

Can Motor Nerve Conduction Velocity Predict Foot Problems in Diabetic Subjects Over a 6-Year Outcome Period?

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OBJECTIVE — This study examined motor nerve conduction velocity (MNCV) and other peripheral nerve and vascular tests as predictors for foot ulceration, amputation, and mortality in diabetes over a 6-year follow-up period.

RESEARCH DESIGN AND METHODS — We recruited 169 diabetic subjects (without significant peripheral vascular disease with an ankle brachial pressure index [ABPI] ≥ 0.75) for the study and separated them into groups (to ensure diversity of nerve function). The control group consisted of 22 nondiabetic people. At baseline, all subjects underwent assessment of MNCV; vibration, pressure, and temperature perception thresholds; peripheral vascular function; and other diabetes assessments.

RESULTS — Over the 6-year outcome period, 37.3% of the diabetic subjects developed at least one new ulcer, 11.2% had a lower-limb amputation (LLA) (minor or major), and 18.3% died. Using multivariate Cox's regression analysis (RR [95% CI] and removing previous ulcers as a confounding variable, MNCV was found to be the best predictor of new ulceration (0.90 [0.84–0.96], $P = 0.001$) and the best predictors of amputation were pressure perception threshold (PPT) (5.18 [1.96–13.68], $P = 0.001$) and medial arterial calcification (2.88 [1.13–7.35], $P = 0.027$). Creatinine (1.01 [1.00–1.01], $P < 0.001$), MNCV (0.84 [0.73–0.97], $P = 0.016$), and skin oxygen levels (14.32 [3.04–67.52], $P = 0.001$) were the best predictors of mortality.

CONCLUSIONS — This study shows that MNCV, which is often assessed in clinical trials of neuropathy, can predict foot ulceration and death in diabetes. In addition, tests of PPT and medial arterial calcification can be used in the clinic to predict LLA in diabetic subjects.

Diabetes Care 25:2010–2015, 2002

Foot problems are an excessive burden for people with diabetes. Biochemical, physiological and sociological factors contribute to their development. Such factors include peripheral neuropathy (PN) (1–5), peripheral vascular disease (PVD) (6–8), trauma, infection, and poor wound healing (9,10). PN affects sensory, motor, and autonomic

sections of the peripheral nervous system and can be assessed in a variety of ways (1,5,11,12). Vibration perception threshold (VPT), pressure perception threshold (PPT), temperature perception threshold (TPT), autonomic neuropathy, muscle strength, reflexes, and neuropathy disability score all predict foot ulceration to some degree (1–5,7,13). In addition, low-

er-limb amputation (LLA) can be predicted by VPT, PPT, and reflexes (6,8). However, the involvement of motor nerve conduction velocity (MNCV) in the development of foot problems in diabetic subjects has not been examined in a long-term study. This is surprising because many clinical trials have employed MNCV as the primary neurological assessment regarding the efficacy of pharmacological interventions for diabetic PN (14).

Both the micro- and macrovascular systems can be affected by PVD in diabetes, and transcutaneous partial pressure of oxygen ($TcpO_2$) can predict diabetic foot ulceration (7). $TcpO_2$, ankle brachial pressure index (ABPI), diminished lower-limb pulses, and medial arterial calcification are also independent risk factors for LLA (6,8). In addition, contralateral amputation in unilateral lower-limb diabetic amputees is associated primarily with measures of PVD ($TcpO_2$ and ABPI) (15).

Therefore, the aim of this study was to examine the contributions of various peripheral nerve tests (including MNCV), vascular tests, and other general assessments to the development of foot ulceration, LLA, and mortality within a 6-year outcome period in diabetic subjects without significant PVD.

RESEARCH DESIGN AND METHODS

Consecutive subjects attending routine clinics (J.E.S., L.V., and A.J.M.B.) at the Manchester Diabetes Center, who agreed to participate, were recruited for the study in 1994 and 1995 and assigned to the following groups at baseline to ensure a wide range of the degree of neuropathy (stratified sample):

- C = Control nondiabetic subjects (staff, relatives, and friends, $n = 22$)
- D = Diabetic subjects without neuropathy ($n = 51$)
- DN = Diabetic subjects with neuropathy ($n = 67$)
- DU = Diabetic subjects with a history of foot ulcers ($n = 34$)

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Received for publication 2 April 2002 and accepted in revised form 8 July 2002.

Abbreviations: ABPI, ankle brachial pressure index; CV, coefficient of variation; LLA, lower-limb amputation; MNCV, motor nerve conduction velocity; PN, peripheral neuropathy; PPT, pressure perception threshold; PVD, peripheral vascular disease; $TcpO_2$, transcutaneous partial pressure of oxygen; $TcpCO_2$, transcutaneous partial pressure of carbon dioxide; TPT, temperature perception threshold; VPT, vibration perception threshold.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

- DCh = Diabetic subjects with Charcot neuroarthropathy ($n = 17$)

For the purposes of categorization into the above groups at baseline, neuropathy was defined arbitrarily as follows: MNCV ≤ 40 m/s or two of three: VPT > 20 V, PPT > 1 g, and TPT $> 2^\circ\text{C}$ (corresponding to the normal limits in our laboratory).

Subjects were excluded from the study if their age was < 20 or > 75 years, if they had intermittent claudication, if their ABPI was < 0.75 , if they had an active foot ulcer or an amputation of any part of the lower limb, or if they had any major disability due to other disorders (e.g., stroke, severe arthritis, or mental health problems). This study was carried out in accordance with the Declaration of Helsinki (1964, revised 1996) of the World Medical Association and was approved by the Manchester Research Ethics Committee. The subjects gave informed consent, and the following general assessments were carried out at baseline: age, sex, and ethnicity; height, weight, and BMI; diabetes type, duration, and treatment; HbA_{1c} and serum creatinine (blood glucose was measured for nondiabetic control subjects only); history of hypertension and history of central or peripheral vascular events (e.g., myocardial infarction, angina, angioplasty, bypass grafting, cerebrovascular accident); and history of foot ulceration.

The following neurological and vascular tests were carried out on the dominant limb at a skin temperature $\geq 30^\circ\text{C}$, measured with a Mikron Thermometer (Model M806-OC; Wyckoff, NJ) and maintained using a controllable heating pad within a leg trough.

Peripheral neurological assessment

Autonomic neuropathy was assessed using the Oxford Medilog 2000 system, (Oxford, U.K.) by the examination of heart rate ratio during 1 min of deep breathing. The patient was asked to take six deep breaths (5 s inspiration and 5 s expiration), and the maximum and minimum RR interval for each breath cycle was determined from the electrocardiogram (measured as beats per minute). The final value was the mean of the ratios between the maximum and minimum rates for each cycle (E:I ratio).

Cutaneous PPT was determined using Semmes Weinstein monofilaments (Gillis

W. Long Hansens' Disease Center, Carville, LA) at one mid-dorsal and three plantar sites (first metatarsal head and fifth metatarsal head and heel) on the foot (16). The dorsal site was scored separately from the plantar sites. If the patient felt the 1-g filament at the dorsal site or all three sites on the plantar surface, a score of 4 was given for each surface of the foot. If the patient could not feel the 1-g filament at any site, the 10-g filament was used, and if it was felt at all sites a score of 5 was given for that surface of the foot. If the 10-g filament was not felt at any site, the 75-g filament was used, and if it was felt at all sites a score of 6 was given. If it was not felt at any site, a score of 7 was given. The filaments were tested three times at each site. Values were categorized as normal (≤ 10 g [scored 4 or 5]) or abnormal (> 10 g [scored 6 or 7]).

VPT was measured using the Neurothesiometer (Horwell; Scientific Laboratory Supplies, Nottingham, U.K.) at the hallux (0–47 V, if vibration could not be perceived at any level, a value of 48 V was assigned). The mean of three assessments was used to give the VPT (16).

Common peroneal MNCV was measured using the MS92a electromyogram machine (Medelec, Surrey, U.K.). Action potentials were recorded using surface electrodes placed at the Extensor Digitorum Brevis muscle, and the common peroneal nerve was stimulated (300 V intensity, 0.1 ms duration) to obtain a supramaximal stimulus. Stimulation was carried out at the head of the fibula and midway between the malleoli on the anterior surface of the limb. Skin temperature was recorded, length of nerve was measured, and proximal and distal latencies were recorded for the determination of MNCV (m/s) (16).

TPT was determined using a forced choice procedure with the Thermo-aesthesiometer (model AZVU; Medical Instruments Department, VU Hospital, Amsterdam, The Netherlands) at the foot dorsum (16).

Peripheral vascular assessment

ABPI was determined using a Doppler ultrasound machine and a portable sphygmomanometer (Sonicaid; Accoson, Oxford, U.K.) by assessing systolic dorsalis pedis pressure and dividing it by systolic brachial pressure (16). ABPI values were subclassified as normal or "calcified" (if dorsalis pedis pressure was > 280

mmHg or ABPI was > 1.5). Those subjects with values < 0.75 were excluded.

TcpO₂ and transcutaneous partial pressure of carbon dioxide (TcpCO₂) were measured at the foot dorsum using a TcpO₂ and TcpCO₂ monitoring system (Radiometer, Sussex, U.K.). The electrode combines a heating element, two temperature sensors, a Clark-type oxygen electrode, and a Severinghaus-type carbon dioxide electrode in a single unit. Before each measurement, the system was calibrated. After calibration, the electrode was fixed at the skin surface, and generated heat was transferred to the skin surface to heat the skin to 43°C . This produced a local vasodilation to increase the permeability of the skin to oxygen and carbon dioxide, rendering a measurement at the skin surface possible. When the oxygen values had stabilized (20 min) the values were recorded at 1-min intervals for a period of 5 min and the mean value taken as the partial pressure (16).

Outcome analysis

For the diabetic subjects, outcomes until 12 December 2000 were assessed by contacting the patient directly at yearly intervals and by examining the Manchester Diabetes Center patient notes and patient database. New foot ulceration was defined as a full thickness break in the skin, and events within the outcome period were defined as either a single ulcer per patient or as recurrent ulceration. The time between baseline assessments to the first ulcer only was recorded. LLA was defined as minor (below ankle joint) or major (above and including joint), and the time from baseline assessments to the amputation was recorded. If a minor amputation was followed by a major amputation of the same limb, only the major amputation was used for analysis. Mortality was noted, and time between baseline assessments and death was recorded.

Statistical analysis

To assess the relationship between the baseline variables and incidence of ulceration (one per subject), amputation (one per subject), or mortality, Cox's proportional hazards regression analysis was carried out and the RR (determined from the hazard ratio) and 95% CIs were estimated. Data were log transformed where appropriate. Univariate analysis provided the information to describe all significant predictors.

Table 1—General information of study subjects at baseline and 6 year outcomes

	C (n = 22)	D (n = 51)	DN (n = 67)	DU (n = 34)	DCh (n = 17)
M/F (n)	15/7	26/25	50/17	23/11	11/6
Age (years)	50 (46–60)	53 (47–60)	58 (48–62)	55 (49–59)	54 (48–62)
Type 1/type 2 diabetes (n)	NA	25/26	34/33	15/19	9/8
Duration (years)	NA	18 (7–25)	18 (10–29)	19 (12–26)	20 (16–31)
Treatment = Diet/OHG/Insulin (n)	NA	6/13/32	4/21/42	0/13/21	0/4/13
BMI (kg/m ²)	26.5 (23.7–29.6)	26.0 (23.3–28.7)	26.9 (24.9–29.9)	28.5 (26.0–32.0)	29.8 (27.0–31.8)
HbA _{1c} (%)	5.2 (4.9–5.7)	8.3 (6.7–9.2)	9.4 (8.1–10.4)	9.4 (8.2–10.3)	10.0 (9.3–10.4)
Serum creatinine (μmol/l)	100 (99–113)	101 (88–112)	109 (101–132)	115 (96–148)	121 (99–178)
History of hypertension [n (%)]	5 (22.7%)	13 (25.4%)	33 (49.3%)	13 (38.2%)	4 (23.5%)
History of vascular event [n (%)]	3 (13.6%)	14 (27.5%)	13 (19.4%)	8 (23.5%)	3 (17.6%)
New ulcers within 6 years (% and n for SU, RU)	NA	15.7 (5, 3)	28.3 (12, 7)	70.6 (10, 14)	70.6 (6, 6)
Amputation within 6 years (% and n for MI, MA)	NA	3.9 (2, 0)	9.0 (1, 5)	26.5 (4, 5)	11.8 (1, 1)
Mortality within 6 years (% and n)	NA	7.8 (4)	16.4 (11)	35.3 (12)	23.5 (4)

Data are median (interquartile range) unless otherwise stated. SU, single ulcer; RU, recurrent ulceration; MI, minor amputation; MA, major amputation.

Multivariate forward and backward stepwise regression methods were then used in order to identify the best subset of independent predictors (SPSS, Version 10). Previous ulceration was removed from the multivariate analysis as it is an important predictor of all outcomes (confirming previous published findings), and we wished to examine which were the best clinical tests for the prediction of foot problems and mortality.

RESULTS

General medical and diabetes information can be seen in Table 1. The absence of diabetes in the control group was confirmed by assessing random blood glucose (5.54 ± 1.00 mmol/l, [mean \pm SD]).

The majority of subjects were of Caucasian origin, but there was one Black and one South Asian subject in group D, one South Asian subject in group DN, and one South Asian and one Chinese subject in group DU. The data for the baseline neurological and vascular assessments can be seen in Table 2. This information is included for descriptive purposes only, as the main aim of this study was to examine the prospective prediction of foot problems and mortality. The groups were included to ensure a wide range of values for all of the baseline neurological variables. In addition, the control group was included to show normal laboratory values for people without diabetes. The outcomes of foot ulceration, amputation, and

mortality from baseline until 12 December 2000 were assessed for the diabetic subjects only (Table 1). The median time to first ulcer/study end was 67.9 months (range 0.6–79.9), for amputation/study end it was 69.7 months (7.3–79.9), and for death/study end it was 69.5 months (0.2–79.9).

Baseline data from the diabetic subjects were pooled, and Cox regression was used to determine the RR (hazard ratio) of foot ulcer development, LLA, and death within 6 years. All baseline variables were assessed, but only significant univariate predictors of foot ulceration ($P < 0.05$; previous ulcer, BMI, HbA_{1c}, autonomic dysfunction, PPT, VPT, MNCV, TPT, and brachial systolic pressure) are shown in

Table 2—Neurological and vascular assessments of study subjects at baseline

	C (n=22)	D (n=51)	DN (n=67)	DU (n=34)	DCh (n=17)
Autonomic E:I	1.20 (1.17–1.30)	1.14 (1.09–1.29)	1.08 (1.04–1.15)	1.04 (1.03–1.09)	1.03 (1.01–1.04)
PPT (foot-dorsum)	4 (4–4)	4 (4–4)	4 (4–4)	4 (4–5)	4 (4–6)
PPT (foot-plantar)	4 (4–4)	4 (4–4)	5 (4–6)	6 (5–6)	6 (6–7)
VPT (hallux) (V)	6 (4–9)	13 (7–15)	25 (17–32)	29 (18–40)	37 (32–48)
MNCV (m/s)	49.2 (46.5–50.8)	43.4 (41.4–45.2)	36.7 (34.1–38.7)	34.6 (30.8–40.2)	31.0 (28.5–32.4)
TPT (°C)	0.5 (0.5–0.5)	0.5 (0.5–0.5)	6.0 (0.5–10)	8.5 (5.5–11.0)	9.5 (7.5–11.0)
DP-pressure (mmHg)	162 (137–170)	151 (130–180)	162 (140–190)	166 (140–194)	158 (121–200)
B-pressure (mmHg)	134 (111–150)	140 (124–150)	150 (132–160)	140 (132–159)	142 (133–153)
ABPI	1.16 (1.07–1.32)	1.15 (1.06–1.23)	1.15 (1.00–1.27)	1.17 (1.03–1.27)	1.12 (0.90–1.34)
Calcification [n (%)]	0 (0)	4 (7.8)	14 (20.9)	8 (23.5)	1/14 (7.1)
TcpO ₂ (mmHg)	57.5 (53.8–63)	51.0 (42.0–56.0)	49.0 (40.5–56.5)	50.0 (41.0–60.0)	52.5 (41.8–60.5)
TcpCO ₂ (mmHg)	32.5 (23.5–39.3)	32.0 (25.0–40.0)	37.0 (29.0–41.0)	35.0 (29.3–42.0)	34.5 (32.3–39.0)

Data are median (interquartile range). DP-pressure, dorsalis pedis systolic blood pressure; B-pressure, brachial systolic blood pressure.

Table 3—Significant predictors of new foot ulceration during the follow-up period (Cox's regression analysis)

Variable	Number of cases (number of ulcers)	Levels of variables	Univariate RR (95% CI)	Univariate P	Multivariate RR (95% CI), P value (no. cases/ulcers)
Previous ulcer	169 (63)	No (n = 120) Yes (n = 49)	1.00 5.81 (3.50–9.66)	<0.001	NA
BMI	169 (63)	—	1.09 (1.04–1.15)	<0.001	—
HbA _{1c}	150 (54)	—	1.23 (1.07–1.40)	0.002	—
Autonomic E:I	116 (43)	—	0.004 (0.00–0.14)	0.003	—
PPT (foot-dorsum)	168 (63)	4,5 (<10 g, n = 148) 6,7 (>10 g, n = 20)	1.00 2.53 (1.37–4.67)	0.003	—
PPT (foot-plantar)	168 (63)	4,5 (<10 g, n = 115) 6,7 (>10 g, n = 53)	1.00 4.12 (2.49–6.84)	<0.001	—
VPT (Hallux)	166 (63)	—	1.05 (1.04–1.07)	<0.001	—
MNCV	130 (39)	—	0.88 (0.83–0.94)	<0.001	0.90 (0.84–0.96) P = 0.001, (128/39)
TPT	167 (63)	—	1.16 (1.08–1.22)	<0.001	—
B-pressure	157 (57)	—	1.01 (1.00–1.03)	0.04	—

Data analyzed as continuous variables except where stated. Significant predictors only shown ($P < 0.05$). B-pressure = brachial systolic blood pressure. Previous ulcer was removed from multivariate analysis as a confounding variable.

Table 3. The significant predictors of amputation (previous ulcer, PPT, VPT, MNCV, TPT, and calcification) are shown in Table 4. Again the significant predictors of mortality (previous ulcer, creatinine, PPT, VPT, MNCV, TPT, calcification, and TcPO₂) are shown in Table 5.

Previous foot ulceration is a strong predictor of new foot problems (1,3,13) and was therefore removed from the multivariate Cox's regression analysis as a confounding variable. MNCV was found to be the best predictor of new ulceration (Table 3), and the best predictors for amputation were PPT and medial arterial calcification (Table 4). Creatinine, MNCV, and skin oxygen levels were the best predictors for mortality (Table 5).

CONCLUSIONS

This study showed that MNCV is an independent predictor for the development of new foot ulcers in people with diabetes. Many clinical studies use MNCV as a “benchmark” for the assessment of distal symmetrical diabetic polyneuropathy (17,18), as it is a very reproducible and objective method of assessment. However, this is the first prospective study to show its usefulness in the prediction of foot ulceration. Other methods used here to measure PN included the assessment of various sensory modalities (PPT, VPT, and TPT). These were all found to predict foot ulceration in univariate analyses but were lost in the multivariate Cox regression. This confirms that these tests for

nerve function assess similar modalities (high interdependency) and therefore are not found to be independent predictors. It is also likely that MNCV was shown to be the best predictor of foot ulceration as it has a much lower coefficient of variation (CV) than the other methods used here (CV %; VPT = 18.3, MNCV = 2.6, TPT = 10.5, ABPI = 4.5, TcPO₂ = 12.4, and TcPCO₂ = 20.2; n = 12).

The independent predictors of LLA were found to be PPT >10 g at the plantar surface of the foot and ankle systolic pressure in the dorsalis pedis artery >280 mmHg or ABPI >1.5 (as an indication of medial arterial calcification). These are both relatively simple tests that can be performed in general practice by any

Table 4—Significant predictors of amputation during the follow-up period (Cox's regression analysis)

Variable	Number of cases (number of amputations)	Levels of variables	Univariate RR (95% CI)	Univariate P	Multivariate RR (95% CI), P (number of cases/ulcers)
Previous ulcer	169 (19)	No (n = 120) Yes (n = 49)	1.00 3.79 (1.52–9.42)	0.004	NA
PPT (foot-dorsum)	168 (19)	4,5 (≤10 g, n = 148) 6,7 (>10 g, n = 20)	1.00 4.06 (1.54–10.69)	0.005	—
PPT (foot-plantar)	168 (19)	4,5 (≤10 g, n = 115) 5,7 (>10 g, n = 53)	1.00 5.34 (2.03–14.05)	<0.001	5.18 (1.96–13.68) P = 0.001, (166/19)
VPT (Hallux)	166 (19)	—	1.05 (1.01–1.08)	0.011	—
MNCV	130 (10)	—	0.86 (0.76–0.97)	0.015	—
TPT	167 (19)	—	1.11 (1.00–1.24)	0.049	—
Calcification	166 (19)	No (n = 139) Yes (n = 27)	1.00 3.37 (1.33–8.57)	0.011	2.88 (1.13–7.35) P = 0.027, (166/19)

Data analyzed as continuous variables except where stated. Significant predictors only shown ($P < 0.05$). Previous ulcer was removed from multivariate analysis as a confounding variable.

Table 5—Significant predictors of death during the follow-up period (Cox's regression analysis)

Variable	Number of cases (number of deaths)	Levels of variables	Univariate RR (95% CI)	Univariate P	Multivariate RR (95% CI) P (number of cases/ ulcers)
Previous ulcer	169 (30)	No (n = 120) Yes (n = 49)	1.00 2.33 (1.14–4.77)	0.021	NA
Creatinine	128 (24)	—	1.003 (1.002–1.005)	<0.001	1.01 (1.00–1.01) P < 0.001, (91/11)
PPT (foot-dorsum)	168 (29)	4,5 (≤10 g, n = 148) 6,7 (>10 g, n = 20)	1.00 3.82 (1.74–8.40)	0.001	
PPT (foot-plantar)	168 (29)	4,5 (≤10 g, n = 115) 6,7 (>10 g, n = 53)	1.00 2.54 (1.23–5.26)	0.012	
VPT (Hallux)	166 (29)	—	1.05 (1.02–1.08)	<0.001	
MNCV	130 (16)	—	0.87 (0.79–0.95)	0.002	0.84 (0.73–0.97) P = 0.016 (91/11)
TPT	167 (29)	—	1.20 (1.09–1.33)	<0.001	
“Calcification”	166 (28)	No (n = 139) Yes (n = 27)	1.00 1.66 (1.24–6.07)	0.013	
TcpO ₂	158 (26)	≥25 mmHg (n = 153) <25 mmHg (n = 5)	1.00 4.89 (1.46–16.36)	0.010	14.32 (3.04–67.52) P = 0.001 (91/11)

Data analyzed as continuous variables except where stated. Significant predictors only shown ($P < 0.05$). Previous ulcer was removed from multivariate analysis as a confounding variable.

healthcare professional. However, care must be taken with the interpretation of the amputation data due to the low number of events ($n = 19$). Numerous studies have shown the importance of the 10-g Semmes Weinstein monofilament (which assesses cutaneous pressure perception) as a predictor for foot ulceration (3,7,13,19) and LLA (6). Our study confirms this latter finding for LLA and adds more evidence to the use of simple monofilament pressure testing in all people with diabetes. In addition, the simple assessment of ankle systolic pressure may identify the diabetic subjects who might be more at risk of having an amputation. With this knowledge, the healthcare professional would be able to tailor intervention strategies (glycemic control, dietary and lifestyle advice, and/or vascular investigation) to individual subjects. Again, it must be noted here that at baseline, subjects with an ABPI <0.75 were excluded. Such subjects will have a relatively severe PVD, as low ABPI values are indicative of peripheral arterial occlusion. However, the measurement of ABPI is complicated by the presence of medial arterial calcification that leads to an apparent increase in ankle systolic pressure and higher ABPI values. Consequently, in the large peripheral arteries, it is likely that arterial occlusion and medial arterial calcification may be occurring at the same time. It is there-

fore important to note increases in ankle systolic pressure as an indicator of potential amputation rather than a confounding factor in the measurement of ABPI.

Finally, serum creatinine, MNCV, and TcpO₂ were found to be independent predictors of death in people with diabetes. The finding with serum creatinine is not new and confirms other studies that have shown the link between serum creatinine, renal disease, and mortality (20). However, the finding in our study that MNCV and TcpO₂ can predict mortality was surprising. It is unlikely that the link is direct. It would be almost impossible to explain how a deficit in function of the common peroneal nerve in the leg can cause death. The majority of deaths were in fact related to a vascular event (i.e., myocardial infarction or cerebrovascular accident), renal disease, or both. The more likely scenario is that the MNCV deficit, TcpO₂, and mortality are caused by similar etiological mechanisms due to the hyperglycemia associated with diabetes. One of the candidate mechanisms is that of nonenzymatic glycation, which leads to the formation of advanced glycation end products, as this process is active in both peripheral nerve (21,22) and arterial components (23–25).

In conclusion, the major novel findings from this study are as follows, MNCV can predict both foot ulceration and mor-

tality in people with diabetes, and simple assessment of both pressure perception using monofilaments or ankle systolic pressure can identify diabetic subjects at high risk of amputation.

Acknowledgments—The study was supported by a grant from the National Health Services Research and Development Initiative. A.L.C., J.E.S., and C.A.A. were supported by grants from the Institute for Diabetes Discovery, Branford, Connecticut. This study was presented in abstract form at the 61st Scientific Sessions of the American Diabetes Association, June 2001 (Philadelphia, PA).

We thank all staff at the Manchester Diabetes Center and Withington Disablement Services Center who helped in this study. We also thank Julie Morris and Alison Wynn Hann for statistical advice.

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