

## NATURAL HISTORY OF PERIPHERAL NEUROPATHY IN PATIENTS WITH NON-INSULIN-DEPENDENT DIABETES MELLITUS

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**Abstract Background.** There is little information on the incidence and natural history of neuropathy in patients with non-insulin-dependent diabetes mellitus (NIDDM).

**Methods.** We studied patients with newly diagnosed NIDDM and control subjects both at base line and 5 and 10 years later. Polyneuropathy was diagnosed on the basis of clinical criteria (pain and paresthesias) and electrodiagnostic studies (nerve conduction velocity and response-amplitude values). We investigated the relation between metabolic variables (results of oral glucose-tolerance tests, serum lipid and insulin concentrations, and glycosylated hemoglobin values) and the development of polyneuropathy.

**Results.** In 10 years, 36 patients with NIDDM and 8 control subjects died; 86 patients and 121 control subjects completed the study. When the study ended, 18 percent of the patients were being treated only with diet, 59 percent with oral hypoglycemic drugs alone, 12 percent with insulin alone, and 11 percent with both insulin and oral hypoglycemic agents. At base line the prevalence of

definite or probable polyneuropathy among the patients with NIDDM was 8.3 percent, as compared with 2.1 percent among the control subjects. These values 10 years later were 41.9 percent and 5.8 percent, respectively. The number of patients with NIDDM who had nerve-conduction abnormalities in the legs and feet increased from 8.3 percent at base line to 16.7 percent after 5 years and to 41.9 percent after 10 years. The decrease in sensory and motor amplitudes, indicating axonal destruction, was more pronounced than the slowing of the nerve conduction velocities, which indicates demyelination. Among the patients with NIDDM, those with polyneuropathy had poorer glycemic control than those without. Low serum insulin concentrations before and after the oral administration of glucose were associated with the development of polyneuropathy, regardless of the degree of glycemia.

**Conclusions.** The prevalence of polyneuropathy among patients with NIDDM increases with time, and the increase may be greater in patients with hypoinsulinemia. (N Engl J Med 1995;333:89-94.)

THERE is little information available on the incidence and natural history of neuropathy diagnosed according to clinical and electrodiagnostic criteria in patients with non-insulin-dependent diabetes mellitus (NIDDM). Up to 7.5 percent of patients with NIDDM have clinical neuropathy at the time of diagnosis. This rate increases to 50 percent among patients who have had diabetes for 25 years.<sup>1</sup> In an earlier study of patients with NIDDM, we found that 15.2 percent had abnormalities in nerve conduction velocity at the time of diagnosis, but only 2.3 percent had clinical signs of polyneuropathy and 1.5 percent had symptomatic polyneuropathy.<sup>2</sup> After five years of follow-up, changes in neurophysiologic measurements in this group were slight and were associated with poor glycemic control.<sup>3</sup> In this report we describe the results of studies of peripheral-nerve function after 10 years of follow-up in this cohort of patients with NIDDM and in control subjects; our goal was to determine the long-term risk of diabetic polyneuropathy and the factors affecting that risk.

### METHODS

We recruited 133 patients with newly diagnosed NIDDM who were 45 to 64 years old at the time of diagnosis and 144 randomly selected nondiabetic control subjects in the same age group (Table 1).<sup>2</sup> Both groups were evaluated between May 1, 1979, and December 31, 1981.<sup>4</sup> The control subjects were recruited from among 180,000 inhabitants of the county of Kuopio in eastern Finland. At base line,

132 patients with NIDDM and 142 control subjects underwent clinical evaluation and measurement of nerve conduction velocity. Of these, 114 patients with NIDDM (86 percent) and 128 control subjects (90 percent) were evaluated after 5 years of follow-up, and 86 (65 percent) and 121 (85 percent), respectively, after 10 years. The diagnosis of diabetes<sup>4</sup> was confirmed by an oral glucose-tolerance test, in which subjects were given 75 g of glucose after a 12-hour overnight fast<sup>5</sup>; the test was performed in both the diabetic patients and the control subjects. Information about cigarette smoking and the use of alcohol was obtained by questionnaire. During the 10-year follow-up period, 36 patients with NIDDM and 8 control subjects died; the cause of death in the patients with NIDDM was most often cardiovascular.<sup>6</sup> The study was approved by the ethics committee of the University of Kuopio, and all the subjects gave informed consent.

The patients were initially treated only with diet. Thereafter, antidiabetic therapy, as well as other therapy, was managed by the patients' primary care physicians. At the five-year examination, 50 percent of the patients were being treated with oral hypoglycemic drugs, 4 percent with insulin, and the rest with diet only. At the 10-year examination, 59 percent were receiving only oral hypoglycemic drugs, 12 percent were taking insulin, 18 percent were treated with diet alone, and 11 percent were treated with both oral hypoglycemic drugs and insulin. The metabolic follow-up data are shown in Table 2.

### Laboratory Studies

Glucose tolerance was assessed by measuring blood or plasma glucose concentrations (in blood at base line and in plasma at 5 and 10 years) and serum insulin and C-peptide concentrations before and one and two hours after the oral administration of 75 g of glucose. Glucose was measured by the glucose oxidase method (at base line and at the 10-year examination) or the glucose dehydrogenase method (at 5 years).<sup>7</sup> Serum insulin was measured by a double-antibody radioimmunoassay (at base line: Novo Industries, Copenhagen, Denmark; at 5 and 10 years: Phasedeph, Pharmacia, Uppsala, Sweden). Serum C peptide was measured by radioimmunoassay (at 5 years: Novo-Nordisk, Copenhagen; at 10 years: 125-I, Incstar, Stillwater, Minn.).<sup>7</sup>

At all examinations, serum lipid concentrations were determined in samples obtained after the subjects had fasted for 12 hours. Lipoproteins were analyzed enzymatically after ultracentrifugation and precipitation.<sup>6,8</sup> Glycosylated hemoglobin was measured at the 5-year and 10-year examinations by liquid cation-exchange chromatography

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(normal range, 4.0 to 6.0 percent). In the base-line study, albumin was measured by immunodiffusion in 24-hour urine samples (Behringswerke, Mahrburg Lahn, Germany).

### Neurologic Examination

A detailed neurologic examination, including a questionnaire on symptoms, was performed at base line and at the 10-year follow-up examination. At the five-year follow-up examination, only electrophysiologic studies were performed.<sup>3</sup> Neuropathic pain was defined as pain in the limbs in the absence of a history of trauma or other evident external cause. Pain that arose during exercise and disappeared at rest, joint pain, and back pain radiating to the legs were not considered neuropathic pain. Bilateral pain or paresthesias of the legs or feet were considered symptoms of polyneuropathy. The limbs were inspected for ulcerations and muscle atrophy. The patellar and Achilles-tendon reflexes were examined. Vibration sensation was tested with a tuning fork (128 Hz) on each medial malleolus. The absence of either Achilles-tendon reflexes or vibration sensation bilaterally was considered a clinical sign of polyneuropathy. All the subjects were also evaluated for carpal tunnel syndrome at base line.

### Neurophysiologic Studies

Measurements of nerve conduction velocity at base line and at the 5-year and 10-year examinations were performed with a DISA 1500 electromyograph (Dantec, Skovlunde, Denmark). Conduction velocity in the median and deep peroneal motor nerves and antidromic conduction velocity in the superficial radial, median, sural, and superficial peroneal sensory nerves were measured by conventional methods with surface electrodes.<sup>9</sup> The measurements in the motor nerves were performed principally on the left side of the body, but the right side was used if a local nerve lesion was suspected or if a response could not be elicited on the left side. The measurements in

Table 1. Characteristics of the Patients with NIDDM and the Control Subjects at Base Line.\*

CHARACTERISTIC	PATIENTS WITH NIDDM (N = 132)	CONTROLS (N = 142)	P VALUE
Age (yr)	56±10	54±6	0.07
Sex (F/M)	63/70	82/62	—
Body-mass index†	30.4±5.2	27.0±4.3	<0.001
Height (cm)			
Men	172±6	173±7	0.40
Women	157±5	158±5	0.05
Blood pressure (mm Hg)			
Systolic	150±18	147±19	0.09
Diastolic	93±10	91±9	0.07
Taking antihypertensive medication (%)	52	21	<0.001
Alcohol consumption (g/wk)	47±98	43±101	0.40
History of smoking >1 yr (%)	47	25	<0.001
Blood glucose (mg/dl)‡			
Fasting	216±72	100±14	<0.001
After glucose administration§	353±113	118±36	<0.001
Serum insulin (mU/liter)¶			
Fasting	25±16	15±9	<0.001
After glucose administration§	65±52	62±52	0.30
Serum cholesterol (mg/dl)¶¶			
Total	249±53	259±45	0.05
HDL	41±11	52±13	<0.001
LDL	161±42	173±40	0.013
VLDL	46±36	33±25	0.001
Serum triglycerides (mg/dl)**	214±144	142±104	<0.001
Urine albumin (mg/24 hr)	35±77	7±8	<0.001

\*Plus-minus values are means ±SD.

†The weight in kilograms divided by the square of the height in meters.

‡To convert values to millimoles per liter, multiply by 0.0555.

§Two hours after the oral administration of 75 g of glucose.

¶To convert values to picomoles per liter, multiply by 6.

¶¶To convert to millimoles per liter, multiply by 0.02586. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and VLDL very-low-density lipoprotein.

\*\*To convert values to millimoles per liter, multiply by 0.0113.

Table 2. Metabolic Data for the Patients with NIDDM and the Control Subjects at the 5-Year and 10-Year Examinations.\*

INDEX	PATIENTS WITH NIDDM	CONTROL SUBJECTS	P VALUE
<b>5-Year examination</b>			
No. of patients	114	128	
Plasma glucose (mg/dl)			
Fasting	214±70	103±23	<0.001
After glucose administration†	357±104	137±54	<0.001
Glycosylated hemoglobin (%)	9.3±2.6	5.8±1.4	<0.001
Serum insulin (mU/liter)			
Fasting	22±23	18±20	0.004
After glucose administration†	60±64	92±103	<0.001
<b>10-Year examination</b>			
No. of patients	86	121	
Plasma glucose (mg/dl)			
Fasting	220±65	108±23	<0.001
After glucose administration†	366±106	128±61	<0.001
Glycosylated hemoglobin (%)	9.0±2.2	5.5±1.4	<0.001
Serum insulin (mU/liter)			
Fasting	15±7	12±7	<0.001
After glucose administration†‡	35±23	59±56	<0.001
Serum C peptide (ng/ml)			
Fasting	1.96±0.97	1.93±1.30	0.88
After glucose administration†	4.32±1.69	6.62±4.26	<0.001

\*Plus-minus values are means ±SD. To convert glucose values to millimoles per liter, multiply by 0.0555; to convert insulin values to picomoles per liter, multiply by 6; to convert C-peptide values to nanomoles per liter, multiply by 0.331.

†Two hours after the oral administration of 75 g of glucose.

‡Not measured in patients receiving insulin treatment.

sensory nerves were performed bilaterally, and the mean of the values for the two sides (or the value for a unilateral measurement, if a response on the other side could not be elicited) was calculated. The amplitudes of the motor and sensory responses were measured to the first negative peak. All studies of nerve conduction velocity were done at room temperature (between 22°C and 24°C). Skin temperatures were measured with an ELLAB TE 3 thermometer (Elektronlaboratoriet, Copenhagen) at the sites of sensory-nerve measurements.<sup>9</sup> Both directly measured values for nerve conduction velocity in the sensory nerves and values adjusted for the effect of temperature were analyzed.<sup>10</sup>

### Definition of Diabetic Polyneuropathy

Because there was no significant decrease in the mean nerve conduction velocities in the control group during the 10-year follow-up period, we did not consider it necessary to correct these values for age,<sup>10</sup> and the same cutoff points were used for normal measurements at all times (control mean, -2 SD). The normal values for the amplitudes of the motor- and sensory-nerve responses were more difficult to determine because of the large variation in values. We tabulated all values for amplitude in the control subjects at the 10-year examination and defined the lower limit of normal as the 10th percentile of the values for the legs and feet in the controls. Although the amplitudes diminished in all subjects during the 10-year follow-up, the cutoff value was so low in relation to the mean that adjustment for age was considered unnecessary. Altogether, six measurements of nerve function in the legs and feet were used as electrophysiologic indicators of polyneuropathy: in the peroneal motor nerves, nerve conduction velocity, ≤39 m per second; amplitude, ≤1 mV; in the peroneal sensory nerves, nerve conduction velocity, ≤37 m per second; amplitude, ≤2 μV; in the sural sensory nerves, nerve conduction velocity, ≤43 m per second; amplitude, ≤3 μV — all at a skin temperature ≥31°C. The subjects were classified as having definite polyneuropathy if four or more values were abnormal, if both the peroneal and sural nerves were involved, and if there were clinical symptoms of polyneuropathy (pain or paresthesias in the legs); they were classified as having probable polyneuropathy if four or more values were abnormal and both the peroneal and sural nerves were involved but there were no symptoms, or if either of the nerves was electrophysiologically involved and there were symptoms. The subjects with definite or probable polyneuropathy were grouped together as subjects

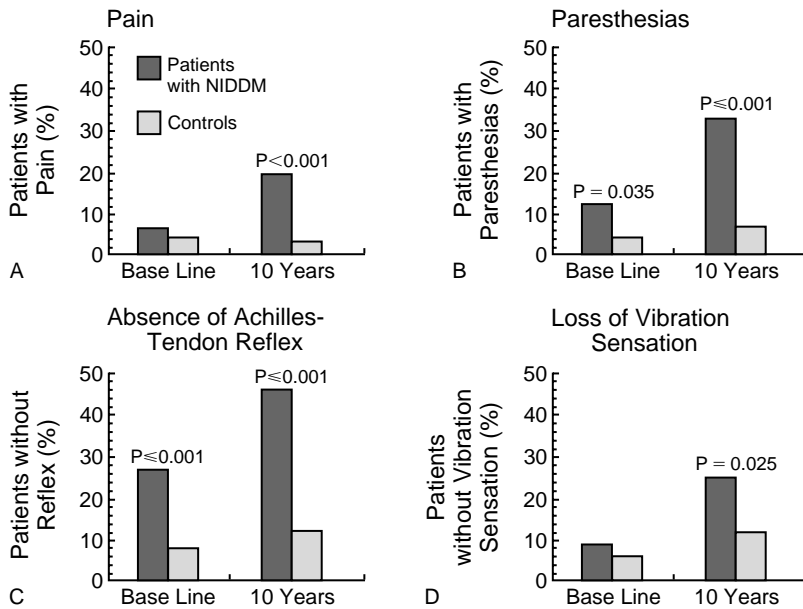


Figure 1. Prevalence of Clinical Symptoms and Signs in Patients with NIDDM and Control Subjects at Base Line and after 10 Years.

Panel A shows the proportion of patients with bilateral pain in the legs and feet. Panel B shows the proportion with bilateral paresthesias of the legs and feet. Panel C shows the proportion with no Achilles-tendon reflexes, and Panel D the proportion with loss of vibration sensation on the medial malleoli. The comparisons of the groups at base line have been previously reported.<sup>2</sup> P values for the comparisons between patients and controls were derived with McNemar's test.

with polyneuropathy. Twenty-four patients with NIDDM and 15 control subjects had carpal tunnel syndrome at base line (P = 0.07). The nerve conduction values in the arms and hands were therefore not used to define polyneuropathy.

**Statistical Analysis**

The differences in mean values between the groups were analyzed by Student's t-test (two-tailed), the Mann-Whitney U test, or analysis of covariance with control for confounding variables. The cate-

gorical variables were analyzed by the chi-square test, McNemar's test, or Fisher's exact test. Time-related changes within a group were analyzed by paired t-tests or the Wilcoxon matched-pairs signed-rank test. Differences in the areas under the serum insulin curve (at base line, 5 years, and 10 years, with insulin-treated patients omitted) between the patients with and without neuropathy were analyzed by repeated-measures analysis of variance (for time of investigation, group, and fasting glucose value at base line and at 5 and 10 years). Serum insulin concentrations were analyzed after logarithmic transformation. The area under the serum insulin curve was calculated by the trapezoidal rule. The Spearman correlation coefficient was calculated for the relation between nerve function and the metabolic variables (glycemic control and serum insulin values). All the data were analyzed with SPSS software (SPSS, Chicago).

**RESULTS**

The proportions of subjects with neuropathic pain or without vibration perception in the NIDDM and control groups at base line were similar, but paresthesias and an absence of Achilles-tendon reflexes were more common in the group with NIDDM (Fig. 1). All values for nerve conduction velocity in sensory and motor nerves were slower, and the sensory amplitude of the radial nerve and the motor amplitude of the median nerve were lower in the group with NIDDM (Table 3).

At the five-year examination the nerve conduction velocity in the sural sensory nerves and the sensory response amplitude of the superficial peroneal nerve had decreased in the NIDDM group.<sup>3</sup> The sensory am-

Table 3. Results of Electrophysiologic Studies of Peripheral-Nerve Function in Patients with NIDDM and Control Subjects at Base Line and at the 10-Year Examination.\*

VARIABLE	PATIENTS WITH NIDDM			CONTROL SUBJECTS			P VALUE	
	BASE LINE (N = 132)	10-YR (N = 86)	P VALUE	BASE LINE (N = 142)	10-YR (N = 121)	P VALUE	BASE LINE: PATIENTS VS. CONTROLS	10-YR: PATIENTS VS. CONTROLS
<b>Nerve conduction velocity (m/sec)</b>								
<b>Sensory nerves</b>								
Peroneal	41.9±3.6	40.1±5.0	0.002	43.1±3.4	43.9±4.5	0.06	0.016	0.001
Sural	48.3±4.7	44.4±5.8	0.001	51.0±4.2	50.5±5.2	0.2	0.001	0.001
Radial	58.0±4.1	56.6±5.9	0.015	59.9±4.0	59.9±5.5	0.9	0.001	0.001
Median	47.7±5.0	47.1±6.7	0.2	48.6±5.1	50.8±4.9	0.002	0.07	0.001
<b>Motor nerves</b>								
Peroneal	43.3±4.4	40.3±6.5	0.001	46.5±4.0	45.8±5.3	0.1	0.001	0.001
Median	51.2±4.0	48.3±7.7	0.001	53.8±3.5	53.9±4.4	0.9	0.001	0.001
<b>Response amplitude</b>								
<b>Sensory nerves (µV)</b>								
Peroneal	6.1±3.1	2.8±1.8	0.001	6.6±3.2	5.0±3.0	0.001	0.1	0.001
Sural	9.2±5.1	5.5±3.6	0.001	10.1±4.7	9.7±6.5	0.3	0.07	0.001
Radial	20.0±7.8	15.8±7.2	0.001	23.2±7.9	21.8±9.8	0.050	0.001	0.001
Median	19.4±7.6	12.7±6.8	0.001	22.3±10.4	18.1±8.8	0.001	0.004	0.001
<b>Motor nerves (mV)</b>								
Peroneal	3.0±2.0	2.0±1.3	0.001	3.2±1.9	2.7±1.5	0.019	0.2	0.001
Median	6.4±3.3	5.1±2.5	0.002	8.0±3.4	5.7±2.6	0.001	0.001	0.05

\*Plus-minus values are means ±SD.

plitude of the median nerve was lower in both the NIDDM group ( $P < 0.001$ ) and the control group ( $P = 0.005$ ) than at base line.

At the 10-year examination, clinical symptoms and signs of neuropathy were more common among the patients with NIDDM than among the control subjects (Fig. 1). The frequency of pain and paresthesias had increased since the base-line evaluation among the patients with NIDDM, as had the frequency with which Achilles-tendon reflexes and vibration perception were absent. None of these variables changed in the control subjects. Of the patients with NIDDM, one had foot ulcerations at base line and two had such ulcerations at the 10-year examination. All values for nerve conduction velocity and response amplitudes were lower in the patients with NIDDM than in the control subjects at the 10-year examination (Table 3). The decrease in the sensory response amplitudes during follow-up was more marked in the group with NIDDM than in the control group. The temperature correction for nerve conduction velocities<sup>10</sup> had no effect on the results. The patients with NIDDM who died during follow-up did not have more neurophysiologic abnormalities earlier than those who survived.

At base line, six of the patients with NIDDM (4.5 percent) had probable polyneuropathy and five (3.8 percent) had definite polyneuropathy. At the 10-year examination, these figures were 18 (20.9 percent) and 18 (20.9 percent), respectively (Fig. 2). At base line, 8.3 percent of the patients had electrophysiologic abnormalities; 16.7 percent had such abnormalities at 5 years, and 41.9 percent at 10 years.

#### Risk Factors for Polyneuropathy

Age, smoking, and the use of alcohol did not predict the occurrence of polyneuropathy at 10 years in the patients with NIDDM. At the five-year examination, the patients with polyneuropathy had lower mean ( $\pm$ SD) blood-pressure levels when seated than those

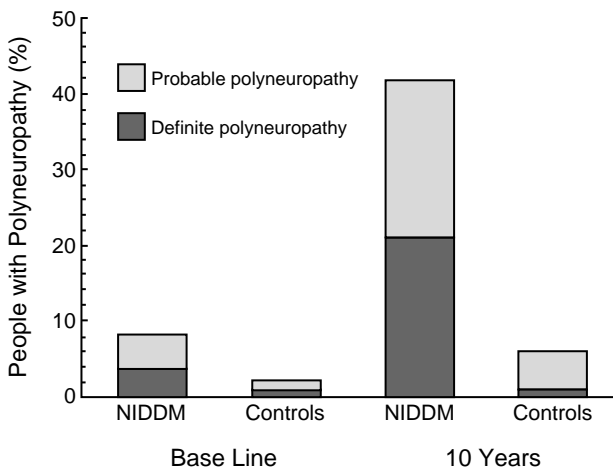


Figure 2. Patients with NIDDM and Control Subjects with Definite or Probable Polyneuropathy at Base Line and after 10 Years.  $P = 0.057$  for the comparison between the groups at base line; at 10 years,  $P \leq 0.001$  — both by the chi-square test.

Table 4. Serum Insulin and C-Peptide Values in Patients with NIDDM in Whom Definite or Probable Polyneuropathy Had Developed by the 10-Year Examination and in Those without Polyneuropathy.

INDEX*	NO POLYNEUROPATHY	POLYNEUROPATHY	P VALUE†
	(N = 50)	(N = 36)	
<i>mean <math>\pm</math> SD</i>			
<b>Base line</b>			
Serum insulin (mU/liter)			
Fasting	27 $\pm$ 17	18 $\pm$ 10	0.001
After glucose administration‡	73 $\pm$ 55	48 $\pm$ 39	0.009
<b>10 Years</b>			
Serum insulin (mU/liter)§			
Fasting	16 $\pm$ 8	16 $\pm$ 7	0.98
After glucose administration‡	39 $\pm$ 23	27 $\pm$ 18	0.023
Serum C peptide (ng/ml)			
Fasting	1.93 $\pm$ 0.94	2.05 $\pm$ 1.03	0.57
After glucose administration‡	4.71 $\pm$ 1.78	3.63 $\pm$ 1.33	0.01

\*To convert insulin values to picomoles per liter, multiply by 6; to convert C-peptide values to nanomoles per liter, multiply by 0.331.

†By two-tailed t-test.

‡Two hours after the oral administration of 75 g of glucose.

§Not measured in patients receiving insulin therapy.

without polyneuropathy ( $135 \pm 15$  vs.  $147 \pm 20$  mm Hg,  $P = 0.003$ , for systolic blood pressure; and  $81 \pm 7$  vs.  $86 \pm 11$  mm Hg for diastolic blood pressure,  $P = 0.013$ ). There were no significant differences in base-line serum lipid values, urinary albumin excretion, or antihypertensive drug therapy between the patients who had polyneuropathy at the 10-year examination and those who did not.

The mean fasting blood or plasma glucose concentrations at base line, 5 years, and 10 years were higher in the patients in whom polyneuropathy developed during the 10-year follow-up period than in those in whom polyneuropathy did not develop ( $223 \pm 23$  vs.  $204 \pm 50$  mg per deciliter [ $12.4 \pm 1.3$  vs.  $11.3 \pm 2.8$  mmol per liter],  $P = 0.002$ ). Accordingly, the mean values for glycosylated hemoglobin at the 5- and 10-year examinations tended to be higher in the group with polyneuropathy ( $9.6 \pm 1.8$  percent vs.  $8.9 \pm 1.8$  percent,  $P = 0.09$ ). At base line, both fasting serum insulin concentrations and concentrations after the administration of glucose were lower in the group in whom polyneuropathy subsequently developed. The serum insulin and C-peptide concentrations in these two groups of patients after the administration of glucose were also different at the 10-year examination (Table 4). The areas under the serum insulin curve at all three examinations were lower for the patients in whom polyneuropathy developed, even after we adjusted for the simultaneous fasting blood or plasma glucose values (or glycosylated hemoglobin, measured at the 5-year and 10-year examinations) ( $P = 0.03$ ). We explored the combined effects of poor glycemic control and low serum insulin concentrations in a variety of multivariate analyses. There was insufficient information to allow us to determine the separate contributions of glycemic control and serum insulin concentrations to the occurrence of polyneuropathy (Fig. 3). The decreases in response amplitudes and nerve conduction velocities during the follow-up period were consistently correlated significantly with

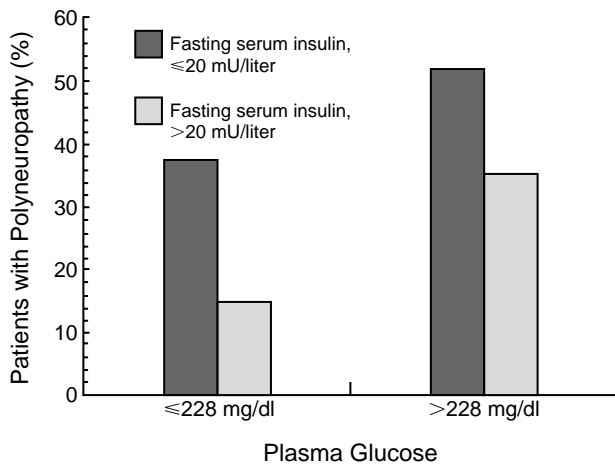


Figure 3. Prevalence of Polyneuropathy after 10 Years of Follow-up in Patients with NIDDM, According to the Mean Fasting Plasma Glucose Concentration and the Base-Line Fasting Serum Insulin Concentration.

In this analysis, we used the mean of the glucose concentrations measured at base line, 5 years, and 10 years. The median glucose value was used as the cutoff point. The prevalence of polyneuropathy was highest in the group with high fasting plasma glucose and low fasting serum insulin concentrations (52 percent). To convert glucose values to millimoles per liter, multiply by 0.0555; to convert insulin values to picomoles per liter, multiply by 6.

both poor glycemic control and low serum insulin values (data not shown).

## DISCUSSION

We examined the occurrence of clinical polyneuropathy and electrophysiologic changes in nerve function during 10 years of follow-up of patients with newly diagnosed NIDDM. The prevalence of polyneuropathy at the time of diagnosis (8.3 percent) was similar to that reported by Pirart,<sup>1</sup> Ratzmann et al.,<sup>11</sup> and Mincu.<sup>12</sup> We found a markedly higher frequency of polyneuropathy at 5 and 10 years in the patients with NIDDM than in the control subjects, suggesting a cumulative effect of neuropathic factors with time.

There is now strong evidence that good glycemic control can prevent the appearance and worsening of polyneuropathy in patients with insulin-dependent diabetes mellitus.<sup>13</sup> Our findings in patients with NIDDM suggest that glycemic control is also important in these patients, but direct proof can be obtained only from controlled intervention studies. Axonal damage in the patients with NIDDM, indicated by decreasing sensory-amplitude values during the 10-year follow-up period, was also related to glycemic control. Moreover, poor glycemic control was associated with increased mortality from cardiovascular diseases in this cohort,<sup>6</sup> a fact that may lessen the value of hyperglycemia in predicting the development of neuropathy.

Early metabolic abnormalities in the nerves of diabetic patients are thought to be due to the direct exposure of nerve tissue or its vascular bed to high concentrations of glucose.<sup>14,15</sup> Hyperglycemia may increase the activity of the polyol pathway, resulting in the ac-

cumulation of sorbitol and fructose and a decrease in  $\text{Na}^+/\text{K}^+-\text{ATPase}$  activity.<sup>16</sup> There is also loss of myelinated fibers,<sup>17</sup> and demyelination may occur.<sup>18</sup> Our results suggest that axonal degeneration is the main cause of diabetic polyneuropathy, because reduction of the amplitudes of the sensory and motor responses, reflecting axonal damage, was a more prominent feature than slowing of nerve conduction velocities, an indicator of demyelination.

In addition to poor metabolic control, the patients with NIDDM in whom polyneuropathy developed had lower serum insulin values at base line and lower serum insulin values after the ingestion of glucose at the 10-year examination. Although patients with poor glycemic control also had lower serum insulin responses to glucose,<sup>19</sup> low serum insulin values were a predictor of polyneuropathy. This novel finding is supported by experimental studies that demonstrate that insulin or C peptide may have direct effects on nerve-tissue metabolism or function.<sup>14,20</sup>

Our results indicate that it is possible to use clinical and electrodiagnostic criteria to diagnose polyneuropathy in patients with NIDDM. The finding that both low serum insulin concentrations and hyperglycemia were related to the risk of diabetic neuropathy suggests that early insulin therapy for patients with NIDDM who have diminished insulin secretion may have neuroprotective effects.

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