

Chapter 15

Neuropathy in Diabetes

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SUMMARY

Population-based studies of neuropathy (inflammation and degeneration of peripheral nerves) in persons with diabetes indicate that neuropathy is a common complication of insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM), with 60%-70% of patients affected. Subclinical neuropathy is much more common than clinical neuropathy. Distal symmetrical polyneuropathy is the most common type of neuropathy, followed by carpal tunnel syndrome, other mononeuropathies, and autonomic

neuropathy. The frequency distribution for neuropathies is similar in IDDM and NIDDM, as are the frequencies of subclinical and clinical distal polyneuropathy and carpal tunnel syndrome. However, severe distal neuropathy is more common in IDDM. Prevalence of neuropathy increases with age, duration of diabetes, and worsening of glucose tolerance. In the Diabetes Control and Complications Trial (DCCT), intensive treatment of diabetes with near-normalization of glycemia reduced by 60% the 5-year incidence of neuropathy in those without neuropathy at study entry.

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INTRODUCTION

When the first edition of *Diabetes in America* was published, there were insufficient population-based data to warrant a chapter on neuropathy in diabetes. The lack of epidemiologic data as of mid-1980 has been reviewed¹. Most information available at the time was from clinic- and hospital-based studies, with prevalence of neuropathy ranging from 5%-80%². Fortunately, this situation has improved and population-based studies are now available.

In 1988 a joint conference of the American Diabetes Association and the American Academy of Neurology adopted standardized nomenclature and criteria for diagnosis of neuropathy in diabetes³ (Table 15.1). This classification recognizes subclinical and clinical neuropathy. Subclinical neuropathy is defined by an abnormal electrodiagnostic test, quantitative sensory threshold, or autonomic function test in the absence of clinical signs and symptoms. Clinical neuropathy is defined as symptoms and signs together, or as symptoms or signs alone plus abnormal test results. Standardized definitions, diagnostic criteria, and validated measures have been used in population-based studies of the epidemiology of neuropathy in diabetes and form the basis of this chapter.

NEUROPATHY COMPLICATIONS IN DIABETES

The most common neuropathy affecting individuals with diabetes is diffuse somatic neuropathy of the distal symmetric sensorimotor type (Table 15.1). Patients most often have a mixed sensorimotor defect and may experience pain, paresthesia, hyperesthesia, dysesthesia, proprioceptive defect, loss of sensation, and muscle weakness and atrophy⁴. Autonomic nerve function is often impaired^{5,6} and occasionally a particular nerve fiber is predominantly affected. Small nerve fiber injury leads to painful neuropathy with preservation of large myelinated fiber function. Deep tendon reflexes, vibration sense threshold, and proprioception are preserved. Neuropathy affecting predominantly the large nerve fibers leads to motor and proprioceptive dysfunction. This form of neuropathy resembles the neuropathy seen in tabes dorsalis and is termed "pseudotabes" form of diabetic neuropathy. Charcot joint disease of the ankle is also a complication of this form of neuropathy, and sensation may be preserved. Neuropathic ulceration is a complication of distal neuropathy that occurs predominantly in individuals with loss of protective sensation. The preferred criteria for diagnosis of distal symmetrical polyneuropathy are abnormalities in two

Table 15.1
Classification and Staging of Diabetic Neuropathy

Subclinical Neuropathy

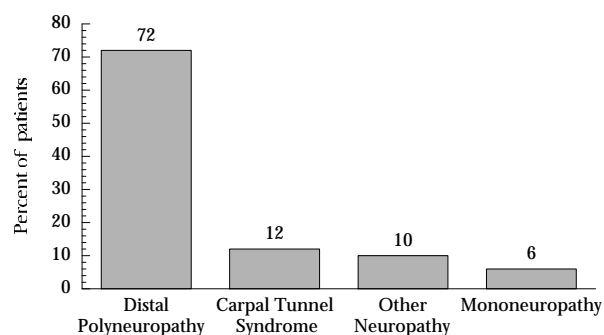
- Abnormal Electrodiagnostic Tests
 - Decreased nerve conduction velocity
 - Decreased amplitude of evoked muscle or nerve action potential
- Abnormal Quantitative Sensory Threshold
 - Vibratory/tactile
 - Thermal warming/cooling
 - Other
- Abnormal Autonomic Function Tests
 - Abnormal cardiovascular reflexes
 - Altered cardiovascular reflexes
 - Abnormal biochemical responses to hypoglycemia

Clinical Neuropathy

- Diffuse Somatic Neuropathy
 - Distal Symmetric Sensorimotor Polyneuropathy
 - Primarily small-fiber neuropathy
 - Primarily large-fiber neuropathy
 - Mixed
- Autonomic Neuropathy
 - Cardiovascular autonomic neuropathy
 - Abnormal pupillary dilatation
 - Gastrointestinal autonomic neuropathy
 - Gastroparesis
 - Constipation
 - Diabetic diarrhea
 - Anorectal incontinence
 - Genitourinary autonomic neuropathy
 - Bladder dysfunction
 - Sexual dysfunction
 - Hypoglycemia unawareness/unresponsiveness
 - Sudomotor dysfunction
- Focal Neuropathy
 - Mononeuropathy
 - Mononeuropathy multiplex
 - Amyotrophy

Source: Adapted from References 2 and 3

Figure 15.1
Frequency Distribution of Neuropathy in the Rochester Diabetes Project, 1945-70



Source: Reference 1

oped neuropathy⁹. However, the retrospective nature of the study may have resulted in ascertainment bias. Distal polyneuropathy was the most common diagnosis, followed by carpal tunnel syndrome, other neuropathy, and mononeuropathy (Figure 15.1). The prevalence of polyneuropathy increased from 4% for diabetes of short duration (<5 years) to 15% after 20 years of diabetes. Half the patients who developed neuropathy developed it within 9 years of diagnosis of diabetes. Distal polyneuropathy and mononeuropathy were more common in patients with poor glycemic control (24%) than in those with good control (10%).

THE ROCHESTER DIABETIC NEUROPATHY STUDY

The Rochester Diabetic Neuropathy Study (RDNS) is a population-based cross-sectional survey and longitudinal follow-up study of diabetic neuropathy in Rochester, MN¹⁰. It uses "quantitative, validated, and unique end points to detect, classify, and stage neuropathy"¹⁰. Diagnostic criteria for neuropathy have been described in detail⁸. This study is complementary to the earlier Rochester Diabetes Project and provides information on all forms of neuropathy, including distal polyneuropathy, proximal symmetric neuropathy, autonomic neuropathy, truncal radiculopathy, cranial neuropathy, and carpal tunnel syndrome.

The RDNS identified all patients with diabetes in Rochester, MN on January 1, 1986. The prevalence (age- and sex-adjusted to the 1990 U.S. Census population) of diabetes was 1.6%¹¹. Type of diabetes was classified by C-peptide levels after glucagon challenge¹⁰. Forty-three percent (380/870) of the patients with diabetes in the population underwent detailed

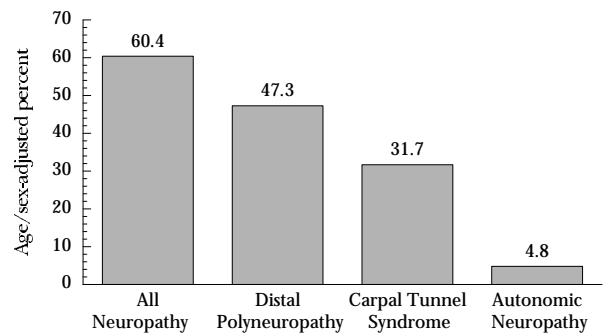
of three areas: symptoms, signs, and quantitative sensory tests or electrodiagnostic studies^{3,7,8}.

Other neuropathies are less common than the distal symmetrical type. Occasionally a single nerve or nerve trunk is damaged, leading to pain and motor dysfunction that is usually reversible. Compression neuropathies such as carpal tunnel syndrome are common in diabetes. Autonomic neuropathy usually occurs in the setting of generalized neuropathy and is diffuse. Dysfunction is seen in autonomic fibers in cranial, visceral, and somatic nerves.

THE ROCHESTER DIABETES PROJECT

The Rochester Diabetes Project was the first community-based study of neuropathy in a U.S. population. Patients with NIDDM diagnosed during 1945-70 in Rochester, MN were studied⁹. Based on medical records, 3% of patients had neuropathy at the time diabetes was diagnosed, and 10% subsequently devel-

Figure 15.2
Prevalence of Neuropathy in the Rochester Diabetic Neuropathy Study, 1986



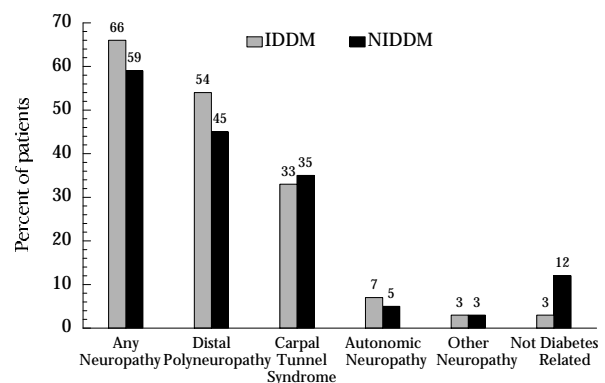
Prevalence figures are age- and sex-adjusted to the Rochester, MN population.

Source: Reference 11

study for neuropathy. Nonparticipants were older, less educated, more likely to be widowed or retired, and had more macrovascular disease¹². However, the prevalence of retinopathy, nephropathy, and neuropathy was similar in respondents and nonrespondents, and the study results are applicable to all diabetic patients in Rochester with respect to these complications¹².

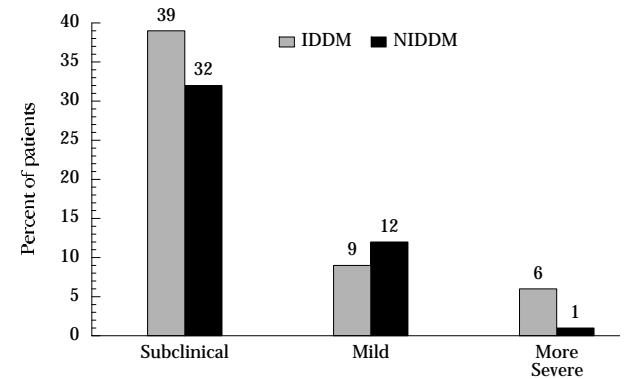
Of the 380 subjects undergoing detailed study, 102 (26.8%) had IDDM and 278 (73.2%) had NIDDM. Almost all participants were white. The prevalence rates for neuropathy (age- and sex-adjusted to the Rochester, MN population) are shown in Figure 15.2. The prevalence of distal polyneuropathy was greatest, followed by carpal tunnel syndrome and autonomic neuropathy. The prevalence of any neuropathy was 66% for IDDM and 59% for NIDDM (Figure 15.3).

Figure 15.3
Prevalence of Neuropathy in the Rochester Diabetic Neuropathy Study, 1986



Source: Reference 11

Figure 15.4
Severity of Distal Polyneuropathy in the Rochester Diabetic Neuropathy Study, 1986

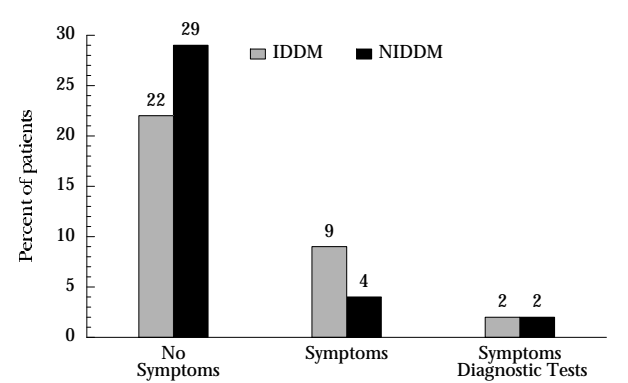


Source: Reference 11

The frequency distribution by type of neuropathy was similar for IDDM and NIDDM (Figure 15.3). Severity of distal neuropathy was also similar for IDDM and NIDDM (Figure 15.4). Subclinical neuropathy occurred in 39% of those with IDDM and in 32% of those with NIDDM. Symptomatic distal polyneuropathy (mild and more severe) occurred in 15% of IDDM and 13% of NIDDM. Only the more severe form of polyneuropathy occurred more commonly in IDDM (6% of IDDM versus 1% of NIDDM, $p < 0.02$) (Figure 15.4)¹¹.

Asymptomatic carpal tunnel syndrome occurred in 22% of those with IDDM and 29% of those with NIDDM (Figure 15.5). The distribution of symptomatic carpal tunnel syndrome was similar in IDDM and NIDDM, occurring in 11% of IDDM and 6% of NIDDM (Figure 15.5). Electrophysiologic evidence of

Figure 15.5
Severity of Carpal Tunnel Syndrome in the Rochester Diabetic Neuropathy Study, 1986



Source: Reference 11

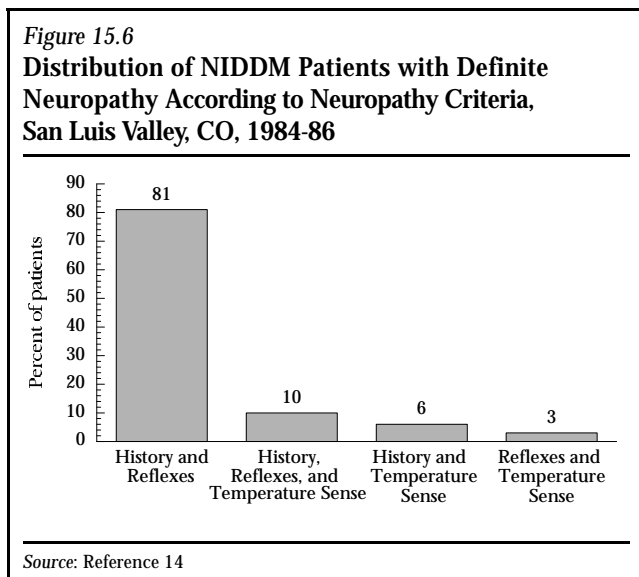
carpal tunnel syndrome correlated significantly with polyneuropathy.

Autonomic neuropathy was the least common form of neuropathy. Age- and sex-adjusted prevalence was 4.8% (confidence interval (CI) 2.7-6.9). Of those with autonomic neuropathy, impotence in men was the most common problem, occurring in 13% of IDDM and 8% of NIDDM. Gastroparesis, night diarrhea, urinary incontinence, and postural fainting occurred in 0%-1% of those with IDDM and NIDDM.

Cranial mononeuropathy and truncal polyneuropathy were not observed. Mononeuropathy multiplex (proximal symmetric polyneuropathy) occurred in 1% of those with IDDM and 1% of those with NIDDM. Ulnar neuropathy and femoral cutaneous neuropathy (meralgia paresthetica) occurred in 2% and 1% of those with IDDM and NIDDM, respectively¹¹.

THE SAN LUIS VALLEY STUDY

The San Luis Valley Study is a geographically based case-control study of NIDDM that used modern diagnostic criteria and validated measures to ascertain distal symmetrical polyneuropathy in 1984-86¹³⁻¹⁵. The survey sample was the entire population of patients with NIDDM in Alamosa and Conejos counties in southern Colorado. Patients were considered to have definite neuropathy if two of three criteria were present: bilateral symptoms of neuropathy, bilateral absent or decreased ankle jerk reflexes, and bilateral absent or altered cold perception. Neuropathy was independently confirmed by measuring vibration perception threshold. Of all patients, 27.8% had definite neuropathy; 97% of these had a history of neuropathy



symptoms. Only 3% had no history of symptoms (Figure 15.6). In these latter patients, diagnosis was based on abnormal reflexes and temperature sense and altered vibration threshold. Among those with definite neuropathy, a history of symptoms was accompanied by abnormal tendon reflexes (81%), abnormal reflexes and temperature sense (10%), or abnormal temperature sense alone (6%) (Figure 15.6).

Patients with only symptoms or only one sign were classified as having possible neuropathy. Of these individuals, 69% had symptoms only, 29% reflex changes, and 3% abnormal sensation¹⁴. Symptoms were qualitatively the same in patients with definite and possible neuropathy with respect to quality, location, and timing of symptoms. The only difference between the two groups was that a higher proportion of patients with definite neuropathy had symptoms daily (49%), compared with patients with possible neuropathy (29%).

The prevalence of distal symmetrical neuropathy was associated with age and glucose tolerance status (Figure 15.7). Among patients with diabetes, the prevalence was lowest in those age 20-44 years (10.3%) and highest in those age 65-74 years (32.3%). Age-adjusted prevalence was 3.9% for subjects with normal glucose tolerance, 11.2% for those with impaired glucose tolerance (IGT), and 25.8% in those with diabetes¹⁴.

Analysis of the data for risk factors for neuropathy in those with diabetes in the study showed that neuropathy was more common in males than in females (34% versus 20.6%). Neuropathy was signifi-

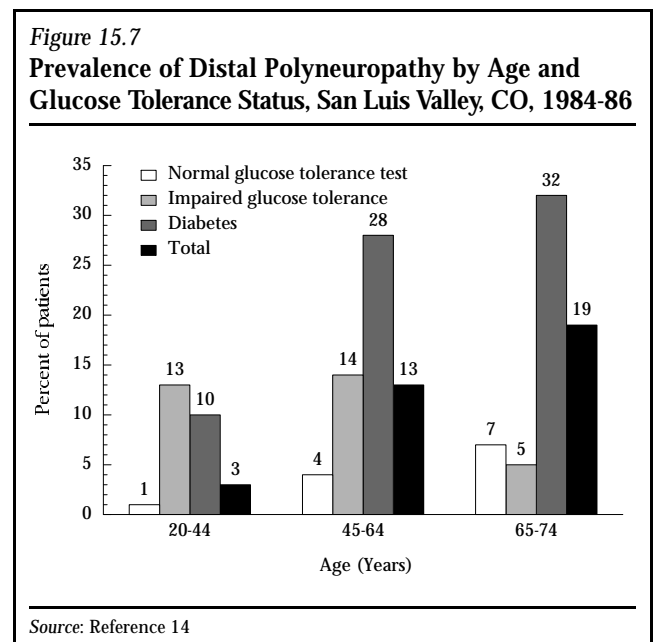
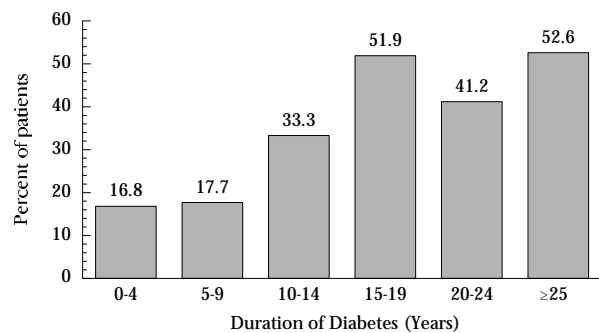


Figure 15.8
Prevalence of Distal Polyneuropathy by Duration of NIDDM, San Luis Valley, CO, 1984-86



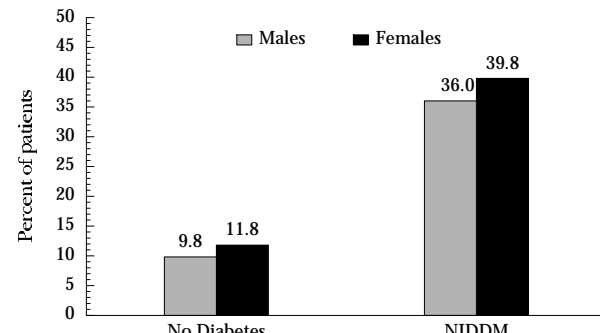
Source: Reference 14

cantly related to duration of diabetes, increasing from 16.8% in those with duration of diabetes ≤ 4 years to 52.6% in those with diabetes ≥ 25 years (Figure 15.8). After adjusting for age and duration of diabetes, there was no effect of ethnic background on prevalence of neuropathy, which was present in 30% of Anglos and 26.8% of Hispanics¹⁵. Neuropathy occurred with equal prevalence among those who had never used alcohol and those who had. The effect of quantity of alcohol consumed in those with a history of alcohol use was not examined. Subjects with neuropathy had significantly higher mean hemoglobin A_{1c} than those without neuropathy (11.2% versus 10.2%). Hemoglobin A_{1c} was also slightly higher in subjects with IGT and neuropathy than in subjects with normal glucose tolerance (7.5% versus 7.2%).

1989 NATIONAL HEALTH INTERVIEW SURVEY (NHIS)

The 1989 NHIS was a population-based structured interview of 84,572 persons age ≥ 18 years¹⁶. In this sample, 2,405 subjects had a physician diagnosis of diabetes, of whom 99.3% answered the questionnaire. A comparison group of 20,037 subjects without a history of diabetes also answered the questionnaire. The questionnaire sought information about sensory symptoms and altered touch and temperature perception affecting the hands and feet. The NHIS was based on symptoms, which would tend to overestimate the prevalence of distal sensorimotor neuropathy. The most sensitive indicator of neuropathy is an abnormality in nerve conduction, followed by abnormal quantitative sensory examination^{8,10}. Sensory symptoms have the lowest predictive value for diabetic neuropathy. On the other hand, a survey based on symptoms might underestimate individuals with

Figure 15.9
Prevalence of Symptoms of Sensory Neuropathy by Sex and Diabetes Status, Age ≥ 18 Years, U.S., 1989



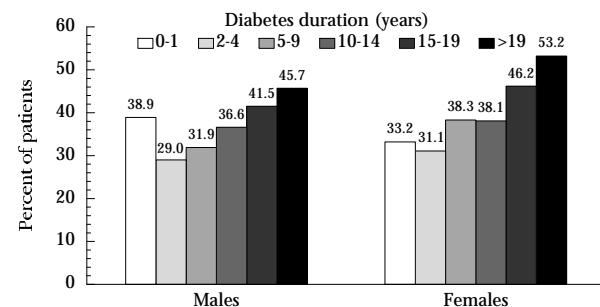
Data are based on interview information obtained in the 1989 National Health Interview Survey.

Source: Reference 17

autonomic neuropathy, focal neuropathies, or insensate distal symmetrical neuropathy¹⁷.

The prevalence of neuropathy symptoms was 30.2% for IDDM and 36% and 39.7% for men and women with NIDDM, respectively. The prevalence was significantly greater ($p < 0.001$) in subjects with diabetes when compared with nondiabetic subjects but was not significantly different in men and women (Figure 15.9). In the NHIS, 9.8% of men and 11.8% of women without a history of diabetes gave a history of neuropathy symptoms. The prevalence of symptoms increased with duration of diabetes similarly in men and women (Figure 15.10). Symptoms were significantly greater in Mexican-American and black subjects with duration of diabetes 5-14 years, but not > 15

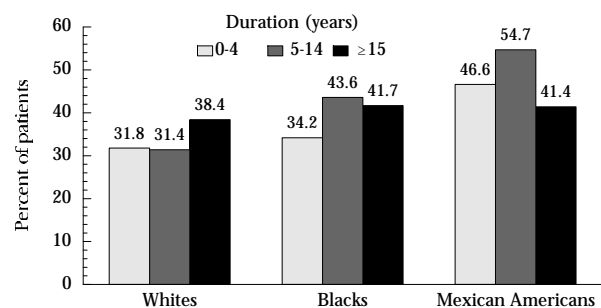
Figure 15.10
Prevalence of Symptoms of Sensory Neuropathy in NIDDM by Sex and Diabetes Duration, Age ≥ 18 Years, U.S., 1989



Data are based on interview information obtained in the 1989 National Health Interview Survey.

Source: Reference 17

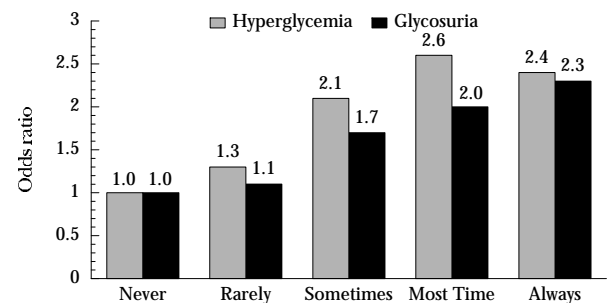
Figure 15.11
Prevalence of Symptoms of Sensory Neuropathy in NIDDM by Race and Diabetes Duration, Age ≥ 18 Years, U.S., 1989



Data are based on interview information obtained in the 1989 National Health Interview Survey.

Source: Reference 17

Figure 15.13
Effects of Hyperglycemia and Glycosuria on the Presence of Sensory Neuropathy in NIDDM, Age ≥ 18 Years, U.S., 1989



Data are based on interview information obtained in the 1989 National Health Interview Survey. Hyperglycemia and glycosuria were self-reported based on results of self blood glucose monitoring and physician's tests for glucose.

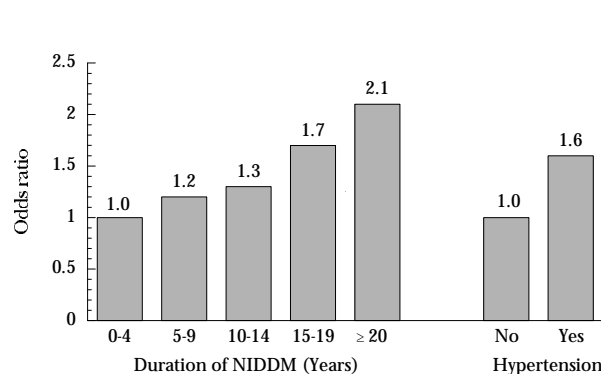
Source: Reference 17

years, and was increased in Mexican Americans with duration of diabetes ≤ 4 years (Figure 15.11). There was a progressive increase in relative risk for symptoms of neuropathy with increasing duration of diabetes, and for a history of hypertension, which was associated with a 60% risk increase (Figure 15.12). The relative risk for symptoms of neuropathy also increased with measures of severity of blood and urine glucose (Figure 15.13).

Comparison of demographic characteristics in subjects with and without neuropathy symptoms showed that absence of symptoms was associated with higher family income ($> \$25,000/\text{year}$) and with lower rates

of retinopathy, nephropathy, proteinuria, macrovascular disease, hypertension, foot and ankle sores, and periodontal disease. Patients with neuropathy were more likely to check their feet $\geq 1/\text{week}$ and to have their feet checked by a health professional, although only 36.8% reported being checked ≥ 2 times in the preceding 6 months. Analysis of the NHIS data by logistic regression showed that duration of diabetes, hypertension, and indices of glycemia were independent risk factors for neuropathy. Ethnicity, age, gender, height, and cigarette smoking were not significant risk factors.

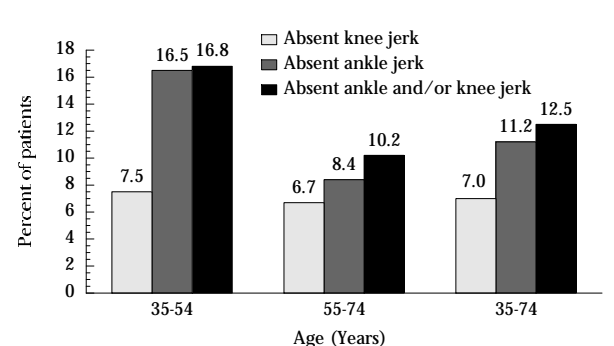
Figure 15.12
Effects of NIDDM Duration and Hypertension on the Presence of Sensory Neuropathy in NIDDM, Age ≥ 18 Years, U.S., 1989



Data are based on interview information obtained in the 1989 National Health Interview Survey.

Source: Reference 17

Figure 15.14
Reflex Changes in Persons with NIDDM, Age 35-74 Years, U.S., 1976-80



Measurements of reflex changes were made during a standardized physician's examination. NIDDM consists of diagnosed NIDDM ascertained through medical history and undiagnosed NIDDM ascertained by oral glucose tolerance test.

Source: Harris MI, National Diabetes Data Group, unpublished data from the 1976-80 National Health and Nutrition Examination Survey

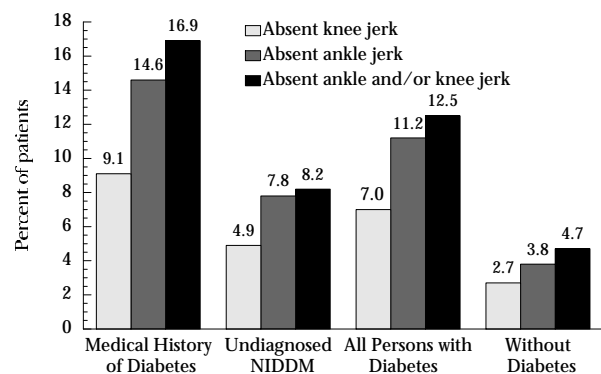
1976-80 NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES II)

Absence of knee and/or ankle jerks was ascertained in the NHANES II¹⁸. Diabetes was ascertained by medical history and oral glucose tolerance test. Among all persons with diabetes age 35-74 years, absence of one or both reflexes was noted in 12.5% and was more common in younger subjects (Figure 15.14). Absence of reflexes was 1.5-2 times more common among those with a medical history of diabetes than those with diabetes detected by glucose tolerance test (Figure 15.15). Reflex changes were two to three times more common in those with diabetes than in persons without diabetes (Figure 15.15).

NATIONAL HOSPITAL DISCHARGE SURVEY

The National Hospital Discharge Survey is a statistical sample of all hospitalizations in the United States¹⁹. Based on this survey, neuropathy was estimated to have been listed as a diagnosis in 547,052 hospitalizations during 1989-91, which represented 6.2% of hospitalizations where diabetes was listed as a diagnosis (Table 15.2). Since the survey counts hospitalizations rather than patients, it is difficult to know the significance of these figures. Ascertainment bias may severely limit the usefulness of these data for assessing the impact of neuropathy on hospitalization rates.

Figure 15.15
Reflex Changes in Persons Age 35-74 Years by Diabetes Status, U.S., 1976-80



Undiagnosed NIDDM detected by oral glucose tolerance test; persons without diabetes were ascertained by medical history and oral glucose tolerance test. Measurements of reflex changes were made during a standardized physician's examination.

Source: Harris MI, National Diabetes Data Group, unpublished data from the 1976-80 National Health and Nutrition Examination Survey

Table 15.2
Hospital Discharges Listing Both Diabetes and Selected Neuropathy Conditions, 1989-91

Condition	ICD9-CM code	Number of discharges	Percent of all diabetes discharges
Polyneuropathy in diabetes	357.2	265,693	3.03
Mononeuritis of lower limb	355	14,801	0.17
Mononeuritis of upper limb	354	15,770	0.18
Neurogenic bladder	344.61	22,529	0.26
Diabetes with neurologic manifestations	250.6	204,443	2.33
Idiopathic peripheral neuropathy	356.8, 356.9	14,504	0.17
Autonomic nervous system disorders	337	9,312	0.11
Total		547,052	6.23

All hospitalizations in which diabetes and the selected neuropathy conditions were listed together on the hospital discharge record are included in the table. Because multiple neuropathy codes can be listed in the same hospitalization record, the data have been analyzed in hierarchical fashion so that, for example, the number of hospitalizations for mononeuritis of lower limb (ICD9-CM 355) does not include any hospitalizations for polyneuropathy in diabetes (ICD9-CM 357.2); the number of hospitalizations for mononeuritis of upper limb (ICD9-CM 354) does not include any hospitalizations in which either polyneuropathy in diabetes or mononeuritis of lower limb are mentioned; etc. ICD9-CM codes for diabetes were 250, 251.3, 357.2, 362.0, 368.41, 648.0, and 775.1. The total number of diabetes hospitalizations during 1989-91 was 8,775,364.

Source: 1989-91 U.S. National Hospital Discharge Surveys

CLINIC, HOSPITAL, COHORT, AND CONVENIENCE SAMPLES

There are numerous reports on neuropathy in the literature based on clinic, hospital, cohort, and convenience samples². Comprehensive review of this literature is beyond the scope of this chapter. However, several studies are unique or have ascertained neuropathy in large random samples using standardized diagnostic criteria and validated methods. These will be discussed.

The Diabetes Control and Complications Trial

Neuropathy prevalence was ascertained in 278 well-characterized patients with IDDM recruited for the feasibility phase of the DCCT⁶. Diagnosis was based on the presence of signs, symptoms (dysesthesia, paresthesia, hyperesthesia, or burning pain), or decreased or absent deep tendon reflexes⁶. The prevalence of clinical neuropathy in the cohort was 39%. Diagnosis was most commonly based on signs (37%), reflex changes (28%), or signs and reflex changes

(18%). Symptoms alone were the basis for diagnosis in only 6%. Patients with neuropathy were older, more often male, had longer duration of diabetes, greater height, and lower stimulated C-peptide levels. Hemoglobin A_{1c} was not significantly different between those with and without neuropathy.

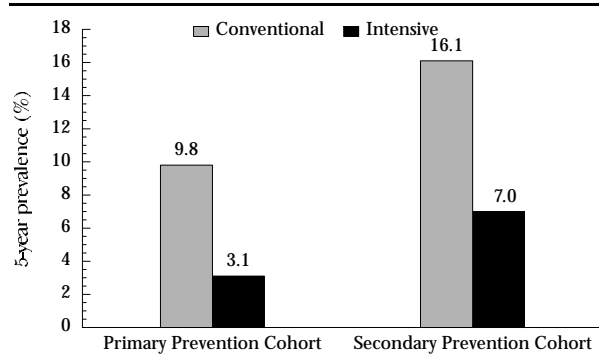
The results of the full DCCT trial have been reported²⁰. Neuropathy was assessed at baseline and after 5 years, and the incidence of neuropathy was reported for patients who did not have neuropathy at study entry. Diagnosis of neuropathy was based on the presence of an abnormal neurological examination confirmed by either abnormal nerve conduction studies in two or more nerves or abnormal autonomic nervous system tests. In the primary prevention cohort, composed of patients who had no vascular complications at study entry, the prevalence of neuropathy at 5 years was 9.8% in the group receiving conventional diabetes treatment and 3.1% in the intensively treated patients (Figure 15.16). In the secondary prevention cohort, composed of patients who had mild to moderate vascular complications at study entry, the 5-year prevalence was 16.1% in the conventional treatment group and 7.0% in the intensive treatment group (Figure 15.16). Thus, intensive treatment of glycemia was associated with 69% (CI 24-87) and 57% (CI 29-73) reductions in the development of neuropathy in the primary and secondary cohorts, respectively²⁰. The risk reduction for the combined cohort was 60% (CI 38-74) (p<0.002). Intensive treatment yielded significant reductions in clinical, nerve conduction, and autonomic nervous system testing

results.

■ The Pittsburgh Epidemiology of Diabetes Complications Study

This is a cohort follow-up study of 628 subjects with IDDM drawn from the Children's Hospital of Pittsburgh (PA) Insulin-Dependent Diabetes Mellitus Registry²¹⁻²³. Analysis of a subset of this population of patients with clinically overt neuropathy has shown that glycemic control, triglyceride concentration, and hypertension are independent risk factors for neuropathy²². In a longitudinal follow-up study of patients with abnormal thresholds for perception of vibration and temperature but without overt neuropathy, reevaluation after 2 years showed limited predictive value of these quantitative measures for development of clinically overt neuropathy²³. Analysis of leisure-time physical activity has shown that neuropathy prevalence is lower in males reporting higher levels of current and historical physical activity²⁴. The effect persisted after controlling for duration

Figure 15.16
Effect of Diabetes Treatment on the Prevalence of Clinical Neuropathy at 5 Years in Subjects Without Neuropathy at Study Entry, DCCT, 1993



DCCT, Diabetes Control and Complications Trial. Neuropathy was defined by abnormal neurologic examination that was consistent with either abnormal nerve conduction in at least two peripheral nerves or unequivocally abnormal autonomic nerve testing; p<0.001, intensive versus conventional treatment groups, for both cohorts.

Source: Reference 20

Table 15.3
Symptoms of Autonomic Neuropathy in 168 Patients with IDDM

	No.	% Prevalence
Postural hypotension		
Orthostatic dizziness	7	4
Fainting on standing	0	
Gastroparesis		
Dysphagia	3	2
Anorexia	5	3
Nausea	11	7
Vomiting	4	2
Vague fullness after meals	6	4
Diabetic diarrhea		
Nocturnal diarrhea	0	
Fecal incontinence	2	1
>20 bowel movements/day	0	
Colonic atony		
<2 bowel movements/week	2	1
<1 bowel movement/3days	4	2
Genitourinary		
Impotence	8	5
Retrograde ejaculation	1	1
Urinary bladder		
Overflow incontinence	0	
Dribbling	1	1
Incomplete emptying	10	6
Increased urine volume	4	2
Decreased frequency	13	8
Sudomotor abnormality		
Diminished sweating of legs	2	1
Feeling of increased sweating elsewhere	7	4
Hypoglycemia unawareness		
Reduced awareness of hypoglycemia	43	26

Source: Adapted from Reference 26

of diabetes in univariate analyses. Historical physical activity remained a significant predictor of neuropathy in multivariate analysis. A trend was seen in the same direction for females but was not statistically significant, perhaps because of the relatively low level of physical activity in the women studied²⁴.

In another report on the Pittsburgh cohort, patients with diabetes of ≥ 25 years duration were evaluated; 19% were found to be free of any complications of diabetes²⁵. The prevalence of neuropathy was 50% in those with diabetes for 25-29 years and 72% in those with diabetes for >30 years. Health behavior variables (recent medical contact, better control of dyslipidemia and blood pressure, regular glucose monitoring, lower glycosylated hemoglobin, physical activity in youth, and regular consumption (at least weekly) of alcohol) were more prevalent in subjects without complications. Using logistic regression, glycosylated hemoglobin level was the only independent predictor of complications after adjusting for health behavior variables²⁵.

■ Autonomic Neuropathy

Autonomic neuropathy was ascertained in a cohort of 168 subjects age 25-34 participating in the Pittsburgh

Epidemiology of Diabetes Complications Study²⁶. Heart rate response to deep breathing, standing, and Valsalva were measured by two techniques. These were an office-based method and the methods used in the DCCT. Data were analyzed in the DCCT's central reading lab for autonomic tests. The methods gave comparable results, and the prevalence of symptoms of autonomic neuropathy was low (Table 15.3). Modeling by logistic regression showed that female gender, presence of hypertension, and low- and high-density cholesterol were independent predictors of heart rate variation during deep breathing.

■ Miscellaneous Studies

In other studies, height has been shown to correlate strongly with absent vibration sense^{27,28}. A clinic-based case-control study has also identified smoking (current and ex-smokers) as a risk factor for distal neuropathy in IDDM but not NIDDM²⁹.

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REFERENCES

1. Melton JL III, Dyck PJ: Clinical features of the diabetic neuropathies. In *Diabetic Neuropathy*. Dyck PJ, Thomas PK, Asbury AK, Winegrad AI, Porte D Jr, Eds. Philadelphia, W.B. Saunders, 1987, p. 27-35
2. Vinik AI, Holland MT, Le Beau JM, Liuzzi FJ, Stansberry KB, Colen LB: Diabetic neuropathies. *Diabetes Care* 15:1926-75, 1992
3. American Diabetes Association, American Academy of Neurology: Consensus statement: Report and recommendations of the San Antonio conference on diabetic neuropathy. *Diabetes Care* 11:592-97, 1988
4. Brown MJ, Asbury AK: Diabetic Neuropathy. *Ann Neurol* 15:2-12, 1984
5. Pfeifer MA, Weinberg CR, Cook DL, Reenan A, Halar E, Halter JB, LaCava EC, Porte D: Correlations among autonomic, sensory, and motor neural function tests in untreated non-insulin-dependent diabetic individuals. *Diabetes Care* 8:576-84, 1985
6. The DCCT Research Group: Factors in development of diabetic neuropathy. *Diabetes* 37:476-81, 1988
7. Dyck PJ, Karnes JL, Daube J, O'Brien P, Service FJ: Clinical and neuropathological criteria for the diagnosis and staging of diabetic polyneuropathy. *Brain* 108:861-80, 1985
8. Dyck PJ: Evaluation procedures to detect, characterize, and assess the severity of diabetic neuropathy. *Diabet Med* 8:S48-S51, 1991
9. Palumbo PJ, Elveback LR, Whisnant JP: Neurologic complications of diabetes mellitus: Transient ischemic attack, stroke, and peripheral neuropathy. *Adv Neurol* 19:593-601, 1978
10. Dyck PJ, Kratz KM, Lehman KA, Karnes JL, Melton III LJ, O'Brien PC, Litchy WJ, Windebank AJ, Smith BE, Low PA, Service FJ, Rizza RA, Zimmerman BR: The Rochester Diabetic Neuropathy Study. *Neurology* 41:799-807, 1991
11. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, Wilson DM, O'Brien PC, Melton III LJ, Service FJ: The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: The Rochester Diabetic Neuropathy Study. *Neurology* 43:817-24, 1993
12. Melton LJ, Ochi JW, Palumbo PJ, Chu C-P: Sources of disparity in the spectrum of diabetes mellitus at incidence and prevalence. *Diabetes* 6:427-31, 1983
13. Hamman RF, Marshall JA, Baxter J, Kahn LB, Mayer EJ, Orleans M, Murphy JR, Lezotte DC: Methods and prevalence of non-insulin-dependent diabetes mellitus in a biethnic Colorado population. *Am J Epidemiol* 129:295-311, 1989
14. Franklin GM, Kahn LB, Baxter J, Marshall JA, Hamman RF: Sensory neuropathy in non-insulin-dependent diabetes mellitus: The San Luis Valley Diabetes Study. *Am J Epidemiol* 131:633-43, 1990
15. Hamman RF, Franklin GA, Mayer EJ, Marshall SM, Marshall JA, Baxter J, Kahn LB: Microvascular complications of NIDDM in Hispanics and non-Hispanic whites. San Luis Valley Diabetes Study. *Diabetes Care* 14:655-64, 1991
16. National Center for Health Statistics: *Current estimates from the National Health Interview Survey, 1989*. *Vital and Health Statistics Series 10*, No. 176, 1990
17. Harris MH, Eastman R, Cowie C: Symptoms of neuropathy in adults with NIDDM in the U.S. population. *Diabetes Care* 16:1446-52, 1993
18. National Center for Health Statistics: *Plan and operation of the Second National Health and Nutrition Examination Survey. Vital and Health Statistics, Series 1*, No. 15. Washington, DC, U.S. Govt. Printing Office, 1981 (DHHS publ. no. PHS 81-1317)
19. National Center for Health Statistics: *National Hospital Discharge Survey. Annual Summary Vital and Health Statistics, Series 13*, No. 109, 112. 1991
20. The Diabetes Control and Complications Trial Research Group: The effect of intensive diabetes treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus: The Diabetes Control and Complications Trial. *N Engl J Med* 329:977-86, 1993
21. Maser RE, Steenkiste AR, Dorman JS, Nielsen VK, Bass EB, Manjoo Q, Drash AL, Becker DJ, Kuller LH, Greene DA, Orchard TJ: Epidemiological correlates of diabetic neuropathy. *Diabetes* 38:1456-61, 1989
22. Maser RE, Nielsen VK, Dorman JS, Drash AL, Becker DJ, Orchard TJ: Measuring subclinical neuropathy: Does it relate to clinical neuropathy? Pittsburgh epidemiology of diabetes complications study-V [published erratum appears in *J Diabetes Complications* 1991;5:205]. *J Diabetes Complications* 5:6-12, 1991
23. Maser RE, Becker DJ, Drash AL, Ellis D, Kuller LH, Greene DA, Orchard TJ: Pittsburgh Epidemiology of Diabetes Complications Study. Measuring diabetic neuropathy follow-up study results. *Diabetes Care* 15:525-27, 1992
24. Kriska AM, LaPorte RE, Patrick SL, Kuller LH, Orchard TJ: The association of physical activity and diabetic complications in individuals with insulin-dependent diabetes mellitus: The Epidemiology of Diabetes Complications Study—VII. *J Clin Epidemiol* 44:1207-14, 1991
25. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Ellis D, LaPorte RE, Kuller LH, Wolfson SK Jr, Drash AL: Factors associated with avoidance of severe complications after 25 yr of IDDM. Pittsburgh Epidemiology of Diabetes Complications Study I. *Diabetes Care* 13:741-47, 1990
26. Maser RE, Pfeifer MA, Dorman JS, Kuller LH, Becker DJ, Orchard TJ: Diabetic autonomic neuropathy and cardiovascular risk. Pittsburgh Epidemiology of Diabetes Complications Study III. *Arch Intern Med* 150:1218-22, 1990
27. Sosenko JM, Gadia MT, Fournier AM, O'Connell MT, Aguiar MC, Skyler JS: Body stature as a risk factor for diabetic sensory neuropathy. *Am J Med* 80:1031-34, 1986
28. Gadia MT, Natori N, Ramos LB, Ayyar DR, Skyler JS, Sosenko JM: Influence of height on quantitative sensory, nerve-conduction, and clinical indices of diabetic peripheral neuropathy. *Diabetes Care* 10:613-16, 1987
29. Mitchell BD, Hawthorne BD, Hawthorne VM, Vinik AI: Cigarette smoking and neuropathy in diabetic patients. *Diabetes Care* 13:434-37, 1990