risk	Number of new foot ulcers	Estimated incidence density	Estimated SE of incidence density	95% CI
916.57	109	11.89	1.66	8.32–14.81

Total intent-to-treat patients is 1,022. The estimated incidence density is calculated as the total number of new foot ulcers divided by the total person-years at risk × 100 and describes the annual incidence of foot ulcer among 100 patients.

Table 4—*Baseline values and simple correlation analyses of the ranks of the predictive neuropathy variables*

Baseline variable	Mean ± SD	Total number of new foot ulcers	*P* value	Time to first foot ulcer	*P* value
VPT (V)	30.7 ± 7.2	0.1128	0.0003	−0.0348	0.266
DPNBL (score)	25.7 ± 5.0	0.1074	0.0006	−0.0589	0.06

Total number of new foot ulcers and time to first foot ulcer determined by Spearman's correlation coefficient. n = 1,022.

of diabetic patients. In addition, our assessment of the risk for foot ulceration in diabetic neuropathic patients may be more accurate than the previous research conducted mostly at single centers since, for example, the effect of specialized health care provision on foot outcomes at any one site will be diluted (10,11). Quality control of patient care/education in a multicenter study of this nature, however, is essential and is provided here by the standardized diabetes foot care education received by all patients in all centers plus regular follow-up visits. The reasons for the higher incidence of foot problems here are unclear, especially as all patients received the standardized foot care education to minimize the incidence of foot ulcers, since targeted education may be a key to reducing the incidence of foot ulceration and amputation (16,17). Evidence of a reduced incidence of lower limb amputation, following a 1-h education session for "high-risk" patients, plus a significantly lower incidence of new foot problems for type 2 patients as a result of an intensive education program (18,19), supports this theory. In the present study, the level of patient knowledge and compliance was not assessed. However, it must be remembered that even knowledgeable patients will develop ulcers if their behavior is not altered (20). It is important to stress that other important risk factors for foot ulceration were not documented in this study, such as foot deformities, calluses, or neuroarthropathy, or the number of patients who were referred for chiropody or orthotic services if required; all of which would have significant impact on the ulceration rate.

Multiple regression analyses successfully demonstrated that VPT at the hallux, plus the muscle strength and reflex components of the Michigan DPN scores, were positively correlated with time to first foot ulcer and incidence density of ulceration. These clinical parameters are independent predictors for foot ulceration in these diabetic patients with established peripheral neuropathy and no previous foot ulceration. These results confirm and extend the findings of previous studies. It was demonstrated, prospectively, that VPT can predict those diabetic patients at increased risk of foot ulceration and that a VPT >25 V carries a sevenfold risk of foot ulceration compared with a VPT <15 V during a 4-year follow-up period (10). In the present study, we have shown that for patients with significant neuropathy (i.e., VPT >25 V), a further 5-V deterioration in VPT is associated with a 28% increased hazard of first foot ulceration. This has great clinical significance as the risk of foot ulceration may now be predicted in patients who have not previously ulcerated. An absent Achilles tendon reflex has also been demonstrated as an independent predictor for foot ulceration in a case-control study (9), which further supports the results of this study. The advantage of the present study over case-control design is that we can establish with certainty that these neurological risk factors identified for foot ulceration actually precede the foot ulcer event.

In the present study, we have now identified abnormal muscle strength, in addition to abnormal reflexes, as a predictive factor for ulceration, which, to date, has not been described elsewhere. This finding further clarifies the clinical significance of motor abnormalities attributable to symmetrical distal polyneuropathy in the etiology of foot ulceration. In addition, we have demonstrated that use of the simple, clinical tests of reflexes and muscle strength described in the Michigan DPN score (11) provides an alternative, convenient method for identifying the patient who is at risk for subsequent foot ulceration. Although clinical tests of muscle strength are subjective and may significantly underestimate the severity of muscle weakness in the lower limb compared with more objective measurements (21), the results here indicate that muscle strength testing is a sufficiently robust clinical tool. The mechanism for this new finding may only be speculated. Reduced muscle strength, as determined by foot, knee, and wrist movements, is related to presence of neuropathy in long-term IDDM patients (22). Indeed, subclinical damage to muscular innervation is common in DPN, with weakness and wasting developing in more advanced cases. Propioceptive loss and progressive motor weakness may eventually lead to gait abnormalities (23), which are major contributory factors to increasing pressures and loads on potential plantar ulceration sites.

Age was found to have a negative relationship with time to first foot ulcer and incidence density of foot ulceration (i.e., with increasing age, the hazard of foot ulcer was found to decrease). A possible cause of this unusual observation may be a selection bias, which selected out older patients who were at greater risk for developing foot ulcers. Indeed, the population has a large percentage of older patients (83% >50 years of age at baseline), yet 95% of these patients did not develop foot ulcers, compared with only 87% of patients <50 years of age who did not develop foot ulcers. Thus, a lesser number of patients in the study are <50 years of age but a greater percentage of these patients have at least one foot ulcer. It appears that the older patients who were randomized into the study are those who were healthier and had some protective mechanism against foot ulcer occurrence.

The sum of the 10-g monofilament scores measured in the right and left great toe from the sensory component of the Michigan DPN scores failed to predict foot ulceration in the present study. Initially, this was surprising since previous work has demonstrated that patients who cannot feel a monofilament of this force applied against the plantar surface of the foot (avoiding areas of callus) have a substantially higher risk of developing ulceration of the foot (24–26). Furthermore, McNeely et al. (9) have demonstrated that the 10-g monofilament is a significant independent predictor for foot ulceration. In the latter study, cutaneous pressure perception was measured at eight standardized plantar sites, and the inability to perceive pressure at any one of these sites was classified as insensate. Neuropathic ulceration occurs more frequently on plantar surfaces of the foot, on the metatarsal heads, and on the heel, compared to the pulp of the toe (1), thus cutaneous pressure perception determined at plantar sites may be a more sensitive method of determining foot ulceration risk than the measurements made at the great toe in the present study.

This may explain the lack of a positive relationship between monofilament scores and time to onset of foot ulcer.

In conclusion, this multicenter study has demonstrated that there is a high incidence of foot ulceration in a population of diabetic patients with established peripheral neuropathy, despite the patients receiving a high level of education. In addition, we have identified a number of strong, independent neurological risk factors for the development of foot ulcers in these patients, which supports results of other smaller, single-center studies (6,9,10). We can confirm that VPT and reflex are important prognostic tests in the clinical setting for identifying patients at risk for foot ulceration. In addition, muscle strength testing has been demonstrated as a further simple clinical tool. Thus, the finding of any of the following abnormalities will lead to patients being identified to be at risk for neuropathic foot ulceration: VPT >25 V, absent ankle reflexes, and significant muscle weakness by clinical examination. Although this may result in some patients being falsely classified as being at risk for foot ulceration, this overcaution is not harmful. These data also highlight the fact that there is an urgent requirement for further research into how to lower the very high incidence of foot problems in diabetic patients with neuropathy, since the conventional intervention of standardized education and regular patient follow-up visits, which was employed in this multicenter study, has failed to prevent foot ulceration.

Acknowledgments— Principal investigators of the research sites involved in this multicenter study are cited as follows: U.S.: Dr. S. Dippe, Scottsdale; Dr. L. Olansky, Oklahoma; Dr. R. Bernstein, Greenbrae; Dr. R.B. Goldberg, Miami; Dr. J. Rosenstock, Dallas; Dr. S. Decherney, Delaware, Newark; Dr. W. Carter, Little Rock; Dr. D. Clarke, Salt Lake City; Dr. R. Freeman, Boston. Canada: Dr. A.P. Belanger, Montreal; Dr. V. Bril, Toronto; Dr. D. Brunet, Quebec; Dr. D. Lau, Ottawa; Dr. V. Cwik, Edmonton; Dr. C. Godin, Quebec. U.K.: Prof. A.J.M. Boulton, Manchester; Dr. A. MacCuish, Glasgow; Dr. J.H.B. Scarpello, Stoke; Dr. J.K. Wales, Leeds; Dr. G. Rayman, Ipswich; Dr. P. Jennings, York; Prof. P.B. Tattersall, Nottingham; Dr. R.J. Guy, Basingstoke; Dr. G.R. Jones, Blackburn; Dr. E.A. Masson, Hull; Dr. A.H. Barnett, Birmingham; Dr. P. O'Hare, Bath; Dr. A. C. Burden, Leicester; Dr. E.A. Hardisty, Sheffield; Dr. A.F. MacLeod, Shrewsbury; Dr. C.J. Burns-Cox, Bristol; Prof. J.D. Ward, Sheffield; Dr. W.J Jeffcoate, Nottingham; Dr. C. Fox, Northampton; Prof. J.E. Tooke, Exeter; Dr. J. Vora, Liverpool; Dr. P.G. Wiles, North Manchester; Prof. P.H. Sonksen, London; Dr. I.A. MacFarlane, Walton; Dr. C. Johnstone, Hemel Hempstead; Dr. I. Borthwick, Stevenage; Dr. S. Hyer, Carshalton; Dr. M.J. Sampson, Norwich; Dr. P.H. Winocour, Welwyn Garden City.

References

1. Boulton AJM: Foot problems in patients with diabetes mellitus. In *Textbook of Diabetes*. Vol. 2., Pickup JC, Williams G, Eds. Blackwell Science, Oxford, U.K., 1997, p. 58.1–58.20
2. Macleod A, Williams DRR, Sonksen PH, Boulton AJM: Risk factors for foot ulcers in hospital clinic attenders (Abstract). *Diabetologia* 34:A39, 1991
3. Most RS, Sinnock P: The epidemiology of lower extremity amputations in diabetic individuals. *Diabetes Care* 6:87–91, 1983
4. Ebskov B, Josephsen P: Incidence of reamputation and death after gangrene of the lower extremity. *Prosthet Orthotics Int* 4:77–80, 1980
5. Caputo GM, Cavanagh PR, Ulbrecht JS, Gibbons GW, Karchmer AW: Assessment and management of foot disease in patients with diabetes. *N Engl J Med* 331:854–860, 1994
6. Pecoraro PE, Reiber GE, Burgess EM: Pathways to diabetic limb amputation: basis for prevention. *Diabetes Care* 13:513–521, 1990
7. Boulton AJM: Peripheral neuropathy and the diabetic foot. *Foot* 2:67–72, 1992
8. Krentz AJ, Acheson P, Basu A, Kilvert A, Wright AD, Nattrass M: Morbidity and mortality associated with diabetic foot disease: a 12-month prospective survey of hospital admissions in a single U.K. centre. *Foot* 7:144–147, 1997
9. McNeely MJ, Boyko EJ, Ahroni JH, Stensel VL, Reiber GE, Smith DG, Pecoraro RE: The independent contributions of diabetic neuropathy and vasculopathy in foot ulceration: how great are the risks? *Diabetes Care* 18:216–219, 1995
10. Young MJ, Veves A, Breddy JL, Boulton AJM: The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds: a prospective study. *Diabetes Care* 17:557–560, 1994
11. Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA: A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. *Diabetes Care* 17:1281–1289, 1994
12. Elashoff JD, Koch GG: Statistical methods in trials of anti-ulcer drugs. In *Ulcer Disease Investigation and Basis for Therapy*. Swabb EA, Szabo S, Eds. New York, Marcel Dekker, 1991, p. 375–406
13. Kleinbaum DG, Kupper LL, Morgenstern H: *Epidemiologic Research: Principles and Quantitative Methods*. Belmont, CA, Lifetime Learning Publications, 1983
14. Lavange LM, Keyes LL, Koch GG, Margolis PA: Application of sample survey methods for modelling ratios to incidence densities. *Stats Med* 13:343–355, 1994
15. Abbott CA, Vileikyte L, Williamson S, Carrington AL, Boulton AJM, the ALCAR Foot Ulcer Study Group: Effect of treatment with acetyl-L-carnitine on diabetic foot ulceration in patients with peripheral neuropathy: a 1 year prospective multi-centre study (Abstract). *J Periph Nerv Syst* 2:254, 1997
16. Boulton AJM: Why bother educating the multi-disciplinary team and the patient: the example of prevention of lower extremity amputation in diabetes. In *New Trends in Patient Education*. Assal J-P, Golay A, Visser AP, Eds. New York, Elsevier, 1995, p. 183–188
17. Bild DE, Selby JV, Sinnock P, Browner WS, Braveman P, Showstack JA: Lower-extremity amputation in people with diabetes: epidemiology and prevention. *Diabetes Care* 12:24–31, 1989
18. Malone JM, Snyder M, Anderson G, Bernhard VM, Hollway GA, Bunt TJ: Prevention of amputation by diabetic education. *Am J Surg* 158:520–524, 1989
19. Barth R, Campbell LV, Allen S, Jupp JJ, Chisholm DJ: Intensive education improves knowledge, compliance and foot problems in type 2 diabetes. *Diabet Med* 8:111–117, 1990
20. Vileikyte L, Shaw JE, Kincey J, Carrington AL, Abbott CA, Boulton AJM: A prospective study of neuropathic and psychological factors in foot ulceration (Abstract). *Diabetologia* 39 (Suppl. 1):A3, 1996
21. Anderson H, Jakobsen J: A comparative study of isokinetic dynamometry and manual muscle testing of ankle dorsal and plantar flexors and knee extensors and flexors. *Eur Neurol* 37:239–242, 1997
22. Anderson H, Poulson PL, Mogensen CE, Jakobsen J: Isokinetic muscle strength in long-term IDDM patients in relation to diabetic complications. *Diabetes* 45: 440–445, 1996
23. Watkins PJ, Edmonds ME: Clinical features of diabetic neuropathy. In *Textbook of Diabetes*. Vol. 2. Pickup JC, Williams G, Eds. Oxford, U.K., Blackwell Science, 1997, p. 50.1–50.20
24. Sosenko JM, Kato M, Sato R, Bild DE: Comparison of quantitative sensory-threshold measures for their association with foot ulceration in diabetic patients. *Diabetes Care* 13:1057–1061, 1990
25. Kumar S, Fernando DJS, Veves A, Knowles EA, Young MJ, Boulton AJM: Semmes-Weinstein monofilaments: a simple, effective and inexpensive screening device for identifying diabetic patients at risk of foot ulceration. *Diabet Res Clin Pract* 13:63–68, 1991
26. Litzelman DK, Marriott DJ, Vinicor F: Independent physiological predictors of foot lesions in patients with NIDDM. *Diabetes Care* 20:1273–1278, 1997