The Prevalence of Symptomatic, Diabetic Neuropathy in an Insulin-treated Population

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The prevalence of symptomatic sensorimotor polyneuropathy has been determined in a population of 382 insulin-treated diabetic subjects aged 15–59 yr. Forty-one subjects (10.7%) were found to have diabetic neuropathy, according to strict diagnostic criteria that required the presence of symptoms and signs of nerve dysfunction in the absence of peripheral vascular disease. There was a significant correlation between glycosylated hemoglobin levels and motor conduction velocity in the median and peroneal nerves in all subjects. This finding further emphasizes the importance of metabolic factors related to hyperglycemia in the impaired nerve function seen in diabetic patients. DIABETES CARE 1985; 8:125–28.

Although peripheral neuropathy is a common long-term complication of diabetes,[1] it is impossible to estimate its prevalence in the population because of a general lack of agreement as to what constitutes diabetic neuropathy.[2] Goodman et al.[3] considered pain and paresthesia in the extremities as sufficient evidence to diagnose neuropathy, and quoted a prevalence rate of 62% among the 261 patients in their series. The importance of abnormal signs in addition to symptoms was recognized by Fry et al.,[4] who considered that 13% of their diabetic patients had peripheral neuropathy. Bruyn and Garland[5] reviewed the literature on this subject, and showed that the frequency of neuropathy varied from 0% to 93%. Many of these studies included patients with peripheral vascular disease and, as vascular and neuropathic symptoms can be difficult to distinguish,[6,7] they have probably overestimated the prevalence of neuropathy. Furthermore, Mayne[8] has shown that symptoms and signs indistinguishable from those of diabetic neuropathy are common in the elderly, nondiabetic population. Thus the need for strict diagnostic criteria for any study of this complication is apparent.

Symmetrical sensory polyneuropathy, the most common of the diabetic neuropathies,[2] is considered to have a metabolic cause,[9,10] and Porte et al.[9] have recently demonstrated an inverse correlation between motor nerve conduction velocities (MCV) and glycosylated hemoglobin levels in non-insulin-dependent diabetic people. Although significant improvements in MCV have been reported in diabetic people treated by continuous subcutaneous insulin infusion (CSII),[11,12] no such correlation between glycosylated hemoglobin and MCV has been demonstrated in insulin-treated adults.

The aims of the present study were, therefore, to determine the prevalence of symptomatic sensory polyneuropathy in an insulin-treated population, and to investigate the relationship of nerve function abnormalities to metabolic parameters in insulin-treated diabetic subjects.

PATIENTS AND METHODS

Three hundred eighty-seven insulin-treated diabetic patients, aged 16–59 yr, attending our diabetes clinic during 10 mo in 1982, were approached to participate in the study. This study was part of a larger project that investigated the feasibility of CSII as an outpatient treatment in a large clinic.[13] (This clinic is one of three National Health Service units attended by the majority of insulin-treated diabetic people living in Sheffield.) Patients who were undergoing renal dialysis, had had a lower limb amputation, or had received insulin for <6 mo were excluded. Three hundred eighty-two subjects (195 men, 187 women) agreed to participate. There were 354 (92.7%) type I diabetic patients (history of ketosis and requirement for insulin <2 yr after developing diabetic symptoms) and 28 (7.3%) type II subjects. Three patients were being treated with phenytoin for epilepsy and two were receiving other anti-epileptic therapy. No patients were treated with isoniazid and none had a history of drug dependence. No patients had a family history of hereditary neuropathic disorders.

Patients were from across the broad spectrum of age range, mean 34.8 yr (12% aged 16–19 yr; 28.2%, 20–29 yr; 22.8%, 30–39 yr; 20.2%, 40–49 yr; and 16.8%, 50–59 yr), and all socioeconomic groups were represented (22.3% profes-

sional and business, 48.8% white-collar and highly skilled manual workers, and 29.9% semi-skilled or unskilled manual).

All measurements of neurophysiologic function were recorded at one visit. The senior physician (J.D.W.) performed fundal assessment of all patients by ophthalmoscopy with dilated pupils. Fundal grading was according to WHO criteria.[14]

Criteria for diagnosis of neuropathy. All subjects who satisfied the following strict criteria were considered to have symptomatic peripheral neuropathy: (1) painful symptoms (paresthesia, burning pains with nocturnal exacerbation, hyperesthesia) for ≥1 yr before study, or a past history of such symptoms together with neuropathic foot ulceration; (2) no history of alcohol abuse, normal biochemical tests of liver function (serum and glutamyltranspeptidase, alkaline phosphatase, alanine and aspartate transaminases); (3) absent ankle reflexes; (4) palpable foot pulses, ankle pressure index ≥1.0,[15] no symptoms of claudication.

Metabolic investigations. Glycosylated hemoglobin was estimated in venous blood using a modification of the colorimetric technique originally described by Fluckiger and Winterhalter.[16] Details of this semi-automated method, which has an interassay coefficient of variation of 6.4%, have been described elsewhere.[17] Plasma creatinine was measured at the time of study (SMAC, Technicon Instrumentation Corporation, Tarrytown, New York) and urine was tested for protein (Albustix, Ames Division, Slough, England). Patients were considered to have diabetic nephropathy if proteinuria was detected and plasma creatinine was elevated (1.36 mg/dl) in the absence of any other known cause of renal disease.

Investigation of nerve function. After a period of rest, all measurements were performed in a room maintained at 23–25°C. MCVs were measured in the right median and peroneal nerves using a Medelec electrophysiologic system as previously described.[18] The normal range of results seen in the Sheffield nondiabetic population is given in Table 1.

Statistics. All results were recorded and analyzed using a PET microcomputer system (CBM Ltd., New York). The Student *t*-test, Mann-Whitney U-test, and Pearson's correlation were used for statistical analyses. Results are shown as mean ± SEM.

RESULTS

Forty-one of the 382 diabetic subjects studied satisfied our criteria and were diagnosed as having symptomatic diabetic peripheral neuropathy, giving a prevalence of 10.7%. Another 34 patients (8.9%) had absent knee or ankle reflexes in the absence of significant symptoms, and 24 (6.3%) had absent foot pulses. The neuropathic patients were significantly older and had a significantly longer duration of diabetes than the non-neuropathic patients (Table 1). There were also significant differences in both median and peroneal nerve MCV between the neuropathic and non-neuropathic subjects, but not in glycosylated hemoglobin levels. The mean peroneal MCV in the group of asymptomatic patients lacking ankle jerks (39.4 ± 1.07 m/s) was significantly reduced compared with those with preserved reflexes (mean 43.1 ± 0.3 m/s) ($T = 3.34$, 294 d.f., $P < 0.001$) but significantly higher than in the group of symptomatic neuropathic subjects (mean 35.2 ± 0.3 m/s) ($T = 3.77$, 72 d.f., $P < 0.001$). No such significant difference was present for median nerve MCV. There was a significant association between neuropathy and diabetic retinopathy (Table 2). Similarly, a greater proportion of neuropathic subjects had biochemical evidence of diabetic nephropathy ($X^2 = 10.1$, 2 d.f., $P < 0.05$). Correlations were sought between glycosylated hemoglobin and MCV for the combined results of all diabetic subjects. A significant inverse correlation was obtained with both the median nerve (Pearson's $r = 0.35$; $P < 0.01$) and the peroneal nerve ($r = 0.31$; $P < 0.01$). In addition, a significant inverse correlation was shown between both median and peroneal nerve MCV with duration of diabetes (median, $r = 0.14$, $P < 0.01$; peroneal $r = 0.30$, $P < 0.01$).

TABLE 1
Results of investigations in neuropathic and non-neuropathic diabetic subjects

	Symptomatic neuropathy (N = 41)	Non-neuropathic diabetic subjects (N = 341)
Mean age (yr)	44.7* ± 1.4	33.7 ± 0.7
Duration of diabetes (yr)	18.5* ± 1.5	13.3 ± 0.5
GHb (%)	11.9 ± 0.4	11.5 ± 0.1
MCV median (m/s) (normal 59.5 ± 5 m/s)	42.8* ± 0.9	48.1 ± 0.3
MCV peroneal (m/s) (normal 49.8 ± 4 m/s)	35.2* ± 0.3	42.7 ± 0.9

Results are given as mean ± SEM.
*$P < 0.001$.

DISCUSSION

The results of this study showed that the prevalence of symptomatic neuropathy in an insulin-treated population of 382 subjects was 10.7%, although including patients with un-

TABLE 2
Prevalence of retinopathy among neuropathic and non-neuropathic diabetic subjects

+ Grade	0	1	2	3
Symptomatic neuropathy (N = 40)	10	10	9	11
Non-neuropathic diabetic subjects (N = 326)	265	19	27	16

+Key: grade 0 = no retinopathy; grade 1 = background retinopathy (WHO a,b);[14] grade 2 = background retinopathy (WHO c,d,e);[14] grade 3 = proliferative retinopathy (WHO f).[14] $X^2 = 63.6$, 3 d.f. $P < 0.001$.

equivocal signs of neuropathy in the absence of symptoms the prevalence would be at least 19.6%, accounting for those subjects with absent tendon reflexes. The study was restricted to insulin-treated patients <60 yr old for two reasons: first, whereas such patients are regularly seen in our clinic, many older, non-insulin-dependent diabetic subjects are discharged to the care of general practitioners, except those with known complications. Inclusion of such patients would therefore add unacceptable bias to the results. Second, as demonstrated by Mayne,[8] symptoms and signs indistinguishable from those of neuropathy are not uncommon in an aging population, a fact that might also explain the higher prevalence of neuropathy in many previous studies.[5] It is suggested that many earlier references have overestimated the prevalence of significant neuropathy, especially those requiring only minor symptoms for the diagnosis.[3] Additionally, difficulties arising in the differential diagnosis between ischemic and neuropathic symptoms in the leg may have distorted the results of earlier studies.[6,7] Fry et al.[4] remarked that a high proportion of their neuropathic subjects, who showed little recovery despite adequate diabetes control, had peripheral vascular disease; several of these subjects may not have been suffering from peripheral neuropathy. Thus, although neuropathy and peripheral vascular disease may occur in the same subject, those with clinical evidence of vascular disease were not included in the neuropathic group in this study.

Gilliatt[19] argued that only subjects seeking medical advice because of symptoms should be accepted as having neuropathy for clinical purposes. This is in agreement with a recent review by Ward,[7] whose diagnostic criteria formed a basis for selection in the present study.

The higher prevalence of microvascular complications in neuropathic subjects is in agreement with the previous studies of Pirart,[20,21] who also showed an increase in the prevalence of neuropathy with increasing duration of diabetes. Although patients with chronic renal failure frequently have neuropathy, such patients were not included in this study because uremia may be a cause of peripheral neuropathy.[22]

The relationship between metabolic control and neuropathy has been studied for many years[2] and several recent studies also point to the role of poor blood glucose control in the pathogenesis of peripheral nerve dysfunction in both insulin-dependent and non-insulin-dependent diabetic subjects.[23–25] Porte[9] demonstrated an inverse correlation between MCV and metabolic control, as judged by fasting blood glucose or glycosylated hemoglobin in newly diagnosed non-insulin-dependent diabetic subjects. We have now shown a similar inverse correlation in an insulin-treated population. Earlier studies demonstrated improvement in MCV after institution of diabetes treatment, but no correlation could be shown between measures of metabolic control and MCV.[18,26,27] The assessment of metabolic control in many of these studies is now shown to be suspect[28] and the availability of glycosylated hemoglobin measurements facilitates more accurate assessment of long-term control. Furthermore, the studies of Porte et al.[9] were conducted in newly diagnosed patients in whom the potentially reversible alterations in nerve conduction velocities may have been caused by acute metabolic disturbances in nerve function present at the time of diagnosis. However, as recently reviewed by Windebank,[29] not all studies confirm a relationship between metabolic control and measurements of peripheral nerve function. Moreover, electron microscopic studies by Williams et al.[30] confirm that microvascular abnormalities are frequently found in sural nerve biopsies from neuropathic patients, suggesting that mechanisms other than metabolic abnormalities may be important in the pathogenesis of diabetic peripheral neuropathy. Young et al.[31] have recently reported a significant correlation between glycosylated hemoglobin and measures of motor and sensory nerve function in a group of diabetic adolescents. The results demonstrate the importance of metabolic control in the causation of nerve damage in young diabetic subjects and confirm the frequent finding of abnormal electrophysiologic investigations in young patients without clinical manifestations of neuropathy. The results of our study provide evidence in diabetic adults, with and without clinical neuropathy, of the association between metabolic control and electrophysiologic abnormalities. Additionally, the relationship between neuropathy and age and duration of diabetes has been demonstrated. Although no differences in glycosylated hemoglobin levels were found between the two groups of patients, we have previously shown that diabetic subjects with neuropathy have significantly higher glycosylated hemoglobin levels when compared with non-neuropathic diabetic people carefully matched for age, sex, and type and duration of diabetes.[17] The present findings provide further evidence of the relationship between metabolic factors and motor nerve function in insulin-treated patients.

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