Diabetologia (1992) 35: 155–159

Diabetologia

Exercise-induced conduction velocity increment: a marker of impaired peripheral nerve blood flow in diabetic neuropathy

S. Tesfaye[1], N. D. Harris[2], R. M. Wilson[1] and J. D. Ward[1]

[1] Diabetes Research Unit, and [2] Department of Medical Physics, Royal Hallamshire, Hospital, Sheffield, UK

Summary. Severe microvascular disease exists at the stage of clinical diabetic neuropathy. A non-invasive test that will identify those diabetic subjects who will eventually develop neuropathy is essential for early intervention. Sural sensory conduction velocity was recorded (×3) in 12 non-neuropathic diabetic subjects, 15 diabetic subjects with established neuropathy and 16 age-matched normal control subjects, before and after exercise to 80% age/sex predicted maximum heart rate. Fixed sural electrodes were used. Subcutaneous temperature was recorded by a needle thermocouple placed near the sural nerve. Sural sensory conduction velocity increased significantly after exercise in normal subjects ($p < 0.01$, mean increase 5.07 m/s) and non-neuropathic diabetic subjects ($p < 0.02$, mean increase 3.99 m/s) but not in neuropathic subjects (mean increase 0.99 m/s). Subcutaneous temperature rose significantly in normal subjects ($p < 0.01$, mean increase 2.07°C) and non-neuropathic diabetic subjects ($p < 0.001$, mean increase 2.52°C) but not in neuropathic subjects (mean increase 0.15°C). However, sural sensory conduction velocity increased by 1.2 $m \cdot s^{-1} \cdot °C^{-1}$ following direct warming of the limb in six neuropathic subjects which was comparable to that of normal and non-neuropathic subjects (1.49 and 1.48 $m \cdot s^{-1} \cdot °C^{-1}$). The impairment of exercise conduction increment in diabetic neuropathy suggests impaired nerve blood flow in diabetic neuropathy.

Key words: Diabetic neuropathy, nerve blood flow, sural nerve, sural sensory conduction velocity, temperature, exercise.

Diabetic neuropathy commonly leads to considerable morbidity and mortality. In any diabetic unit the greatest pressure on resources stems from foot ulceration and infection [1]. Neuropathy is the initiating factor in most of over 35,000 major amputations that take place every year in the United States [2]. Neuropathic pain can cause considerable disability and depression [3]. Yet, the aetiology and pathogenesis of human diabetic neuropathy remains unknown [4], although microvascular/hypoxic [5] and metabolic [6, 7] mechanisms have been postulated.

The case for microvascular disease in diabetic neuropathy is strong. Fibre loss in human sural nerve is multifocal, suggesting ischaemia [8]. The degree of endoneurial vessel disease has been related to the severity of neuropathy [9, 10]. People with chronic obstructive airways disease develop the so called "hypoxic neuropathy" in which microvascular changes similar to those associated with diabetic neuropathy occur [11]. In rats with experimental diabetic neuropathy nerve blood flow [12] is reduced and oxygen supplementation has improved deterioration in nerve conduction velocity [13]. Similarly, in human diabetic neuropathy, there is impaired nerve blood flow [14], epineurial arteriovenous shunting [15] and a reduction in sural nerve oxygen tension [16].

One way of increasing blood flow in the distal extremity is by physical activity [17]. Sural nerve conduction velocity has been shown to increase significantly during the first 30 min following walking [18]. However, the effect of exercise on nerve conduction has not been studied in diabetes. We have therefore studied the effect of exercise on nerve conduction velocity in normal and diabetic subjects with and without neuropathy. This study may provide further information about the role of peripheral nerve blood flow in the causation of diabetic neuropathy.

Subjects and methods

Fifteen subjects with chronic sensory-motor diabetic neuropathy, 12 non-neuropathic diabetic subjects and 16 healthy volunteers were studied (Table 1). Diabetic subjects were classified as having Type 1 diabetes on the basis of having a short history (< 2 months) of severe symptoms, marked weight loss, moderate or high ketonuria and insulin requirement within a year of diagnosis of diabetes. Two normal subjects, three neuropathic and one non-neuropathic

Table 1. Clinical characteristics of study subjects

	Diabetic neuropathic subjects	Non-neuropathic diabetic subjects	Normal control subjects
No.	15	12	16
Age ± SD	50.1 ± 8.5	49.8 ± 10.7	44.6 ± 7.7
M:F	12:3	9:3	9:7
Type 1:Type 2	9:6	6:6	–
Duration (years)	7.3 ± 6.2	7.9 ± 5.6	–
HbA_1 (3.5–6.8%)	9.9 ± 2.4%	9.4 ± 2.2%	–
Creatinine (μmol/l)	85 ± 12.7	96 ± 16.6	–
Retinopathy	7 BR, 2 PR, 6 Nil	1 BR, 1 PR, 10 Nil	–
Neuropathy score	Stage 2... 8 Subjects	Stage 0... 11 Subjects	–
	Stage 3... 7 Subjects	Stage 1... 1 Subject	

BR – Background retinopathy; PR – Proliferative retinopathy; Neuropathy score, Stage 0, no neuropathy; Stage 1, asymptomatic neuropathy; Stage 2, symptomatic neuropathy; Stage 3, disabling neuropathy

diabetic subjects smoked cigarettes. Subjects underwent: (1) full history and examination which included neuropathic symptom and deficit scores; (2) ankle pressure index using a Doppler ultrasound stethoscope, model BF4A (Med Sonics, Mountain View, Calif., USA) as described by Yao et al. [19]; (3) vibration perception threshold over the great toe and medial malleolus using a Biothesiometer (Biomedical Instrument Co, Newbury, Ohio, USA); (4) median and peroneal motor conduction velocities and median and sural sensory conduction velocities at a skin surface temperature of 33 ± 1°C, using a Dantec 2000 M electrophysiological system (Dantec Ltd, Bristol, UK) with signal averaging facility; (5) autonomic function tests of R-R variation at rest, with deep breathing and standing recorded using computer-assisted autonomic function testing and a standard resting 12-lead ECG. Exclusion criteria included any history of cardiac disease, autonomic neuropathy using age-related normal ranges [20], the presence of active proliferative retinopathy, peripheral vascular disease with either absence of foot pulses or ankle pressure index less than 1 and the presence of other neurological disorders or peripheral neuropathies from causes other than diabetes. Actively training athletes, and subjects on potentially neurotoxic, anti-arrhythmic, and peripherally vasodilating or vasoconstricting drugs were also excluded. Using the above criteria we had to exclude a large number of diabetic subjects with severe neuropathy, often with unrecordible sural sensory conduction velocity (SSCV). The group was therefore composed of relatively fit neuropathic subjects who did not have any difficulty in walking.

Clinical details of subjects are summarized in Table 1. Neuropathy staging was carried out using Dyck's neuropathy scoring on a 0 to 3 scale, taking into account results of neuropathy symptom (NS) and deficit (ND) scores, nerve conduction (NC), quantitative sensory testing (QST) and autonomic function tests (AF) as shown below [21].

Stage 0 (no neuropathy): fewer than two abnormalities among 1) NC; 2) ND 3) QST, AF; or 4) NS.
Stage 1 (asymptomatic neuropathy): two or more abnormalities among 1) NC; 2) ND; 3) QST or AF, but no abnormality of NS.
Stage 2 (symptomatic neuropathy): two or more abnormalities among 1) NC; 2) ND; 3) QST or AF; or 4) NS. Neuropathic symptoms are present but are of lesser severity than stage 3.
Stage 3 (disabling neuropathy): two or more abnormalities among 1) NC; 2) ND; 3) QST or AF; or 4) NS. Disabling neuropathic symptoms are present.

All the groups were matched for age, and the diabetic groups for duration of diabetes and diabetes control. All subjects had normal serum creatinine. Nine subjects had retinopathy in the diabetic neuropathy group compared to two in the non-neuropathic group.

Subcutaneous temperature and SSCV were recorded three times, at 10-min intervals, before and after exercise. Subjects exercised on a treadmill up to 80% age/sex predicted maximum heart rate [22–24] starting at stage 2 of the modified Bruce Protocol [24]. All subjects were exercised for a minimum of 3 min and heart rate was continuously monitored during the exercise period using a 3-lead ECG. SSCV was measured at the level of the lateral malleolus with the stimulating electrodes placed approximately 140 mm proximal to the active electrode. An earth strap was positioned between the stimulating and recording electrodes. Fixed 15 × 5 mm Biotab surface electrodes (Medical and surgical Bioadhesive, Marlborough, UK) were used throughout. Sensory sural action potential was averaged over 30 sweeps at a rate of 1/s. Temperature was measured using a digital thermometer with a needle thermocouple (CP Instruments, Bishops Stortford, UK) inserted subcutaneously (7 mm) near the sural nerve approximately 30 mm above the recording electrode. The study took place at room temperature of 24 ± 1°C and subjects were rested for 10 min before measurements were commenced.

The effect of direct warming of the limb on SSCV was measured in six randomly selected subjects from the diabetic neuropathy group (mean age ± SD 43.3 ± 5.6 years) Six normal (44.6 ± 5.5 years) and six non-neuropathic diabetic subjects (46.3 ± 9.2 years) were also selected such that all the groups were matched for age and sex, and the diabetic groups for duration of diabetes (mean ± SD: non-neuropathic diabetic group 7.5 ± 4.1 years; neuropathic group 5.7 ± 3.3 years). At least six measurements of SSCV and subcutaneous temperature were recorded in each subject except in two non-neuropathic diabetic and one neuropathic diabetic subjects who had five measurements. The SSCVs were measured using fixed electrodes and the subcutaneous temperature by a needle thermocouple as described. The measurements were made over a period of 30 min following immersion of the limb for 10 min in a 44°C water bath. Because of differing rates of limb cooling, a variable number of measurements were obtained over the 30-min period (Fig. 1).

All the subjects gave their informed consent and the study was approved by the local ethical committee.

Statistical analysis

Statistical analysis was conducted using paired and unpaired Student's *t*-test as appropriate. The changes in SSCV post-exercise between neuropathic subjects with and without retinopathy were compared using the two-tailed Mann-Whitney U test.

Results

The mean values of SSCVs and subcutaneous temperatures in normal control subjects, non-neuropathic diabetic and diabetic neuropathic subjects, before and after exercise are shown in Table 2. There is a wide inter-subject variation in the absolute values of the SSCV depending mainly on age. However, using fixed electrodes, the intra-subject pre-exercise baseline SSCV measurements were highly reproducible (coefficient of variation less than 2% in all the groups). We therefore calculated the change in SSCV after exercise for each subject. The SSCV and subcutaneous temperature recordings immediately before exercise were used as baseline measurements. Following exercise, the maximal SSCV with its corresponding temperature were taken as the end point. The changes in the mean SSCV and subcutaneous temperature in each group are shown in Figures 2 and 3. A scatter plot of the maximal changes in SSCV after exercise in the three groups is de-

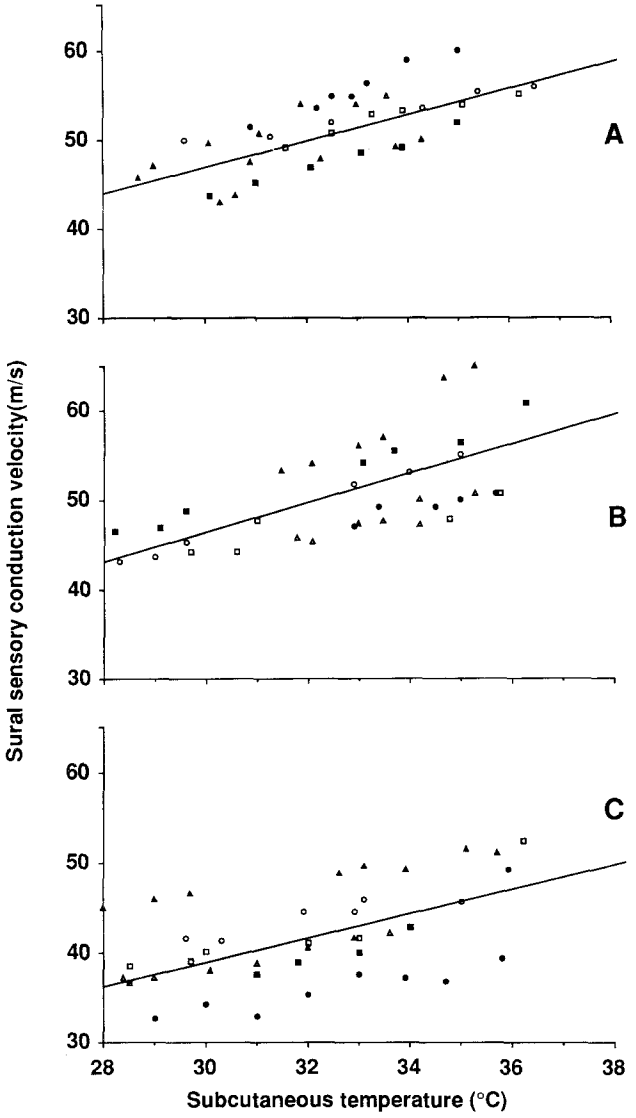

Fig. 1 A–C. The effect of direct warming of a limb on sural sensory conduction velocity in: **A**, normal control subjects (r = 0.69), **B**, non-neuropathic diabetic subjects (r = 0.62) and **C**, diabetic neuropathic subjects (r = 0.54). In each group different subjects are represented by different symbols

picted in Figure 4. SSCV increased significantly after exercise in normal subjects ($p < 0.01$, mean increase 5.07 m/s) and non-neuropathic diabetic subjects ($p < 0.02$, mean increase 3.99 m/s) but not in neuropathic subjects (mean increase 0.99 m/s). In four subjects with diabetic neuropathy SSCV decreased after exercise, and the four neuropathic subjects who managed an increase in SSCV (≥ 2 m/s) all had mild symptomatic neuropathy (Dyck's neuropathy stage 2) with normal neurophysiological tests.

In general, the increase in SSCV after exercise was accompanied with an increase in subcutaneous temperature. However, in three subjects (one from each group) subcutaneous temperature increased by less than 0.5 °C but the SSCV increased by greater than 3 m/s. Although subjects with active proliferative retinopathy were excluded from the study, there was a significant difference ($p < 0.01$) in the increase in SSCV post-exercise in the neuropathic subjects without retinopathy (n = 6; mean increase 2.07 m/s) compared to those with retinopathy (n = 9; mean increase 0.28 m/s), despite being matched for age (mean ± SD; with retinopathy 51.2 ± 9.5 years; without retinopathy 48.3 ± 7.9) and duration of diabetes (mean ± SD; with retinopathy 7.7 ± 7.6 years, without retinopathy 6.6 ± 4.7).

Subcutaneous temperature near the sural nerve rose significantly in normal subjects ($p < 0.01$, mean increase 2.07 °C) and non-neuropathic diabetic subjects ($p < 0.001$, mean increase 2.52 °C) but not in neuropathic subjects (mean increase 0.15 °C). There were significant differences in the mean increments in SSCV and temperature when comparing either of the normal or non-neuropathic diabetic groups with the neuropathic group ($p < 0.001$). However, there was no significant difference in both the variables between the normal and non-neuropathic diabetic groups.

There was an increase in SSCV with subcutaneous temperature on direct warming of the limb in all subjects (Fig. 1). In each group the relationship between SSCV and limb temperature was determined by applying a least squares linear regression using all the measurements within that group. The values from the regression are shown below.

Normal control subjects
SSCV = 2.61 + 1.49* temp r = 0.69 (38 points)
Non-neuropathic diabetic subjects
SSCV = 0.62 + 1.48* temp r = 0.62 (36 points)
Diabetic neuropathic subjects
SSCV = 3.25 + 1.2* temp r = 0.54 (42 points)

The results show that on direct warming of the limb SSCV increased by 1.2 $m \cdot s^{-1} \cdot °C^{-1}$ in neuropathic subjects, which was comparable to that of normal and non-neuropathic diabetic subjects 1.49 and 1.48 $m \cdot s^{-1} \cdot °C^{-1}$).

Although all subjects exercised to 80 % maximal heart rate, there was a significant difference in the exercise duration between normal control subjects (mean ± SD;

Table 2. Sural sensory conduction velocity (SSCV) and subcutaneous temperature before and after exercise in normal control subjects (NC), non-neuropathic diabetic subjects (NND) and diabetic neuropathic subjects (DN)

Time (min)		Pre-exercise			Post-exercise		
		0	10	20	0	10	20
SSCV	NC	49.3 ± 4.6	49.0 ± 4.6	48.9 ± 4.7	52.9 ± 5.5	53.3 ± 5.6	52.9 ± 5.3
(mean ± SD	NND	42.7 ± 3.5	42.5 ± 4.0	42.2 ± 4.0	46.0 ± 3.8	45.3 ± 3.9	44.9 ± 4.0
m/s)	DN	39.3 ± 6.6	39.3 ± 6.6	39.6 ± 6.5	39.7 ± 6.4	40.1 ± 6.7	39.9 ± 6.7
Subcutaneous	NC	29.7 ± 2.0	29.7 ± 2.0	29.5 ± 2.1	30.8 ± 2.0	31.3 ± 1.7	31.3 ± 1.4
temperature	NND	28.3 ± 1.7	28.6 ± 1.5	28.6 ± 1.5	30.9 ± 1.5	30.6 ± 1.3	30.4 ± 1.4
(mean ± SD °C)	DN	29.4 ± 2.3	29.6 ± 2.4	29.7 ± 2.5	29.7 ± 2.1	29.8 ± 2.3	29.7 ± 2

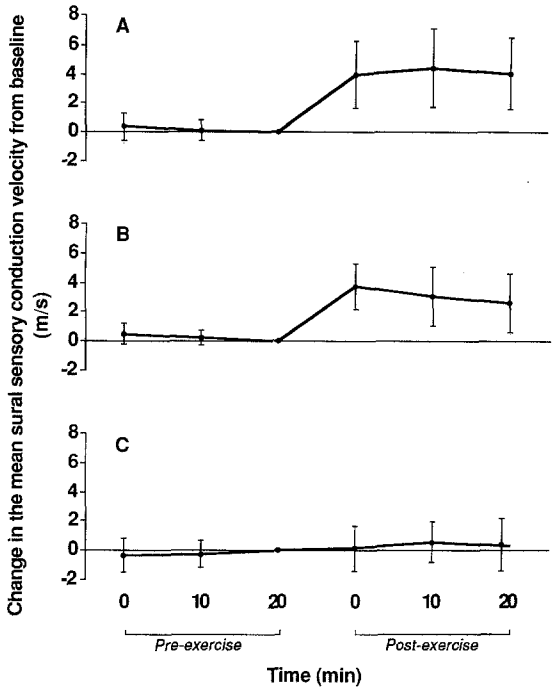

Fig. 2 A–C. The effect of exercise on sural sensory conduction velocity in: **A**, normal control subjects, **B**, non-neuropathic diabetic subjects and **C**, diabetic neuropathic subjects. Baseline measurements taken at 20 min pre-exercise. Unpaired *t*-tests for: A vs B $p = 0.22$, A vs C $p < 0.001$, B vs C $p < 0.001$

332 ± 68 s) and both non-neuropathic (275 ± 61 s) and neuropathic (244 ± 69 s) diabetic subjects, as normal subjects were fitter. There was no significant difference in exercise duration between the diabetic groups. Furthermore, five neuropathic subjects were exercised for 5 or more min and two for a maximum 6 min without significant increase in SSCV (mean increase 1.1 m/s).

Discussion

Strenuous exercise is the most stressful condition which the normal circulatory system faces. There is an increase in distal extremity blood flow brought about by a fall in tissue oxygen levels [17]. In this study, both SSCV and subcutaneous temperature near the sural nerve increased significantly after exercise in both normal and non-neuropathic diabetic subjects but not in neuropathic subjects. However, on direct warming of a limb in a warm water bath, SSCV increased by comparable amounts in all three groups. This demonstrates that the neuropathic nerve is capable of increasing its nerve conduction on direct warming but not with exercise. These findings suggest that the impairment of exercise-induced conduction velocity increment in diabetic neuropathy could be due to impaired nerve blood flow. This is not surprising as the epineurial nutrient vessels supplying the nerve appear diseased in diabetic neuropathy [14, 25] and consequently nerve blood flow is unlikely to increase with exercise. Furthermore, in normal subjects the increase in nerve conduction per °C was greater after exercise (2.45 $m \cdot s^{-1} \cdot °C^{-1}$) compared with direct warming of a limb (1.49 $m \cdot s^{-1} \cdot °C^{-1}$) suggesting that other factors apart from a pure temperature effect on nerve conduction [26] may be important.

Despite the availability of neurophysiological and quantitative sensory testing, we do not have a marker of early diabetic neuropathy or impaired peripheral nerve blood flow, if indeed this is an important factor. Of the 12 non-neuropathic diabetic subjects, two with a neuropathy score of 0 did not significantly increase their SSCV after exercise. We speculate that these may be the subjects who are at risk of developing neuropathy. If this is the case, this simple and non-invasive test which is within the

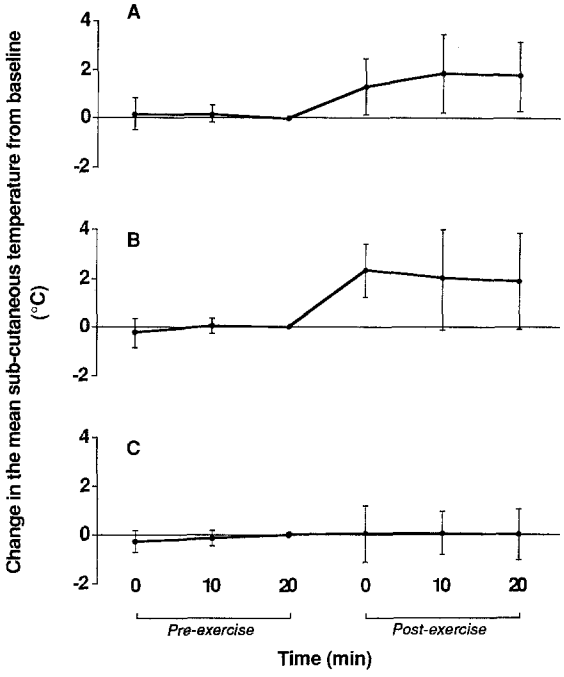

Fig. 3 A–C. The effect of exercise on sub-cutaneous temperature near the sural nerve in: **A**, normal control subjects, **B**, non-neuropathic diabetic subjects and **C**, diabetic neuropathic subjects. Baseline measurements taken at 20 min pre-exercise. Unpaired *t*-tests for: A vs B $p = 0.39$, A vs C $p < 0.001$, B vs C $p < 0.001$

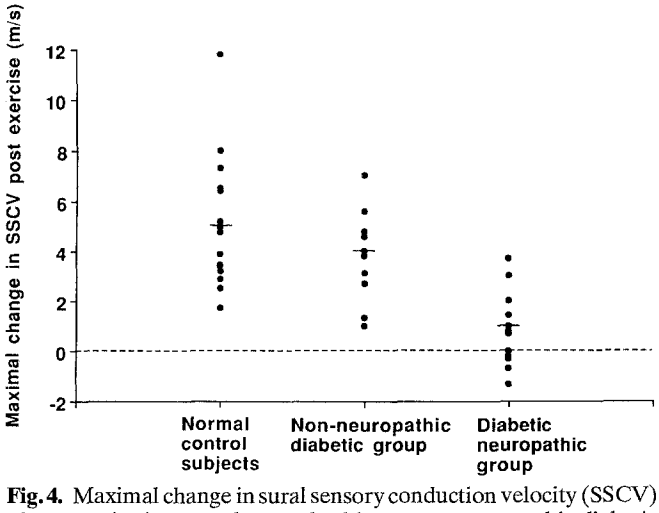

Fig. 4. Maximal change in sural sensory conduction velocity (SSCV) after exercise in normal control subjects, non-neuropathic diabetic and diabetic neuropathic subjects

means of most hospitals, may be regarded as an early marker of impaired peripheral nerve blood flow. Such a test is essential for early intervention.

Although severe microvascular disease [27–29] and nerve hypoxia [5, 16] exist at the stage of clinical diabetic neuropathy, metabolic factors may be important very early in the course of the disease. Nerve sorbitol accumulation on its own [6] or with associated depletion of myo-inositol and depression of Na/K ATPase activity have been implicated [7]. Clearly, the non-neuropathic diabetic subjects that do not increase their nerve conduction velocity with exercise need to be investigated further with nerve epineurial vessel photography [15], fluorescein angiography [14] and biopsy to see if they have early abnormalities of nerve blood flow and microvasculature. If they do indeed have these early abnormalities that are not yet clinically apparent, impairment of exercise-induced conduction velocity increment in asymptomatic diabetic subjects may be used as an indication for therapeutic intervention with aldose reductase inhibitors or peripheral vasodilators.

Acknowledgements. Department of Medical Illustration, Royal Hallamshire Hospital, Sheffield.

References

1. Ward JD (1982) The diabetic leg. Diabetologia 22: 141–147
2. Levin ME, O'Neal LW (1983) Preface: the diabetic foot. 3rd edn. Mosby, St. Louis, pp XI
3. Watkins PJ (1984) Pain and diabetic neuropathy. Br Med J 288: 168–169
4. Ward JD (1989) Diabetic neuropathy. Diabetes. Br Med Bull 45: 111–126
5. Dyck PJ (1989) Hypoxic neuropathy: does hypoxia play a role in diabetic neuropathy? Neurology 39: 111–118
6. Dyck PJ, Zimmerman BR, Todd HV et al. (1988) Nerve glucose, fructose, sorbitol, myo-inositol and fibre degeneration and regeneration in diabetic neuropathy. N Engl J Med 319: 542–548
7. Greene DA, Lattimer SA, Sima AAF (1987) Sorbitol, phosphoinositides, and sodium-potassium-ATPase in the pathogenesis of diabetic complications. N Engl J Med 316: 599–606
8. Dyck PJ, Lais A, Karnes JL, O'Brien P, Rizza R (1986) Fibre loss is primary and multifocal in sural nerves in diabetic polyneuropathy. Ann Neurol 19: 425–439
9. Malik PA, Newrick PG, Sharma AK et al. (1989) Microangiopathy in human diabetic neuropathy: relationship between capillary abnormalities and the severity of neuropathy. Diabetologia 32: 92–102
10. Britland ST, Young RJ, Sharma AK, Clarke BF (1990) Relationship of endoneurial capillary abnormalities to type and severity of diabetic polyneuropathy. Diabetes 39: 909–913
11. Malik RA, Masson EA, Sharma AK et al. (1990) Hypoxic neuropathy: relevance to human diabetic neuropathy. Diabetologia 33: 311–318
12. Tuck RR, Schmelzer JD, Low PA (1984) Endoneurial blood flow and oxygen tension in the sciatic nerves of rats with experimental diabetic neuropathy. Brain 107: 935–950
13. Low PA, Ruck RR, Dyck PJ, Schmelzer JD, Yao JK (1984) Prevention of some electrophysiologic and biochemical abnormalities with oxygen supplementation in experimental diabetic neuropathy. Proc Natl Acad Sci USA 81: 6894–6898
14. Tesfaye S, Harris N, Jakubowski J, Mody C, Ward JD (1990) Impaired blood flow and arterio-venous shunting in human diabetic sural nerve. Diabetic Med 7: [Suppl 2] 29A (Abstract)
15. Tesfaye S, Harris N, Jakubowski J, Mody C, Ward JD (1990) Evidence of arteriovenous shunting in human diabetic sural nerve. Diabetes 39: 153A (Abstract)
16. Newrick PG, Wilson AJ, Jakubowski J, Boulton AJM, Ward JD (1986) Sural nerve oxygen tension in diabetes. Br Med J 293: 1053–1054
17. Astrand P-O, Rodahl K (1986) Textbook of work physiology. McGraw-Hill, New York
18. Halar EM, Hammond MC, Dirks S (1985) Physical activity: its influence on nerve conduction velocity. Arch Phys Med Rehabil 66: 605–609
19. Yao ST, Hobbs JT, Irvine WT (1969) Ankle systolic measurements in arterial disease affecting the lower extremities. Br J Surg 56: 676–679
20. O'Brien IAD, O'Hare P, Corrall RJM (1986) Heart rate variability in healthy subjects: effect of age and derivation of normal ranges for tests of autonomic function. Br Heart J 55: 348–354
21. Dyck PJ (1988) Detection, characterization, and staging of polyneuropathy. Muscle & Nerve 11: 21–32
22. Lester FM, Sheffield LT, Reeve TJ (1967) Electrocardiographic changes in clinically normal older men following near maximal exercise. Circulation 36: 5–14
23. Sheffield LT, Maloof JA, Sawyer JA, Roitman D (1978) Maximal heart rate and treadmill performance of healthy women in relation to age. Circulation 57: 79–84
24. Sheffield LT (1988) Exercise stress testing. In: Braunwald E (ed) Heart disease: a textbook of cardiovascular medicine, 3rd edn. W. B. Saunders, Philadelphia, pp 223–241
25. Korthals JK, Gieron MA, Dyck PJ (1988) Intima of epineurial arterioles is increased in diabetic polyneuropathy. Neurology 38: 1582–1586
26. Greathouse DG, Currier DP, Joseph BS, Shippee RL, Matulionis DH (1989) Electrophysiologic responses of human sural nerve to temperature. Phys Ther 69: 914–922
27. Timperly WR, Boulton AJM, Davies Jones GAB, Jarrat JA, Ward JD (1985) Small vessel disease in progressive diabetic neuropathy associated with good metabolic control. J Clin Pathol 38: 1030–1038
28. Yasuda H, Dyck PJ (1987) Abnormalities of endoneurial microvessels and sural nerve pathology in diabetic neuropathy. Neurology 37: 20–28
29. Johnson PC, Doll SC, Cromey DW (1986) Pathogenesis of diabetic neuropathy. Ann Neurol 19: 450–457

Received: 24 July 1991
and in revised form: 7 October 1991

Dr. S. Tesfaye
Floor P
Royal Hallamshire Hospital
Glossop Road
Sheffield S10 2JF
UK