Diabetologia (1993) 36: 68–72

Diabetologia

Nerve function and its determinants in patients with newly-diagnosed Type 2 (non-insulin-dependent) diabetes mellitus and in control subjects – a 5-year follow-up

J. M. Lehtinen[1], L. Niskanen[2], K. Hyvönen[1], O. Siitonen[2] and M. Uusitupa[3]

Departments of [1] Clinical Neurophysiology, [2] Medicine and [3] Clinical Nutrition, University of Kuopio, Kuopio, Finland

Summary. In order to assess the changes in nerve function 5 years after the diagnosis of diabetes mellitus and the determinants of progression of neuropathy, we studied 113 Type 2 (non-insulin-dependent) diabetic patients and 127 non-diabetic control subjects. Motor and sensory nerve conduction velocities were measured at the time of diagnosis of diabetes and 5 years later. At both examinations conduction velocities and response amplitudes were lower in diabetic patients than in control subjects. During the follow-up sural nerve conduction was impaired in both diabetic and control subjects, but, in general, changes in neurophysiological parameters were slight and inconsistent. In 12 diabetic patients nerve function deteriorated significantly during the follow-up. These patients had higher glycaemic indices at both examinations and lower baseline blood pressure levels as compared to the rest of the diabetic patients. No differences between these patient groups were found in other baseline risk factors (age, obesity, use of alcohol, smoking, serum insulin levels, albuminuria, lipids). In conclusion, Type 2 diabetic patients have disturbed nerve function at the time of diagnosis, but neurophysiological impairment during the next 5 years is on the average slight. Poor glycaemic control seems to be the most important risk factor in the deterioration of nerve function in these patients.

Key words: Type 2 (non-insulin-dependent) diabetes mellitus, newly-diagnosed diabetes, diabetic neuropathy, nerve function, glycaemic control.

Only a few studies have reported on the natural history of diabetic neuropathy and its determinants, or "risk factors", especially in patients with Type 2 (non-insulin-dependent) diabetes mellitus. In short-term follow-up studies an improvement in nerve conduction after institution of therapy in newly-diagnosed diabetic patients has been described [1, 2]. On the other hand, it is known that the prevalence of diabetic neuropathy increases with the duration of diabetes [3]. Increased prevalence of neuropathy has been found to be related to poor glycaemic control [3, 4], but recently other determinants of neuropathy, e. g. traditional cardiovascular risk factors [5], have also been suggested.

A confounding factor in assessing peripheral neuropathy is that ageing per se is associated with degeneration of the nervous system and decrease of nerve conduction velocities [6, 7]. Therefore, it is essential that an adequate non-diabetic control population is included, when diabetic neuropathy and time-related changes in nerve function in middle-aged and elderly populations are investigated.

This study was a part of a larger multi-disciplinary study on non-insulin-dependent diabetes and its complications [8, 9]. We have previously shown, that patients with non-insulin-dependent diabetes have decreased nerve conduction velocities and diminished response amplitudes compared with the non-diabetic population at the time of diagnosis [10]. The present study was conducted in order to assess the change of nerve conduction parameters 5 years after the diagnosis of diabetes, and the determinants for deterioration of nerve function in these patients and in control subjects.

Subjects and methods

The baseline study population consisted of 132 patients with newly-diagnosed non-insulin-dependent diabetes mellitus, aged 45–64 years and 142 randomly selected non-diabetic control subjects from the same age group. Both groups were recruited from a defined area with 180,000 inhabitants in the county of Kuopio in Eastern Finland during the years 1979–1981 [8]. Approval for the study was given by the Ethics Committee of the University of Kuopio and the University Central Hospital. Informed consent was given by all subjects.

The diabetic patients (69 men, 63 women) were referred to the study by physicians working in community health centres and by pri-

vate practitioners working in the survey area. The diagnosis of diabetes, primarily made in the clinical setting [8] was confirmed by an oral glucose tolerance test using the diagnostic criteria recommended by the WHO [11]. Patients with previously diagnosed hyperglycaemia, secondary diabetes, renal insufficiency, thyroid diseases, malignancies, overt psychiatric disorders or alcoholism or those in institutional care were excluded from the study. At the time of diagnosis all the patients were non-ketotic and none required insulin treatment for at least 3 months after diagnosis. The non-diabetic control subjects (60 men, 82 women) from the same area and age group were randomly selected from the population registers. The same exclusion criteria used for diabetic patients were applied to the control group. The formation of the study population, their representativeness and methods of the baseline examination have been described previously in detail [8, 10]. The 5-year follow-up examination of diabetic patients and control subjects was conducted in 1985 and 1986 [12].

Eighty diabetic patients participated in a diet intervention study lasting 1 year [13]. Other patients were referred to primary health care after the baseline examination and the same applied also for the participants of the diet intervention study after its completion. During the follow-up nine diabetic patients (six men, three women) and two control subjects (one man, one woman) died. The data given are those of the 113 diabetic patients (58 men, 55 women) and 127 control subjects (55 men, 72 women), who participated in the neurophysiological examination both at the baseline and 5-year follow-up (87.6% of the original population).

Methods

The examinations at the 5-year follow-up study were carried out, whenever possible, according to the same methods and by the same personnel as at the baseline study.

Anthropometric measurements. Standing height was measured without shoes and read to the nearest 0.5 cm. Body weight was measured with an electric scale (Seca modell 708, Hamburg, FRG) with the subject barefoot and dressed in shorts. Body mass index (BMI) was calculated as body weight (kg)/height $(m)^2$.

Neurophysiological examination. Nerve conduction velocity (NCV) measurements were made by two neurophysiologists (J.L., K.H.) with a two-channel DISA 1500 electromyograph with signal averager (Dantec, Skovlunde, Denmark).

Motor NCVs of the median and deep peroneal nerves, antidromical sensory NCVs of the median, radial, sural and superficial peroneal nerves were measured by conventional methods with surface electrodes. Sensory NCVs in radial, sural, and superficial peroneal nerves were measured bilaterally and the results of both sides were averaged. Other NCVs were measured principally on the left side. The right side was used if a traumatic or surgical nerve lesion (e.g. sciatica) was suspected on the left side. If no response could be obtained on either side, the subject was not included in the analysis of this nerve. All NCV studies were done at a room temperature between 22–24°C. The effect of temperature on NCVs was controlled by statistical methods [14]. Skin temperatures were measured with an ELLAB TE 3 thermometer (Elektrolaboratoriet A/S, Copenhagen, Denmark).

Laboratory examinations. An oral glucose tolerance test was performed using a 75 g glucose dose. Whole venous blood samples were taken before the test with the patient fasting and at 1 and 2 h after glucose administration. Samples for serum insulin were taken into pre-chilled tubes, centrifuged and stored without delay at −20°C until analysed.

At the baseline examination blood glucose was determined by a glucose oxidase method (Glox; Kabi AB, Stockholm, Sweden). At the 5-year examination plasma glucose was determined by a glucose dehydrogenase method (Merck Diagnostica, Darmstadt, FRG). To compare plasma glucose values with blood glucose values at the baseline, blood glucose levels were multiplied by 1.12. HbA_1 was measured by column chromatography (Quick-Sep Fast Hemoglobin Test System; Isolab Inc., Akron, Ohio, USA, normal range 5.5–8.5%). At both examinations serum insulin was determined by radioimmunoassay (at baseline: antiserum M 8309, Novo, Copenhagen, Denmark; at the 5-year examination: Phasedeph; Pharmacia, Uppsala, Sweden).

Statistical analysis

Analysis of co-variance (ANCOVA) was used in the statistical analysis for continuous variables between the groups for controlling the effect of age and other confounding factors. Highly skewed distributions (plasma insulin, serum triglycerides) were normalised by logarithmic transformations before the statistical analysis. Chi-square or Fisher's test were used for dichotomous variables. Differences in NCV values at the baseline and 5-year examination were analysed by Student's paired t-test. Before the analysis both baseline and 5-year NCV values were adjusted to skin temperature of 33°C by regression analysis. Differences between diabetic and control groups in response amplitudes were assessed by Mann-Whitney U-test and time-related changes within the group by Wilcoxon's test.

A probability level of $p < 0.05$ was considered as statistically significant.

Results

The baseline clinical characteristics of the diabetic patients and control subjects are shown in Table 1. At baseline, diabetic patients were older, more obese and had higher serum total triglycerides and lower HDL cholesterol (but not total cholesterol) levels compared with non-

Table 1. Baseline clinical characteristics in diabetic and control subjects by sex

Subject characteristics	Men		Women	
	Diabetic	Control	Diabetic	Control
Study population *(n)*	58	55	55	72
Age (years)	54.8 ± 6.3	53.5 ± 5.3	58.1 ± 4.8	54.8 ± 5.8[d]
Height (cm)	172.3 ± 6.3	172.4 ± 6.3	157.2 ± 5.2	158.5 ± 5.0
BMI (kg/m^2)	29.3 ± 4.5	26.8 ± 3.3[d]	31.2 ± 5.7	27.3 ± 4.9[d]
Fasting plasma glucose (mmol/l)	11.2 ± 3.5	5.7 ± 0.9[d]	12.6 ± 4.2	5.4 ± 0.7[d]
Fasting serum insulin (mU/l)	22.8 ± 15.7	15.7 ± 10.8[b]	26.5 ± 17.4	15.5 ± 7.4[d]
Serum cholesterol (mmol/l)	6.4 ± 1.4	6.7 ± 1.3	6.4 ± 1.4	6.7 ± 1.1
HDL cholesterol (mmol/l)	0.99 ± 0.31	1.27 ± 0.31[d]	1.17 ± 0.32	1.42 ± 0.34[d]
Serum triglycerides (mmol/l)	2.47 ± 1.76	1.86 ± 1.58[c]	2.29 ± 1.67	1.38 ± 0.61[d]
Frequency of hypertension (%)[a]	58.6	36.4[b]	72.7	40.5[d]

[a] drug treatment or blood pressure greater than 160/95 mm Hg or both; [b] $p < 0.05$, [c] $p < 0.01$, [d] $p < 0.001$ diabetic vs control subjects. Values shown are mean ± SD

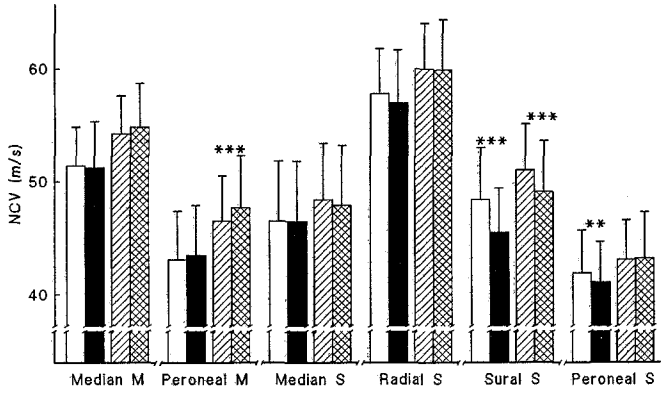

Fig. 1. Nerve conduction velocities (NCV, mean ± SD) at baseline and 5-year examination. Diabetic patients at baseline □, at 5-year examination ■, control subjects at baseline ▨, at 5-year examination ▩ ** $p < 0.01$, *** $p < 0.001$ baseline vs 5-year examination. M, Motor; S, sensory

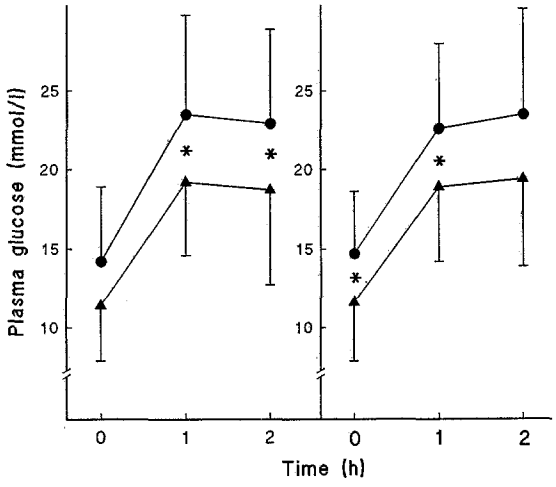

Fig. 2. Fasting- and post-glucose 1- and 2-h plasma glucose levels (mean ± SD) at baseline (left panel) and 5-year examination (right panel) in neurophysiologically deteriorated (●) and non-deteriorated (▲) diabetic patients. * $p < 0.05$ deteriorated vs non-deteriorated patients

diabetic control subjects. Also, the frequency of hypertension was markedly higher in diabetic patients than in control subjects.

At the 5-year examination no significant difference in mean age was found between the diabetic and control groups (59.1 ± 5.7 vs 58.0 ± 5.1 years for men; 62.3 ± 5.5 vs 59.1 ± 5.6 years for women). The diabetic patients were more obese than control subjects (BMI 28.4 ± 3.7 vs 26.7 ± 3.5 kg/m^2 for men, $p = 0.001$; 29.0 ± 5.2 vs 27.6 ± 4.8 kg/m^2 for women, $p = 0.229$, ANCOVA controlling for age). On the average, metabolic control was poor among diabetic patients at the 5-year examination as estimated by fasting plasma glucose (11.5 ± 3.8 mmol/l for men, 12.4 ± 3.9 mmol/l for women) or HbA_1 (8.9 ± 1.9% for men, 9.8 ± 1.9% for women).

At the 5-year examination 50 (44.2%) diabetic patients were treated with diet only, and 58 (51.3%) were on oral therapy. Insulin treatment had been started in 5 (4.4%) patients.

The mean NCVs at the 5-year examination were lower in diabetic patients than in control subjects (p values: median motor < 0.001, deep peroneal motor < 0.001, median sensory 0.058, radial sensory < 0.001, sural sensory < 0.001, peroneal sensory < 0.002, ANCOVA controlling for age and height). Figure 1 shows NCVs at baseline and 5-year examination. Sural nerve sensory NCV decreased significantly during the follow-up in both diabetic patients and control subjects. In diabetic patients superficial peroneal NCV also decreased. Otherwise changes between baseline and 5-year examinations were slight and inconsistent.

Response amplitudes were smaller in diabetic patients than in control subjects at both examinations (Table 2), especially at the 5-year examination. During the 5-year follow-up amplitudes tended to diminish, particularly in diabetic patients, in control subjects the changes were more inconsistent.

No significant differences were found in baseline nerve conduction parameters between those subjects who died during the follow-up and those who participated in the 5-year examination.

In 12 diabetic patients, but in none of the control subjects, a significant impairment (an NCV progressing from

Table 2. Evoked response amplitudes in diabetic and control subjects at baseline and 5-year examinations

Nerve	Diabetic patients		Control subjects	
	Baseline	5-year	Baseline	5-year
Motor (mV)				
Median	6.8 ± 3.2[b]	6.3 ± 2.5[a]	8.3 ± 3.4[e]	6.9 ± 2.7
Deep peroneal	2.9 ± 2.0	2.7 ± 1.6[a]	3.2 ± 2.0	3.3 ± 2.0
Sensory (μV)				
Median	20.4 ± 7.2[c]	18.2 ± 8.1	23.3 ± 10.4[d]	21.2 ± 10.6
Radial	19.7 ± 7.7[c]	19.2 ± 7.0[c]	23.4 ± 8.6	24.0 ± 9.7
Sural	9.2 ± 4.9	9.3 ± 4.5[a]	10.0 ± 4.8[f]	11.6 ± 6.1
Superficial peroneal	6.1 ± 3.1[f]	5.1 ± 3.0[a]	6.5 ± 3.2	6.3 ± 3.8

[a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.001$ diabetic vs control subjects; [d] $p < 0.05$, [e] $p < 0.01$, [f] $p < 0.001$ baseline vs 5-year examination. Values shown are mean ± SD

Table 3. Baseline risk factors in neurophysiologically deteriorated and non-deteriorated diabetic patients

Risk factor	Deteriorated patients ($n = 12$)	Non-deteriorated patients ($n = 101$)
Age (years)	57.2 ± 4.7	55.4 ± 10.4
Sex (male/female)	3/9 (25/75%)	55/46 (54/46%)
BMI (kg/m^2)	31.2 ± 7.2	30.4 ± 5.1
Use of alcohol (> 30 g/week) (%)	17	30
Smoking history (%)	25	48
Fasting serum insulin (mU/l)	27 ± 22	25 ± 16
Urinary albumin (≥ 35 mg/24 h) (%)	25	17
Systolic blood pressure (mm Hg)	143 ± 14	150 ± 18[b]
Diastolic blood pressure (mm Hg)	86 ± 8	93 ± 9[c]
Cholesterol (mmol/l)	6.3 ± 1.1	6.4 ± 1.4
Triglycerides (mmol/l)	2.2 ± 1.1	2.5 ± 1.8
HbA_1[a] (%)	10.7 ± 2.2	9.2 ± 1.8[b]

[a] at 5-year examination; [b] $p < 0.05$, [c] $p < 0.01$ deteriorated vs non-deteriorated diabetic patients. Values shown are mean ± SD

normal to pathological, defined as a decrease below the 95% confidence limit of the baseline value of the sex-specific control group, or a previously normal response that could not be elicited at 5-year examination, or both) was found in at least three nerves of six measured. In Table 3 these patients, referred to as the "deteriorated" group are compared with the rest of the diabetic patients, or "non-deteriorated" group, regarding various risk factors. Both fasting and post-glucose plasma glucose values (Fig. 2) and HbA_1 levels were significantly higher in the deteriorated compared with the non-deteriorated group. Blood pressure values, both systolic and diastolic, were significantly higher in the non-deteriorated than in the deteriorated group. No significant differences were found for the other risk factors.

Two of 12 patients (16.7%) in the deteriorated group and three of 101 (3.0%) in the non-deteriorated group ($p = 0.08$) were being treated with insulin at the 5-year examination.

Discussion

Nerve conduction velocities were significantly lower and response amplitudes smaller in diabetic patients than in non-diabetic control subjects. This phenomenon can be seen at the time of diagnosis of non-insulin-dependent diabetes [10] due to the fact that the diagnosis of non-insulin-dependent diabetes can be preceded by a long period of disturbed glucose metabolism [15], during which functional and structural alterations may develop in peripheral nerves. Interestingly the changes in neurophysiological parameters during the follow-up were on average slight and insignificant in most of the nerves, even in diabetic patients. Normal age-related degeneration of peripheral nerves [7] explains why some impairment was also seen in non-diabetic subjects.

We used only neurophysiological methods at the 5-year examination because they are sensitive and objective indicators of neuropathy and also easy to quantify [16]. Certainly, valuable information would have been gained by clinical neurological investigation; this will be included in the forthcoming 10-year examination.

Even if the changes in neurophysiological parameters during the 5-year follow-up were, in general, small, we could identify 12 diabetic patients of 113, in whom nerve function had significantly deteriorated during the follow-up. In these patients glycaemic indices at both examinations were significantly higher than in the rest of diabetic patients. This finding favours the idea of hyperglycaemia as the major determinant of deterioration of nerve function in diabetes. Our result is in agreement with that of Hillson et al. [17], who followed-up newly-diagnosed patients with non-insulin-dependent diabetes and found that deterioration of vibration sense during 5 years was correlated with the degree of hyperglycaemia, although the deterioration in general was slight. Association between slowing of NCV and poor glycaemic control has been shown in young Type 1 (insulin-dependent) diabetic patients [18] and also in untreated non-insulin-dependent diabetes [2, 19], but no reports from controlled long-term studies of development of NCVs in relation to metabolic control and other possible risk factors in non-insulin-dependent diabetes are available.

In addition to hyperglycaemia, other risk factors that have been found to be related to diabetic neuropathy include serum lipids, hypertension, smoking [5], retinopathy, proteinuria [18], use of alcohol [20], age and male gender [21]. In our study, among other risk factors only blood pressure levels were significantly lower in the deteriorated compared to the non-deteriorated group. The significance of this finding is unclear and needs confirmation before any conclusions can be drawn. In other studies results opposite to this have been found [5, 21]. None of the above-mentioned factors were shown to be a significant risk factor for impairment of nerve conduction in our patients. Most of the previous studies on risk factors for diabetic neuropathy have been cross-sectional and included mainly patients with insulin-dependent diabetes, who were considerably younger than our patients. Therefore the results of these studies are not directly comparable with our study, although it has been suggested that very few differences in the risk factor profiles for diabetic complications exist between the two types of diabetes [22].

In conclusion, it seems that the degree of hyperglycaemia is the strongest correlate of deterioration of nerve function in non-insulin-dependent diabetes and the postulated effects of other risk factors on diabetic neuropathy are of minor importance. Thus, improvement of glycaemic control is the most effective way to prevent the progression of neuropathy in patients with non-insulin-dependent diabetes.

Acknowledgements. This work has been supported by grants from The Academy of Finland, Finnish Cultural Foundation, Finnish Medical Foundation, Emil Aaltonen Foundation, Orion Corporation Research Foundation and Hoechst Fennica Research Foundation.

References

1. Ward JD, Fisher DJ, Barnes CG, Jessop JD, Baker RWR (1971) Improvement of nerve conduction following treatment in newly diagnosed diabetics. Lancet I: 428–431
2. Graf RJ, Halter JB, Pfeifer MA, Halar E, Brozovich F, Porte D (1981) Glycemic control and nerve conduction abnormalities in non-insulin-dependent diabetic subjects. Ann Intern Med 94: 307–311
3. Pirart J (1978) Diabetes mellitus and its degenerative complications: a prospective study of 4400 patients observed beween 1947 and 1973 (Part 1). Diabetes Care 1: 168–188
4. Palumbo PJ, Elveback LR, Whisnant JP (1978) Neurologic complications of diabetes mellitus: transient ischemic attack, stroke and peripheral neuropathy. In: Schoenberg BS (ed) Advances in neurology, vol 19. Raven Press, New York
5. Maser RE, Steenkiste AR, Dorman JS et al. (1989) Epidemiological correlates of diabetic neuropathy. Report from Pittsburgh epidemiology of diabetic complications study. Diabetes 38: 1456–1461
6. Mayne N (1965) Neuropathy in the diabetic and non-diabetic populations. Lancet II: 1313–1316
7. Dorfman L, Bosley TM (1979) Age-related changes in peripheral and central nerve conduction in man. Neurology 29: 38–44

8. Uusitupa M, Siitonen O, Aro A, Pyörälä K (1985) Prevalence of coronary heart disease, left ventricular failure and hypertension in middle-aged, newly diagnosed type 2 (non-insulin-dependent) diabetic subjects. Diabetologia 28: 22–27
9. Siitonen O, Uusitupa M, Pyörälä K, Voutilainen E, Länsimies E (1986) Peripheral arterial disease and its relationship to cardiovascular risk factors and coronary heart disease in newly diagnosed non-insulin-dependent diabetics. Acta Med Scand 220: 205–212
10. Lehtinen JM, Uusitupa M, Siitonen O, Pyörälä K (1989) Prevalence of neuropathy in newly diagnosed NIDDM and nondiabetic control subjects. Diabetes 38: 1307–1313
11. WHO Expert Committee on Diabetes Mellitus (1980) Second report. WHO Tech Report Series No. 646, Geneva
12. Niskanen LK, Uusitupa M, Sarlund H, Siitonen O, Pyörälä K (1990) Five-year follow-up study on plasma insulin levels in newly diagnosed NIDDM patients and nondiabetic subjects. Diabetes Care 13: 41–48
13. Korhonen T, Uusitupa M, Aro A et al. (1987) Efficacy of dietary instructions in newly diagnosed non-insulin-dependent diabetic patients: comparison of two different patient education regimens. Acta Med Scand 222: 31–32
14. Kuusela V, Lang AH (1979) Elimination of systematic variance in laboratory measurements and the P-value; a method for reporting laboratory results. In: Lindberg DAB, Reichertz PL (eds) Lecture notes in medical informatics, vol 5. Springer, Berlin Heidelberg New York, pp 435–443
15. Jarrett RJ, Keen H, Fuller JH, McCartney M (1979) Worsening to diabetes in men with impaired glucose tolerance ("borderline diabetes"). Diabetologia 16: 25–30
16. Dyck PJ (1991) Evaluative procedures to detect, characterize, and assess the severity of diabetic neuropathy. Diabetic Med 8 [Suppl]: S 48–S 51
17. Hillson RM, Hockaday TDR, Newton DJ (1984) Hyperglycaemia is one correlate of deterioration in vibration sense during the 5 years after diagnosis of type 2 (non-insulin-dependent) diabetes. Diabetologia 26: 122–126
18. Young RJ, McIntyre CCA, Martyn CN et al. (1986) Progression of subclinical polyneuropathy in young patients with type 1 (insulin-dependent) diabetes: associations with glycaemic control and microangiopathy (microvascular complications). Diabetologia 29: 156–161
19. Graf RJ, Halter JB, Halar E, Porte D (1979) Nerve conduction abnormalities in untreated maturity-onset diabetes: relation to levels of fasting plasma glucose and glycosylated hemoglobin. Ann Intern Med 90: 298–303
20. McCulloch DK, Campbell IW, Prescott RJ, Clarke BF (1980) Effect of alcohol intake on symptomatic peripheral neuropathy in diabetic men. Diabetes Care 3: 245–247
21. The DCCT research group (1988) Factors in development of diabetic neuropathy. Baseline analysis of neuropathy in feasibility phase of Diabetes Control and Complications Trial (DCCT). Diabetes 37: 476–481
22. Knuiman MW, Welborn TA, McCann VJ, Stanton KG, Constable IJ (1986) Prevalence of diabetic complications in relation to risk factors. Diabetes 35: 1332–1339

Received: 1 June 1992
and in revised form: 14 September 1992

Dr. J. Lehtinen
Department of Clinical Neurophysiology
Kivelä Hospital
Sibeliuksenkatu 12–14
SF-00260 Helsinki
Finland