# THE EPIDEMIOLOGY OF DIABETIC NEUROPATHY

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**Abstract**

*One of the major complications of diabetes mellitus (DM) is represented by the diabetic neuropathy (DN). Different peripheral nerves may be affected through many pathological processes and, therefore, there are many types of diabetic neuropathy: distal symmetric polyneuropathy, autonomic polyneuropathy, nerve entrapment syndromes, proximal asymmetric mononeuropathy, truncal radiculopathy, cranial mononeuropathy, cronic inflammatory demyelinating polyradiculopathy. Several studies focused on the incidence and prevalence of distal polyneuropathy and cardiac autonomic neuropathy. The results differed because of the criteria for the definition of the specific terms, type of DM, duration of DM, glycemic control. Other case–control and prospective studies demonstrated a higher risk of foot ulcer in association with sensory lower limb neuropathy as measured with the 5.07 monofilament or the biothesiometer. Although the studies did not evaluate the difference between the prevalence of neuropathy between the two types of DM, it can be speculated that tight control may have a greater effect on reducing incidence of diabetic neuropathy in type 1 DM compared with type 2 DM. There is evidence that subjects with impaired glucose tolerance are at risk for the development of neuropathy. Other studies are requested in order to bring light in the field of diabetic neuropathy and its pathogenesis. It is possible that in the future all this work will lead to methods for preventing this complication of DM.*

***key words****: diabetic polyneuropathy, autonomic neuropathy, diabetic amyotrophy, chronic inflammatory demylinating polyradiculopathy*

## Introduction

The diabetic neuropathy (DN) represents one of the major complications of diabetes mellitus (DM). It is associated with debilitating symptoms and therefore it is associated with higher risk for other complications, in particular those involving the lower extremity [1]. The epidemiology of diabetic neuropathy is not completely understood, when compared with other complications of diabetes including retinopathy and nephropathy. Different peripheral nerves may be affected through many pathological processes and, therefore, there are many types of DN [1]:

– Distal symmetric polyneuropathy;
– Autonomic polyneuropathy;
– Nerve entrapment syndromes;
– Proximal asymmetric mononeuropathy;

– Truncal radiculopathy;
– Cranial mononeuropathy;
– Cronic inflammatory demyelinating polyradiculopathy.

In the study of the epidemiology of diabetic neuropathy, some problems may occur. One problem may be the measurement error in the assessment of the presence or the absence of the neuropathy. Nerve conduction velocity is the most accurate method for the diagnosis of this complication but, it can also result in misclassification. Sometimes, nerve conduction velocity may be normal in diabetic subjects with distal polyneuropathy [2].

**Distal symmetric polyneuropathy – prevalence and risk factors**

The first community-based study of neuropathy was the Rochester Diabetes Study. The subjects with non-insulin dependent diabetes mellitus (NIDDM) from Rochester, USA, diagnosed during 1945 and 1970 were included in the study [3]. The neuropathy was defined if two criteria were satisfied [4]: abnormal nerve conduction in more than one nerve or abnormal test of autonomic function (low heart rate variation in response to breathing or the Valsalva maneuver) and neuropathic symptom or sign or abnormal quantitative sensory testing.

According to the medical records, 3% of the subjects had neuropathy when diabetes was diagnosed and 10% developed neuropathy subsequently [3]. The most common diagnosis was distal polyneuropathy followed by carpal tunnel syndrome other neuropathy and mononeuropathy. The presence of polyneuropathy increased from 4% for diabetes of short duration (less then 5 years) to 15% after 20 years of diabetes [3]. Distal polyneuropathy and mononeuropathy were common in subjects with poor glycemic control (24%) compared to those with good glycemic control (only 10%).

The Rochester Diabetic Neuropathy Study (RDNS) was a population-based cross-sectional survey and longitudinal follow-up study of diabetic neuropathy in Rochester; it was complementary the earlier Rochester Diabetes Study and it provided information on all forms of neuropathy. It used "quantitative, validated, and unique end points to detect, classify, and stage neuropathy" [4]. The RDNS identified all persons with diabetes in Rochester, Minnesota, USA on January 1$^{st}$ 1986. Type of diabetes was classified by C-peptide levels after glucagons challenge. Median duration of diabetes was 14.5 years for subjects with type 1 diabetes and 8.1 years for subjects with type 2 diabetes. Although the prevalence of neuropathy was high, most subjects with neuropathy were asymptomatic (about 71%). From all of the subjects with DM (870) only 370 (43%) underwent detailed study for neuropathy. 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. The frequency distribution by type of neuropathy was similar for IDDM and NIDDM. Severity of distal neuropathy was also similar for IDDM and NIDDM. 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 1) [5].

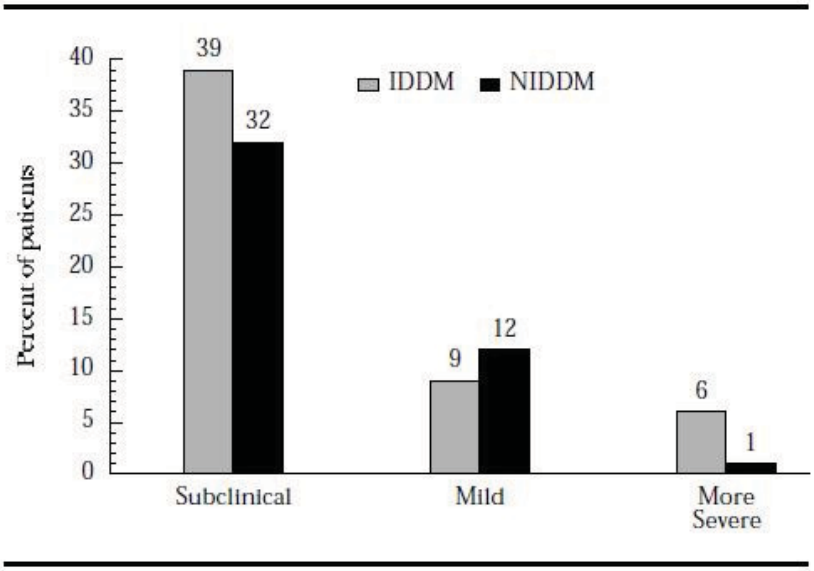


**Figure 1. Severity of distal polyneuropathy in the Rochester Diabetic Neuropathy Study, 1986 (adapted after [5])**

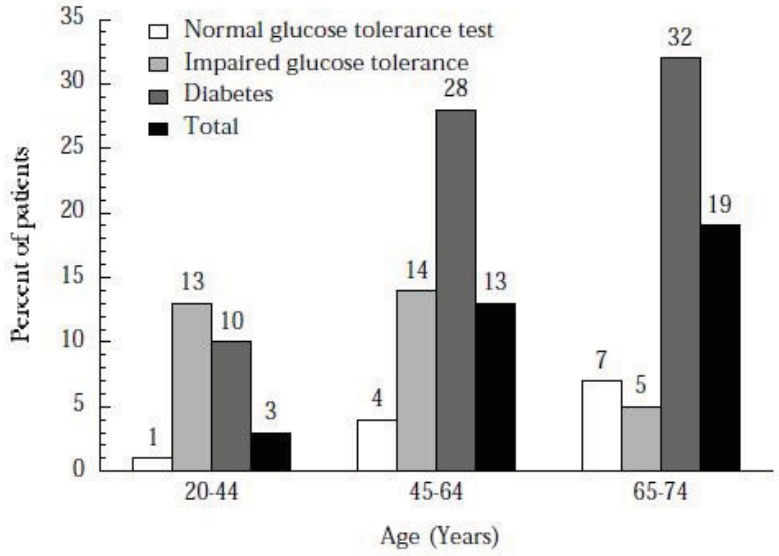


**Figure 2. The prevalence of distal polyneuropathy by age and glucose tolerance status, San Luis Valley Study, 1984-86 (adapted from [6])**

The San Luis Valley Study is a geographically based study that used modern diagnostic criteria and validated measures to assess distal symmetrical polyneuropathy. The subjects were the entire population with type 2 DM in Alamosa and Conejos counties in southern Colorado in 1984-86 [6]. The patients had neuropathy if two of the following criteria were met: 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. In

subjects with definite neuropathy, a history of symptoms was associated with abnormal tendon reflexes (81%), abnormal reflexes and temperature sense (10%), or abnormal temperature sense alone (6%) [6]. Significantly higher prevalence of neuropathy was found in relation to greater age, diabetes duration, hemoglobin A1c, male gender and insulin use. Factors not associated with neuropathy prevalence included blood pressure, height, smoking, previous alcohol use, ankle-arm index, and serum cholesterol, lipid, and lipoprotein levels [1].

The prevalence of distal symmetrical neuropathy was associated with age and glucose tolerance status. Among subjects 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 DM (Figure 2).

The risk factors for neuropathy were evaluated in subjects with diabetes. DN was more common in men than in women (34% vs 20.6%). Also, DN was significantly associated with the duration of diabetes increasing from 16.8% in those with duration of diabetes ≤4 years to 52.6% in those with diabetes ≥25 years. After adjusting for age and duration of diabetes, there was no effect of ethnic background on prevalence of DN. The prevalence of DN was equal 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 A1c than those without neuropathy (11.2% vs 10.2%) [6].

The 1989 National Health Interview Survey (NHIS) was a population-based structured interview of 84,572 persons age >18 years. 2,405 of the subjects had a physician diagnosis of diabetes. A comparison group of 20,037 subjects without a history of diabetes who answered the questionnaire was used. The questionnaire sought information about sensory symptoms and altered touch and temperature perception affecting the hands and feet [7]. As a remark, the NHIS was based only on symptoms, which would tend to overestimate the prevalence of distal sensorimotor neuropathy.

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. In the NHIS, 9.8% of men and 11.8% of women without a history of diabetes had a history of neuropathy symptoms. The prevalence of symptoms increased with duration of diabetes similarly in men and women. The relative risk for symptoms of neuropathy increased with higher blood and urine glucose levels. The NHIS data were analyzed using logistic regression. The results 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 [7].

The National Health and Nutrition Examination Survey (NHANES II) took place in 1976-80 [8]. Diabetes was assessed 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. 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. Reflex changes were 2-3 times more common in those with diabetes than in persons without diabetes.

The Pittsburgh epidemiology of diabetes complications study included 363 subjects with type 1 diabetes more than 18 years of age in a defined community (Allegheny County, PA). Two of three of the following criteria had to be satisfied to fulfill the definition of neuropathy: abnormal sensory or motor signs on clinical examination, neuropathic symptoms and abnormal tendon reflexes. Overall neuropathy prevalence was 34% (18% in 19–29 years old and 58% in those 30 years or older). Higher prevalence of neuropathy was associated with longer diabetes duration, higher glycosylated hemoglobin, lower HDL-cholesterol, smoking, and presence of peripheral vascular, coronary artery, or cerebrovascular disease [9]. Another analysis of the Pittsburgh population explored the association between physical activity and distal symmetric polyneuropathy among 628 subjects with type 1 diabetes between 8 and 48 years of age. Male subjects who reported higher historical levels of leisure time physical activity (adjusted for diabetes duration, age, and current activity levels) had a significantly lower prevalence of neuropathy. No association between historical levels of physical activity and neuropathy prevalence was seen in females [10].

Neuropathy prevalence was ascertained in 278 well characterized patients with type 1 DM, recruited for the feasibility phase of the DCCT (Diabetes Control and Complications Trial). Diagnosis was based on the presence of signs, symptoms (dysesthesia, paresthesia, hyperesthesia, or burning pain), or decreased or absent deep tendon reflexes. The prevalence of clinical neuropathy in this group was 39%. Diagnosis was most commonly based on signs (37%), reflex changes (28%), or signs and reflex changes (18%) [11]. Subjects with neuropathy were older, more often male, had longer duration of diabetes, greater height, and lower stimulated C-peptide levels. Hemoglobin A1c was not significantly different between those with and without neuropathy.

DN was assessed also in the full DCCT. Neuropathy was evaluated at baseline and after 5 years and the incidence of neuropathy was reported only for those 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, with subjects 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. 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. Thus, intensive treatment of DM was associated with 69%

(95%CI=24-87) and 57% (95%CI=29-73) reductions in the development of neuropathy in the primary and secondary cohorts, respectively. The risk reduction for the combined cohort was 60% (95%CI=38-74) ($p<0.002$). Intensive treatment yielded significant reductions in clinical, nerve conduction, and autonomic nervous system testing results [12]. These data demonstrate the crucial role of hyperglycemia in the development of distal symmetric polyneuropathy, but also suggest that neuropathy will continue to develop even in intensively treated subjects exposed to milder degrees of hyperglycemia.

The UK Prospective Diabetes Study examined the association between neuropathy and potential risk factors among newly diagnosed subjects with type 2 diabetes. Neuropathy was defined as absence of both ankle reflexes or both knee reflexes or mean biosthesiometer reading from both great toes of 25 V or greater. A cross-sectional report on 2337 subjects at the onset of the study revealed that 5% of subjects had absent ankle or knee reflexes and 7% had abnormal biosthesiometer readings. Neuropathy was significantly related to the presence of smooth or hairless skin, but unrelated to HbA1c, fasting plasma glucose, smoking, serum lipid and lipoprotein levels, and the albumin: creatinine ratio [13].

The European Diabetes Prospective Complications Study identified risk factors for the development of distal symmetric polyneuropathy in 1172 subjects with type 1 DM in 31 centers throughout Europe. The subjects were evaluated for neuropathy at baseline and again an average of 7.3 years later. Neuropathy was defined if the patient had two or more of the four measures: the presence of one or more symptoms such as numbness or burning in the feet, the absence of two or more reflexes of the ankle or knee tendons, a vibration-perception threshold measured by biothesiometer that was abnormal for the patient's age, and abnormal autonomic function (loss of heart rate variability with an R-R ratio of less than 1.04, postural hypotension with a fall in systolic blood pressure of 20 mmHg or more, or both). At follow-up, 23.5% of the subjects had developed neuropathy. After adjusting for complications of diabetes, which included urinary albumin excretion rate, retinopathy and cardiovascular disease, the risk factors for incident diabetic neuropathy were duration of diabetes in years, current glycosylated hemoglobin, change in glycosylated hemoglobin value during follow-up period, body-mass index and smoking. The presence of cardiovascular disease at baseline was independently associated with a higher incidence of neuropathy [14].

### Prevalence, incidence and risk of autonomic neuropathy

Diabetic autonomic neuropathy was the subject of fewer investigations in comparison with distal symmetric polyneuropathy. The Framingham Heart Study performed a cross-sectional evaluation of the 1919 people from the Framingham Offspring Study who had ambulatory electrocardiographic recordings available. Subjects were categorized according to normal fasting blood glucose (<110mg/dL), impaired fasting blood glucose (>110 and <126mg/dL), or DM (fasting blood glucose >126mg/dL and/or the use of insulin or an oral hypoglycemic agent). Autonomic neuropathy

was defined by a time domain variable, the standard deviation of normal RR intervals and three frequency domain variables [15]. Multivariable regression analysis adjusting for age, sex, body-mass index, heart rate, systolic and diastolic blood pressure, hypertension treatment, cardiac medications, cigarette smoking, and coffee and alcohol consumption was performed. This revealed that heart rate variability was decreased in subjects with diabetes, in comparison with subjects with normal fasting glucose. The subjects with impaired fasting glucose had decreased heart rate variability intermediate between those with diabetes and those with normal fasting glucose.

Autonomic neuropathy was evaluated in 168 subjects with type 1 DM, age between 25 and 34 enrolled in the Pittsburgh Epidemiology of Diabetes Complications Study [16]. Abnormal autonomic function, as measured by the expiratory:inspiratory (E:I) ratio and the mean circular resultant, was associated with female gender, high LDL-cholesterol and hypertension. Moreover, abnormal E:I ratio was related to low HDL-cholesterol, whereas abnormal mean circular resultant was associated with higher serum triglycerides. The authors did not provide definitions for abnormal E:I ratio or mean circular resultant.

DCCT also evaluated autonomic neuropathy. There were mixed results regarding the association between intensive glucose control and 5 years cumulative incidence of autonomic neuropathy defined as R–R variation with breathing less than 15 per minute, Valsalva ratio less than 15 with R–R variation with breathing less than 20 per minute or orthostatic blood pressure drop of 10 mmHg or more with a blunted catecholamine response. Greater R–R variation with breathing was seen with intensive treatment in the primary prevention cohort only at the end of follow-up, whereas Valsalva ratio did not differ by intensive treatment in either cohort [17].

The UK Prospective Diabetes Study evaluated the heart-rate response to deep breathing. There was no difference between the intensive and conventional diabetes treatment groups after 12 years of follow-up. However, the median basal heart rate was 69.8 beats per minute in the intensively treated group in comparison with 74.4 beats per minute in the conventional group ($p < 0.001$) [18].

The Steno-2 Study randomized 160 subjects with type 2 DM with microalbuminuria to conventional treatment or to intensive, multifactorial treatment that targeted hyperglycemia, hypertension, dyslipidemia and microalbuminuria, along with secondary prevention of cardiovascular disease with aspirin. Subjects were followed for a mean of 7.8 years. Autonomic neuropathy was defined as heart rate variation on deep breathing. R–R variation higher than 6 beats per minute was considered normal, 4–6 was considered impaired, and less than 4 to have absent variation. Orthostatic hypotension was defined as a drop in systolic blood pressure of 25 mmHg or more. At baseline, 27% of these subjects with microalbuminuria had autonomic neuropathy. Autonomic neuropathy progressed in 43 subjects (53%) in the conventional treatment group and in 24 subjects (30%) in the intensive-therapy group. The hazard ratio was 0.37 (95% CI 0.18–0.79) [19].

The assessment of risk factors for diabetic autonomic neuropathy is less consistent in comparison with data in the literature available for distal polyneuropathy. The only risk factor reported in more than one study was female gender, found to be associated with higher risk by two authors. The absence of a powerful relationship between glucose control and autonomic neuropathy risk may imply that the course of this complication is set soon after diabetes development and it is not amenable to change thereafter [1].

### Diabetic amyotrophy and mononeuropathies in persons with diabetes

There have been no prospective, population-based studies of diabetic amyotrophy and mononeuropathies in subjects with diabetes. Some prevalence figures for these types of neuropathy can be derived from a few cross-sectional studies. In RDNS, asymptomatic carpal tunnel syndrome (CTS) was found in 22% of those with type 1 DM and 29% of those with type 2 DM, while the corresponding prevalence for symptomatic cases was 11% and 6%, respectively. Ulnar and femoral cutaneous entrapment was found in 2% of type 1 DM and 1% of type 2 DM subjects. Cranial mononeuropathy and truncal radiculopathy were not observed in the Rochester population, but proximal asymmetric polyneuropathy was identified in 1% of type 1 DM and type 2 DM subjects. No incidence data were available for any of these types of neuropathy [5].

In a cross-sectional, hospital-based study, O'Hare et al. studied the presence of various types of neuropathy (by interview assessment) in 800 consecutive subjects with diabetes (336 type 1, 464 type 2) treated in one diabetes center and 100 subjects without diabetes attending an otolaryngology clinic. The prevalence of neuropathy in subjects with diabetes was 22.9%. Less common types included amyotrophy (total prevalence: 0.8%), oculomotor neuropathy (0.1%), peroneal neuropathy (0.1%), and truncal neuropathy (0.1%). Risk factors for neuropathy in type 1 diabetes were age (56.7±15 years in subjects with neuropathy vs 44.9±18 years in those without neuropathy, $p$ <0.001) and duration of diabetes (17±10 years in subjects with neuropathy vs 13±9 years in those without neuropathy, $p$ <0.001). In type 2 diabetes, age was also associated with neuropathy (64.2±9 years in subjects with neuropathy vs 60±12 years in those without neuropathy, $p$ <0.002) [20].

Other studies [21, 22] indicate that blood glucose may be risk factor for CTS. One of the studies presented the results of multivariable analysis (in which diabetes was a significant risk factor with CTS) and stratified analysis using obesity as a stratifying factor. After adjusting for obesity, diabetes was no longer a significant risk factor [21].

### Chronic inflammatory demylinating polyradiculopathy (CIDP) in persons with diabetes

CIDP is a relatively new diagnosis introduced in 1991 by the American Academy of Neurology and it is defined by clinical and electrophysiological criteria [23]. In one study, the prevalence of CIDP was evaluated by neurologist in four Thames health regions in southeast England. The degree of certainty for the diagnosis of CIDP was classified as definite, probable, possible, or suggestive. The

prevalence of definite and probable CIDP in this region was 1/100,000 [24]. Another study took place in a region in Australia. The prevalence of CIDP was 1.9/100,000 and the annual incidence was 0.15/100,000 [25]. One large cross-sectional study assessed the possible association between diabetes and CIDP. From 1127 subjects, 189 subjects (16.8%) had diabetes [26]. The prevalence of CIDP was 16.9% in subjects with diabetes and 1.8% in subjects without diabetes (OR 11.04, 95% CI=6.1–21.8, $p < 0.001$). There was no difference in the prevalence of CIDP in type 1 and type 2 diabetes (26.7% vs 16.1%, $p = 0.49$).

**Neuropathy as a risk factor for diabetic foot ulcer**

A key factor in the pathogenesis of diabetic foot complications is represented by the loss of protective sensation due to advanced neuropathy. Several case–control and prospective studies demonstrated a higher risk of foot ulcer in association with sensory lower limb neuropathy as measured with the 5.07 monofilament or the biothesiometer [1].

One of the studies addressed whether neuropathy and artheriopathy were risk factors for foot ulceration in 46 subjects with diabetes and foot ulcers and 322 control subjects in a general medicine clinic. In multivariable logistic regression analysis, absence of Achilles tendon reflexes (adjusted OR 6.48, 95% CI=2.37–18.06) and abnormal 5.07 monofilament test (adjusted OR 18.42, 95% CI 3.83–88.47) were significant risk factors for foot ulceration [27]. One prospective study evaluated 356 diabetic American Indians with impaired foot sensation to the 5.07 monofilament and it proved that they had a 9.9 fold increase in risk of incident foot ulcer over a mean of 2.7 years of follow-up [28]. In another prospective study, 248 subjects from three large diabetic foot centers were screened for neuropathy, using the Neuropathy Symptom Score, the Neuropathy Disability Score, the biothesiometer, and the 5.07 monofilament [29]. After 30 months, risk factors for foot ulcers were a Neuropathy Disability Score ≥5 (RR=3.1. 95% CI=1.3–7.6), a VPT ≥25 V (RR=3.4, 95% CI=1.7–6.8), abnormal 5.07 monofilament test (RR=2.4, 95% CI=1.1–5.3), and a plantar foot pressure ≥6 kg per $cm^2$ (RR=2.0, 95% CI=1.2–3.3).

The largest prospective cohort study followed 749 subjects with diabetes for an average of 3.7 years [30]. At baseline the subjects underwent a very thorough evaluation of multiple potential risk factors. Independent risk factors for foot ulceration included foot insensitivity to the 5.07 monofilament, past history of amputation, past history of foot ulceration, insulin use, Charcot deformity, 20 kg higher body weight and 13 mmHg orthostatic BP fall [30]. All these studies emphasized the importance of screening for loss of protective sensation in daily clinical practice in order to identify those subjects at risk who require intensive education and other interventions in order to prevent foot ulceration.

Another important issue is which one of the two major types of DM is associated more with neuropathy. There is little data in comparing it. A comparison between different studies is difficult because of the different methods used for defining neuropathy. When considering, for instance, the greatest trials DCCT and UKPDS, it was observed in the

first one that 15–30% of the subjects with type 1 diabetes that were tightly controlled and 40–52% of controls after 5 years follow-up presented abnormal nerve conduction in at least two nerves [17]. In the UKPDS, which studied subjects with type 2 diabetes, after 6 years follow-up, biosthesiometer readings in both toes were abnormal in 19% of intensively treated subjects and in 21% of conventionally treated controls. Although these two studies cannot be compared directly, the striking with which the control subjects in the DCCT developed neuropathy can be observed and one can conclude that tight control may have a greater effect on reducing incidence of diabetic neuropathy in type 1 DM compared with type 2 DM [1] where other factors may be involved.

Other important topic to be discussed is whether IGT represents a risk factor for DN. The San Luis Valley Diabetes Study found a higher prevalence of distal sensory neuropathy among subjects with IGT in comparison with NGT (11.2% vs 3.5%) [6]. This finding was not supported in an other study that compared 51 Swedish subjects with persistent IGT for 12 to 15 years with 62 age-matched nondiabetic controls [31]. However, abnormal heart rate variation with breathing was more common in IGT vs NGT subjects (29% vs 8%, $p$ <0.01), suggesting that IGT may increase the risk of developing autonomic neuropathy. The Framingham Heart Study found that heart rate variability was lower in subjects with impaired fasting glucose, in comparison with subjects with normal fasting glucose, but this result was not statistically significant after adjusting for clinical variables [15]. Whether IGT increases risk of diabetic sensory or autonomic neuropathy cannot be determined from current available data, therefore more research is needed.

**Conclusions**

The study of the epidemiology of ND is just at an earlier stage. Due to different methods for defining neuropathy, there appear different results. There would be considerable advances in this field of research if standardized definitions were developed. These definitions should be easily applicable and not too burdensome for the participants. Identifying methods to predict de development of ND and its risk factors would help the physicians in finding the persons with diabetes that request early treatment for ND. Further studies should focus also on confounding variables such as dyslipidemia, alcohol consumption, obesity and possibly nutritional factors (the beneficial effect of thiamine or thiamine derivates is well known). It is possible that in the future all this work will lead to methods for preventing this complication of DM.

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