

# Prevalence of Neuropathy in IDDM Patients in Piemonte, Italy

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**OBJECTIVE**— In view of the scarce data available in Italy, to assess the prevalence of neuropathy in various subgroups of IDDM patients living in the Piemonte region of Italy and to develop, based on existing guidelines, and test the practicality of a standardized assessment of diabetic neuropathy.

**RESEARCH DESIGN AND METHODS**— All IDDM patients (766) attending 23 outpatient clinics, evenly distributed in the region, were stratified into 3 age-groups (15–29, 30–44, and 45–59 yr) and into 3 groups of diabetes duration (1–7, 8–14, and  $\geq 15$  yr). A random sample of 467 patients was selected; 81% of whom participated in the studies (196 men and 183 women). The following data were collected: personal and clinical data, structured questionnaire (SQ), neurological examination (NE), vibration sensation (tuning fork) (VS), and two cardiovascular tests (CTs). Patients were classified as follows: stage 0, (no neuropathy)  $< 2$  abnormalities among SQ, NE, VS, and CT; stage 1, (asymptomatic neuropathy)  $> 1$  abnormality among NE, VS, and CT; stage 2, (symptomatic neuropathy) abnormalities in SQ and in NE, and/or VS, and/or CT.

**RESULTS**— The prevalence rates were as follows: stage 0 = 71.5%, stage 1 = 7.2%, and stage 2 = 21.3% and all had a 95% CI. No difference was found between men and women. The prevalence of neuropathy (stages 1 and 2) was higher ( $P < 0.01$ ) in groups of longer diabetes duration or older age.

**CONCLUSIONS**— Polyneuropathy is a frequent complication in a north Italian IDDM population. Our results suggest that IDDM patients  $> 30$  yr of age, with diabetes of  $> 15$  yr duration, and who complain of symptoms suggestive of neuropathy, should be promptly assessed for the presence of diabetic polyneuropathy.

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IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; SQ, STRUCTURED QUESTIONNAIRE; NE, NEUROLOGICAL EXAMINATION; VS, VIBRATION SENSATION; CT, CARDIOVASCULAR TEST; CI, CONFIDENCE INTERVAL; DBT, DEEP BREATHING TEST; PBPT, POSTURAL BLOOD PRESSURE TEST.

The reported prevalence of diabetic neuropathy varies from 5 to 100% (1–5). This discordance may depend on the different criteria used to diagnose and classify neuropathy and on the fact that, to our knowledge, all published studies deal separately with either somatic or autonomic neuropathy. Furthermore, because the prevalence of neuropathy may be influenced by age (6), diabetes duration (7), and type of diabetes (8), IDDM and NIDDM should be considered separately, and a control group of nondiabetic subjects should be used to obtain a correct estimate of the prevalence of neuropathy.

The panel of the San Antonio Consensus Conference on Diabetic Neuropathy focused on diabetic polyneuropathy and published recommendations on the assessment and classification of this complication (9). The panel also stated that large-scale epidemiological studies are lacking and should be encouraged. The aims of this study were to assess the prevalence and severity of neuropathy in IDDM patients living in Piemonte, which is in northwest Italy, and the practicality of a screening procedure.

## RESEARCH DESIGN AND METHODS

Study group participants are listed in the APPENDIX. All IDDM patients (766) between 15 and 59 yr of age attending 22 outpatient clinics, evenly distributed in the Piemonte region, were stratified into 3 age-groups (15–29, 30–44, and 45–59 yr), 3 groups of diabetes duration (1–7, 8–14, and  $\geq 15$  yr), and by sex, for a total of 14 groups (Table 1). Diagnostic criteria for IDDM were diagnosis before 31 yr of age and continuous insulin therapy, except for the first year.

In Italy, virtually all IDDM patients are referred to the nearest diabetic clinic because this is the only way to obtain insulin, syringes, and home monitoring devices free of charge. Hence, the population examined can be taken as representative of the IDDM patients in the community.

Table 1—Calculated sample size by sex, age, and diabetes duration with classes definition

DIABETES DURATION (YR)	MEN/AGE-GROUPS (N = 27 FOR EACH)			WOMEN/AGE-GROUPS (N = 27 FOR EACH)		
	15–29 YR	30–44 YR	45–59 YR	15–29 YR	30–44 YR	45–59 YR
1–7	CLASS A	CLASS D		CLASS H	CLASS M	
8–14	CLASS B	CLASS E		CLASS I	CLASS N	
≥15	CLASS C	CLASS F	CLASS G	CLASS L	CLASS O	CLASS P

A total of 378 subjects: 189 men, 189 women.

For the study to reach sufficient statistical power, 27 patients were required for each group (189 men and 189 women) (Table 1). The sample size was calculated by estimating a 20% prevalence of neuropathy, by accepting a 15% error between the prevalence in the sample and the prevalence in the whole population, and with a 95% CI.

A random sample (60%, 467 patients), stratified by age and duration of diabetes, was selected from the clinics' files (Table 2). A group of 117 normal, nondiabetic subjects (59 men and 58 women), distributed in identical age-groups, were examined for the definition of normal ranges. The results obtained

from these subjects were used as reference values. The following data were collected from patients and control subjects (Table 3):

1. Personal and clinical data: history, current medication, alcohol consumption, smoking habits, and hypoglycemic treatment.
2. Structured questionnaire (SQ): a true-false designed questionnaire was used. The 15 questions were phrased to elicit symptoms related to peripheral motor function (4 questions), sensory function (4 questions), autonomic function (3 questions), and impotence (4 questions, only for men). Each positive answer received a score of 1, and each of the four sections was considered separately. The questionnaire was designed according to the suggestions of Dyck (10). As

the 95th percentile symptom score values were higher for women than for men, symptoms were judged present if the score was >1 in at least one section of the questionnaire for men and >2 for women.

3. Neurological examination (NE): ankle and knee reflexes (graded present or absent) and neuropathic ulcers (graded absent or present, if past or actual ulcers were noted) were evaluated (9). NE was considered abnormal if one of the reflexes was absent or ulcers were present.
4. Vibration sensation (VS): this was assessed with a 128-Hz tuning fork on the right big toe and the lateral malleolus. On each site, the sensation was recorded as absent or present (11). VS was considered altered if absent at one or more sites.
5. Cardiovascular tests (CTs): two

Table 2—Eligible, randomized, and sampled IDDM patients by class

CLASS	ELIGIBLE	RANDOMIZED	SAMPLED
A	133	41	41
B	64	37	31
C	19	19	15
D	32	32	23
E	57	38	30
F	65	40	31
G	53	37	25
H	86	38	33
I	64	37	34
L	24	24	20
M	16	16	14
N	40	35	27
O	61	38	30
P	52	37	25
TOTAL	766	467	379 (81% OF RANDOMIZED)

Table 3—Data vehicles collected from sampled IDDM patients and normal control subjects

AUTONOMIC NEUROPATHY	SOMATIC NEUROPATHY
STRUCTURED QUESTIONNAIRE	STRUCTURED QUESTIONNAIRE
AUTONOMIC SYMPTOMS	MUSCLE WEAKNESS
IMPOTENCE	SENSATION
—	NEUROLOGICAL EXAMINATION
	KNEE AND ANKLE REFLEXES
	NEUROPATHIC ULCERS
	VIBRATION SENSATION
	(TUNING FORK)
CARDIOVASCULAR TESTS	
DEEP BREATHING TEST	
POSTURAL HYPOTENSION	

**Table 4—Dyck staging of diabetic polyneuropathy modified for epidemiological purposes (electrophysiological studies not performed)**

DYCK STAGE	NEUROPATHY STATUS	DEFINITION
STAGE 0	NO NEUROPATHY	<2 ABNORMALITIES AMONG SQ, NE, VS, AND CT
STAGE 1	ASYMPTOMATIC NEUROPATHY	>1 ABNORMALITY AMONG NE, VS, AND CT
STAGE 2	SYMPTOMATIC NEUROPATHY	ABNORMALITIES IN SQ AND NE, AND/OR VS, AND/OR CT

tests were performed and evaluated as described previously (12); a deep breathing test (DBT)—the heart rate response to deep breathing at 6 cycles/min; and a postural blood pressure test (PBPT)—the blood pressure response to standing up. Reading of the electrocardiographic strips and evaluation of the tests were performed by two independent examiners. CTs were graded as normal or abnormal: DBT was considered abnormal if the mean expiratory inspiratory difference was <15 beats/min in the 15–29 yr age-group, <11 beats/min in the 30–44 yr age-group, and <10 beats/min in the 45–59 yr age-group; PBPT was considered abnormal if the fall in systolic arterial pressure was >30 mmHg.

Patients were classified according to the system of Dyck (10) as shown in Table 4. The staging was modified following the recommendation of the San Antonio Conference (9): electrodiagnostic studies were not included because of the nature of the epidemiological study.

An 8-h training program was run for all the operators participating in the study to standardize the collection of the data and the performance of the examinations and tests. The  $\chi^2$  test was used for statistical analysis.

**RESULTS**— A total of 196 men and 183 women (81% of the random sample) participated in the study. Table 2 shows the distribution of the patient sample in the 14 groups.

Of the 88 patients who did not participate, 72 (81.8%) could not be lo-

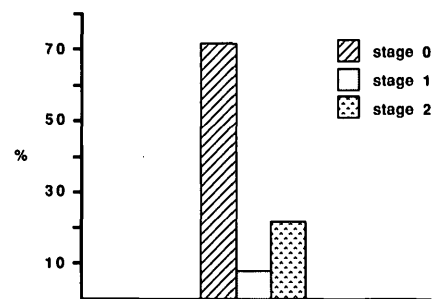
cated, 10 (11.3%) refused, and 6 (6.9%) had diseases that could have interfered with the evaluation. These missing patients were older and had longer duration of diabetes than the population sampled.

The prevalence of symptoms suggestive of neuropathy is shown in Table 5. The prevalence rates were: stage 0 = 71.5% (95% CI 67.5–75.5%), stage 1 = 7.2% (95% CI 5.9–8.5%), and stage 2 = 21.3% (95% CI 17.2–25.4%) (Fig. 1).

No difference was found between men and women (Fig. 2, Table 6). A significant, higher prevalence of neuropathy was observed in the older age-groups ( $P < 0.01$ ) (Fig. 3) and in those with longer diabetes duration ( $P < 0.01$ ) (Fig. 4, Table 6).

**CONCLUSIONS**— The reported prevalence of diabetic neuropathy ranges from 5 to 100% (5) depending on the different minimal diagnostic criteria and procedures used. As a consequence, the magnitude of this complication of diabetes as a health problem remains unclear (3).

To our knowledge, this is the first large epidemiological study that reports



**Figure 1—Prevalence of neuropathy (modified Dyck staging) in IDDM patients living in Piemonte, Italy.**

on the prevalence of diabetic somatic and autonomic neuropathy considered as a single entity.

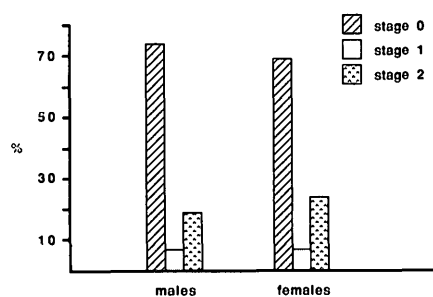
The prevalence of neuropathy in a representative sample of IDDM patients living in Piemonte, Italy, stratified by age and diabetes duration was 28.5%.

It is difficult to compare the prevalence rates found in this study with data reported in the literature because the latter refer separately to either somatic (2,3,8,13–16) or autonomic (6,17–26) neuropathy, and, as stated earlier, different evaluation procedures were used. In particular, higher prevalences are reported from those studies that performed electrophysiological measurements (3).

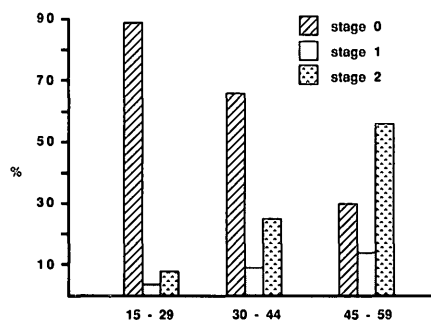
In this study, we observed a higher prevalence of neuropathy in older age-groups and in those with longer diabetes duration. These data are in agreement with the reported direct relation between age and prevalence of somatic (8,13–15) or autonomic neuropathy (6,7,27–29) and between diabetes dura-

**Table 5—Prevalence (%) of symptoms suggestive of neuropathy in IDDM patients by sex**

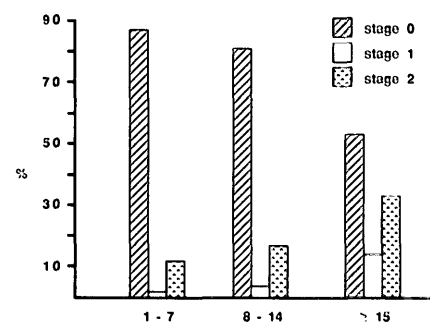
SEX	SYMPTOMS			
	MUSCLE WEAKNESS	SENSATION	AUTONOMIC	IMPOTENCE
MEN (N = 196)	20.9	13.7	6.6	7.1
WOMEN (N = 183)	27.3	20.2	4.9	—



**Figure 2**—Prevalence of neuropathy (modified Dyck staging) by sex in IDDM patients living in Piemonte, Italy.



**Figure 3**—Prevalence of neuropathy (modified Dyck staging) by age in IDDM patients living in Piemonte, Italy.



**Figure 4**—Prevalence of neuropathy (modified Dyck staging) by diabetes duration in IDDM patients living in Piemonte, Italy.

tion and prevalence of somatic (15,16, 30) or autonomic neuropathy (6,12,21, 22,24,31,32).

No difference was observed in the prevalence of neuropathy between men and women: note that different criteria were used to define symptomatic neuropathy in men and women because the female normal population showed higher scores in the symptom scales. This is in agreement with the data reported by Dyck (10).

Subclinical (asymptomatic) neurological impairment was less common than symptomatic neuropathy, possibly attributable to the staging method proposed by Dyck (10). In fact, to enhance the specificity of the diagnosis, patients were not considered neuropathic if only

one test was abnormal among NE, VS, or CT. On the other hand, at the stage when  $\geq 2$  assessments are abnormal, the symptoms are frequently well established.

Two major caveats should be taken into account when analyzing the data. First, the 88 randomized patients who did not participate in the study (mainly because it was not possible to trace them) were significantly older, and their diabetes was of longer duration than in those who did. It is not possible to ascertain if the prevalence rates would have changed if all the patients had been examined. Presumably, they might have been higher. Second, only 19 IDDM patients in class C (Table 2), 16 in class M, and 24 in class L were eligible. For these

classes, and for classes D, G, and P, the tested sample size did not meet the requirements (27 patients for each group). Therefore, this study has the power to permit conclusions regarding prevalence rates in the whole population but less so in the case of age or diabetes duration, for which only a trend can be identified.

In conclusion, this study demonstrates that standardized methods for the screening of diabetic polyneuropathy can be applied effectively even during routine outpatient visits. It shows also that polyneuropathy, both symptomatic (21.3%) and asymptomatic (7.2%), is a frequent complication of diabetes mellitus in a north Italian IDDM population. Because a trend toward higher preva-

**Table 6**—Prevalence rates of neuropathy and 95% CIs in IDDM patients by age, duration of diabetes, and sex

	STAGE 0		STAGE 1		STAGE 2	
	PREVALENCE (%)	95% CI	PREVALENCE (%)	95% CI	PREVALENCE (%)	95% CI
AGE (yr)						
14-29	88.5	83.8-93.2	3.8	1.0-6.6	8.0	4.0-12.0
30-44	65.8	58.3-73.3	9.0	4.5-13.5	25.1	18.3-31.9
45-59	30.0	17.3-42.7	14.0	6.2-21.8	56.0	52.3-59.7
DURATION OF DIABETES (yr)						
1-7	86.4	80.0-92.8	1.9	0.0-4.4	11.7	5.7-17.7
8-14	80.3	73.2-87.4	3.3	0.2-6.4	16.4	9.8-23.0
≥15	52.7	44.6-60.8	14.5	8.8-20.2	32.8	25.2-40.4
SEX						
MEN	73.9	67.8-80.0	7.1	3.5-10.7	18.8	16.0-21.6
WOMEN	68.8	66.0-71.6	7.1	5.2-9.0	24.1	22.3-25.9

lence was observed with increasing age and duration of diabetes, it suggests that patients >30 yr old and with diabetes duration longer than 15 yr should be thoroughly assessed for diabetic polyneuropathy as soon as this becomes symptomatic.

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**APPENDIX**—THE NEUROPATHY STUDY GROUP OF THE ITALIAN SOCIETY FOR THE STUDY OF DIABETES, PIEMONTE AFFILIATE

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