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Article:
Tesfaye, S, Boulton, AJM, Dyck, PJ et al. (2010) Diabetic neuropathies : update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care, 33 (10). pp. 2285-2293. ISSN: 0149-5992

https://doi.org/10.2337/dc10-1303

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Diabetic Neuropathies: Update on Definitions, Diagnostic Criteria, Estimation of Severity, and Treatments

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Preceding the joint meeting of the 19th annual Diabetic Neuropathy Study Group of the European Association for the Study of Diabetes (NEURODIAB) and the 8th International Symposium on Diabetic Neuropathy in Toronto, Canada, 13–18 October 2009, expert panels were convened to provide updates on classification, definitions, diagnostic criteria, and treatments of diabetic peripheral neuropathies (DPNs), autonomic neuropathy, painful DPNs, and structural alterations in DPNs.

Diabetes Care 33:2285–2293, 2010

CLASSIFICATION AND DEFINITION OF DIABETIC NEUROPATHIES

— The neuropathies developing in patients with diabetes are known to be heterogenous by their symptoms, pattern of neurologic involvement, course, risk covariates, pathologic alterations, and underlying mechanisms (1,2). Thomas (3) and Boulton et al. (4) separated these into generalized and focal/multifocal varieties (e.g., multiple mononeuropathy, lumbosacral, thoracic, and cervical radiculoplexus neuropathies) (3,4). It is known that similar patterns of neuropathy occur in patients without diabetes (2). Moreover, diabetic patients can develop chronic inflammatory demyelinating polyradiculopathy.

The evidence that generalized varieties can be further classified into at least two major subgroups seems compelling (3,4). The typical DPN is a chronic, symmetrical, length-dependent sensorimotor polyneuropathy (DSPN) and is thought to be the most common variety (1). It develops on (or with) a background of longstanding hyperglycemia, associated metabolic derangements (increased polyol flux, accumulation of advanced glycation end products, oxidative stress, and lipid alterations among other metabolic abnormalities) and cardiovascular risk factors (5–7). Alterations of microvessels, similar to those observed in diabetic retinopathy and nephropathy, appear to be associated with the pathologic alterations of nerves (8). Total hyperglycemic exposure is perhaps the most important risk covariate (5,7). This variety has been shown to be stabilized, perhaps even improved, by rigorous glycemic control. This polyneuropathy has been shown to be statistically associated with retinopathy and nephropathy (1,6). Autonomic dysfunction and neuropathic pain may develop over time.

The atypical DPNs are different from DSPN in several important features, i.e., onset, course, manifestations, associations, and perhaps putative mechanisms (3,4,9). They appear to be intercurrent varieties, developing at any time during the course of a patient's diabetes (3,9). Onset of symptoms may be acute, subacute, or chronic, but the course is usually monophasic or fluctuating over time. Pain and autonomic symptoms are typical features (3,9) and altered immunity has been suggested. Studies have suggested that impaired fasting glucose or impaired glucose tolerance (IGT) is more common in chronic idiopathic axonal polyneuropathy, but other studies do not support this view (3,10).

Diabetic sensorimotor polyneuropathy

Case definition. The 1988 San Antonio Conference on Diabetic Neuropathy (11), Boulton et al. (4), and the American Academy of Neurology (AAN), American Association of Electrodiagnostic Medicine (AAEM), and American Academy of Physical Medicine and Rehabilitation (AAPM&R) (12) have proposed criteria for diabetic neuropathies.

We propose separate definitions for typical DPN (DSPN) and atypical DPNs. DSPN is a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure (diabetes) and cardiovascular risk covariates. An abnormality of nerve conduction tests, which is frequently subclinical, appears to be the first objective quantitative indication of the condition. The occurrences of diabetic retinopathy and nephropathy in a given patient strengthen the case that the polyneuropathy is attributable to diabetes. Other causes of sensorimotor polyneuropathy

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Received 8 July 2010 and accepted 20 July 2010.
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DOI: 10.2337/dc10-1303
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need to be excluded. For epidemiologic surveys or controlled clinical trials of DSPN, we advocate the use of nerve conduction (NC) testing as an early and reliable indicator of the occurrence of this neuropathy. To be reliable the test must be done rigorously using appropriate reference values corrected for applicable variables. Volunteered or elicited symptoms and signs and other clinical neurophysiologic abnormalities are also needed to characterize the symptoms, signs, and overall severity of the polyneuropathy. Recent studies emphasize the importance of the proficiency of the clinical neurologic assessment (13,14). Atypical DPNs have been less well characterized and studied.

Estimating severity. Estimating the severity of DSPN has not received the attention it deserves. For a given patient with diabetes, it is not sufficient to simply identify patients as having or not having DSPN—severity also needs to be ascertained. We suggest a reliable objective and quantitative measure (i.e., NC abnormality) as the minimal criteria for the diagnosis of DSPN. When NC values have not been assessed, it is not possible to provide a confirmed diagnosis of DSPN—only a possible or probable diagnosis. Since the severity of DSPN is a combination of neuropathy symptoms, signs, neurophysiologic test abnormalities, and other dysfunctions and impairments, the sum scores of various measures of neurologic signs, symptoms, neurophysiologic test abnormalities, or scores of function of activities of daily living may provide an indication of the severity (13).

An alternative approach to estimating severity is to indicate severity by grades. Dyck (15) described the stages of severity:

- Grade 0 = no abnormality of NC, e.g., Σ 5 NC normal deviates <95th percentile or another suitable NC criterion
- Grade 1a = abnormality of NC, e.g., Σ 5 NC normal deviates ≥95th percentile without symptoms or signs
- Grade 1b = NC abnormality of stage 1a plus neurologic signs typical of DSPN but without neuropathy symptoms
- Grade 2a = NC abnormality of stage 1a with or without signs (but if present, <2b) and with typical neuropathic symptoms
- Grade 2b = NC abnormality of stage 1a, a moderate degree of weakness (i.e., 50%) of ankle dorsiflexion with or without neuropathy symptoms.

Definitions of minimal criteria for typical DPN

1. Possible DSPN. The presence of symptoms or signs of DSPN may include the following: symptoms–decreased sensation, positive neuropathic sensory symptoms (e.g., "asleep numbness," prickling or stabbing, burning or aching pain) predominantly in the toes, feet, or legs; or signs–symmetric decrease of distal sensation or unequivocally decreased or absent ankle reflexes.

2. Probable DSPN. The presence of a combination of symptoms and signs of neuropathy include any two or more of the following: neuropathic symptoms, decreased distal sensation, or unequivocally decreased or absent ankle reflexes.

3. Confirmed DSPN. The presence of an abnormality of NC and a symptom or symptoms or a sign or signs of neuropathy confirm DSPN. If NC is normal, a validated measure of small fiber neuropathy (SFN) (with class 1 evidence) may be used.

To assess for the severity of DSPN, several approaches can be recommended: the graded approach outlined above, various continuous measures of sum scores of neurologic signs, symptoms or nerve test scores, scores of function of acts of daily living or of predetermined tasks or of disability. Irrespective of which approach is used, it is necessary to ensure good performance of evaluations with monitoring proficiency.

4. Subclinical DSPN. The presence of no signs or symptoms of neuropathy are confirmed with abnormal NCs or a validated measure of SFN (with class 1 evidence).

We recommend that definitions 1, 2, or 3 be used for clinical practice and definitions 3 or 4 be used for research studies.

Atypical DPNs

Before further classification of these polyneuropathies, setting the minimal criteria for diagnosis and estimating severity and further characterizing of epidemiologic and mechanistic studies are needed. The issue of painful, autonomic, and nerve morphologic abnormalities are discussed in subsequent sections.

PAINFUL DPN — A definition of peripheral neuropathic pain (NP) in diabetes, adapted from a definition recently proposed by the International Association for the Study of Pain (16), is "pain arising as a direct consequence of abnormalities in the peripheral somatosensory system in people with diabetes." The prevalence of NP in the diabetic population is difficult to estimate as definitions have varied enormously among studies; however, it is crudely estimated that between 3 and 25% of patients might experience NP (17). Similarly, there are limited data on the natural history of painful DPN with some studies suggesting that painful symptoms improve with the worsening of the sensory loss and others reporting no appreciable occurrence of remissions (17).

In practice, the diagnosis of painful DPN is a clinical one, which relies on the patient's description of pain. The symptoms are distal, symmetrical, often associated with nocturnal exacerbations, and commonly described as prickling, deep aching, sharp, like an electric shock, and burning (13) with hyperalgesia and frequently allodynia upon examination (17). The symptoms are usually associated with the clinical signs of peripheral neuropathy, although occasionally in acute painful DPN, the symptoms may occur in the absence of signs. A number of simple numeric rating scales can be used to assess the frequency and severity of painful symptoms (18), and other causes of NP must be excluded. The severity of pain can be reliably assessed by the visual analog scale, which is the oldest and best validated measure, or the numerical rating scale, e.g., the 11-point Likert scale (0 = no pain, 10 = worst possible pain), which has been most widely used in neuropathic pain studies. A number of validated scales and questionnaires including the Neuropathic Pain Symptoms Inventory, Brief Pain Inventory, Neuropathic Pain Questionnaire, and McGill Pain Questionnaire, may be used (18). Quality of life (QoL) improvement should also be assessed, preferably using a validated neuropathy-specific scale such as Neuro-Qol or the Norfolk Quality of Life Scale (19). Outcomes must be measured using patient-reported improvement in scales for pain and QoL as measured on validated instruments. External observers can play no part in the assessment of the subjects' responses to new therapies for NP; thus, measures such as the "physician's global impression of response" are not valid.

For clinical trials of putative new therapies for painful DPN, rigorous patient selection with the use of NP scales and outcome measures are indicated. Inclusion criteria for such trials would nor-

mally include NP associated with DPN for >6 months duration, mean weekly pain score of between 4 and 10 on an 11-point numerical rating scale, exclusion of pain not associated with DPN, mononeuropathies or proximal neuropathies, nonneuropathic chronic pain, and central pain.

Pharmacological management of painful DPN almost exclusively consists of symptomatic therapies (those that improve symptoms of painful DPN without an effect on underlying causes or natural history) (20). The antioxidant α-lipoic acid administered intravenously is the only pathogenetic treatment that has efficacy confirmed from several randomized controlled trials and confirmation in a meta-analysis (level A evidence [12]) (21). Although spinal cord stimulation might be useful in refractory painful DPN (22), insufficient evidence exists for any nonpharmacological therapies.

Level A evidence exists to support the use of tricyclic antidepressants (e.g., amitriptyline), the anticonvulsants gabapentin and pregabalin, and the serotonin and norepinephrine reuptake inhibitor duloxetine (20,23–26). There is also randomized controlled trial (RCT) evidence for the use of opiates such as oxycodone and tramadol in painful DPN (20,23). There is no evidence available to support the use of the cannabinoids (27). Preliminary evidence shows promise for topical treatment using a 5% lignocaine plaster applied to the most painful area (28), although larger RCTs are required. First-line therapies for painful DPN are a tricyclic antidepressant, duloxetine, pregabalin, or gabapentin, taking into account patient comorbidities and cost (20,23). Combinations of first-line therapies may be considered if there is pain, despite a change in first-line monotherapy (20,23). If pain is still inadequately controlled, opiods such as tramadol and oxycodone may be added in a combination treatment (20,23). A number of areas relating to painful DPN warrant further investigation including population-based prevalence and natural history studies, trials using active comparators rather than placebo, assessment of combination therapies in addition to placebo, and longer-term studies of the efficacy and durability of treatments of painful DPN (23).

DIABETIC AUTONOMIC NEUROPATHY

— Diabetic autonomic neuropathy (DAN) is a disorder of the autonomic nervous system in the setting of diabetes or metabolic derangements of pre-diabetes after the exclusion of other causes. DAN may affect cardiovascular, gastrointestinal (GI), and urogenital systems, and sudomotor function. It may result in signs and symptoms or may be subclinically detectable by specific tests.

Cardiovascular autonomic neuropathy

Epidemiology. Cardiovascular autonomic neuropathy (CAN) is defined as the impairment of autonomic control of the cardiovascular system. The prevalence of CAN varies widely from 2.5 to 50%. Factors that influence the prevalence of CAN include the diagnostic criteria used, patient age, and the duration of diabetes (29,30). Additional clinical correlates and predictors of CAN include glycemic control, presence of DPN, nephropathy and retinopathy, blood pressure (BP) levels, obesity, smoking, and cholesterol and triglycerides levels (30,31). Intervention studies have documented the protective effect of glycemic control in type 1 diabetes (32) and a multifactorial strategy aimed at lifestyle change with pharmacological correction of hyperglycemia, hypertension, dyslipidemia, and microalbuminuria (33).

CAN is significantly associated with overall mortality (34) and in some—but not all—studies with morbidity such as silent myocardial ischemia, coronary artery disease, stroke, diabetic nephropathy progression, and perioperative morbidity. Some pathogenetic mechanisms may link CAN to cardiovascular dysfunction and diabetic complications (34). Thus, CAN assessment may be used for cardiovascular risk stratification in patients with and without established cardiovascular disease; as a marker for patients requiring more intensive monitoring during the perioperative period and other physiological stresses; and as an indicator for more intensive pharmacotherapeutic and lifestyle management of comorbid conditions.

CAN assessment. Cardiovascular reflex tests are the gold standard in clinical autonomic testing. These tests have good sensitivity, specificity, and reproducibility and are noninvasive, safe, well-standardized, and easily performed (35). However, a Valsalva maneuver must not be performed in patients with proliferative retinopathy. The most widely used tests assessing cardiac parasympathetic function are based on the time-domain heart rate (HR) response to deep breathing, a Valsalva maneuver, and postural change. Of these tests, HR to deep breathing has the greatest specificity (~80%). Cardiovascular sympathetic function is assessed by measuring the BP response to orthostatic change and a Valsalva maneuver. The performance of these tests should be standardized, and the influence of confounding variables such as medications, hydration, and antecedent activity should be minimized. Age normative values should be used. The combination of cardiovascular autonomic tests with sudomotor function tests may allow a more accurate diagnosis of DAN (36).

Diabetic patients with features of cardiac autonomic dysfunction such as unexplained tachycardia, orthostatic hypotension, and poor exercise tolerance, or with other symptoms of autonomic dysfunction should be evaluated for the presence of CAN. Screening for CAN should be performed at the diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes, particularly in patients at greater risk of CAN due to a history of poor glycemic control, cardiovascular risk factors, DPN, and macro- and microangiopathic diabetic complications.

Diagnostic criteria and staging of CAN are still being debated. We suggest that the presence of one abnormal cardiovagal test identifies possible or early CAN (29); at least two abnormal HR tests are required for a definite or confirmed diagnosis of CAN (30); and orthostatic hypotension (asymptomatic or symptomatic), in addition to HR test abnormalities, identify a condition of severe or advanced CAN (31). Progressive stages of CAN are associated with an increasingly worse prognosis (34).

Assessment of potential consequences of CAN. Attenuation (nondipping) or loss of BP nocturnal fall (reverse dipping) on ambulatory BP monitoring have been associated with CAN and attributed to the disruption of the circadian variation in sympathovagal activity (37). In diabetic patients, nondipping or reverse dipping are independent predictors of cardiovascular events and the progression of diabetic nephropathy. Ambulatory BP monitoring may be useful in patients with CAN to detect nondipping and to address 24-h BP control (Table 1).

QT prolongation is an independent predictor of mortality in diabetic patients and is weakly associated with CAN (38)

Table 1—*Cardiovascular autonomic tests and suggested indications for their use*

	Clinical diagnosis	Research	End point in clinical trials
HR cardiovascular tests	Yes	Yes	Yes
Orthostatic hypotension test	Yes	Yes	No (low sensitivity)
QT interval	Yes (additional information and risk stratification)	Yes	No (low sensitivity)
ABPM for dipping status	Yes (risk stratification)	Yes	No (low sensitivity)
HRV time- and frequency-domain indices	Yes (early additional information and risk stratification)	Yes	Yes
BRS measures	No (offers early additional information and risk stratification but low availability)	Yes	Yes
Scintigraphic studies	No (low availability and limited standardization)	Yes	Yes
MNSA	No (low availability and limited data in CAN)	Yes	Possible (used in lifestyle intervention trials in obesity)
Catecholamine assessment	No (low availability)	Yes	Possible (used in lifestyle intervention trials in obesity)

ABPM, ambulatory BP monitoring; HRV, heart rate variability; MNSA, muscle sympathetic nerve activity.

(Table 1). The pathogenesis of QT prolongation is multifactorial and correlates include female sex, nephropathy, coronary heart disease, glycemic control, systolic BP, physical activity, and BMI.

CAN testing for clinical trials and research. The time-domain HR tests and the BP response to postural change have the reproducibility necessary for clinical trials. These tests were used as end points in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) and other clinical trials.

Frequency-domain indexes obtained by applying spectral analysis to HR variability of short (5–7 min) and longer (24-h) electrocardiogram recordings provide a measure of sympathetic and parasympathetic modulation of HR. HR spectral power in the high-frequency region is a measure of parasympathetic modulation, while spectral power in the low-frequency region provides a measure of both sympathetic and parasympathetic modulation. The low-frequency BP variability may provide a measure of sympathetic modulation. To correctly assess the significance of the different regions, respiration should be measured or controlled breathing performed. These methods, which need standardization, have been widely used in research and as end points in clinical trials.

Sympathetic outflow, at rest and in response to various physiological perturbations, can be measured directly via microelectrodes inserted into a fascicle of a distal sympathetic nerve to the skin or muscle. The technique is invasive and time-consuming. Whole-body sympathetic activity is most accurately assessed by measurements of plasma concentrations of noradrenaline and adrenaline.

Assessment of cardiac vagal baroreflex sensitivity (BRS) combines information derived from both HR and BP in response to pharmacological or spontaneous BP perturbations. Cardiac vagal BRS is a well-established prognostic index in the general and diabetic populations (39) and is frequently used in research studies (Table 1). Cardiac sympathetic BRS can be measured with simultaneous recordings of muscle sympathetic nerve activity.

Scintigraphic studies with radio labeled noradrenaline analogues allow a direct semi-quantitative ([^{123}I]-metaiodobenzylguanidine [MIBG] and single photon emission computed tomography) and quantitative assessment ([^{11}C]-hydroxyephedrine [HED] and positron emission tomography) of cardiac sympathetic integrity. Scintigraphic abnormalities are associated with CAN but may also be present in patients with normal cardiovascular autonomic tests (40). No standardized methodology or normative values exist, and available data on reproducibility are limited. Scintigraphic studies are appropriate to explore the effects of sympathetic dysfunction on cardiac metabolism and function and are useful in assessing cardiac sympathetic function in research studies.

Issues for future research. Research issues include: *1*) the need for multivariate longitudinal studies to clarify the natural history of CAN in diabetes and prediabetes, to evaluate the impact of pharmacologic and lifestyle interventions targeting CAN, and to determine the effect of CAN on clinical outcomes; *2*) the refinement and standardization of research measures to permit more widespread use; and *3*) the need for studies of combined cardiovascular autonomic and other autonomic measures to improve diagnosis and outcome assessment.

GI autonomic neuropathy

GI motor, sensory, and secretory functions are modulated by the interaction of the autonomic (sympathetic and parasympathetic) and enteric nervous systems with underlying rhythmicity generated by the interstitial cells of Cajal located within the smooth muscle. Evaluation of GI autonomic function is difficult in humans, and the diagnosis of GI autonomic neuropathy is often one of exclusion. While irreversible autonomic neuropathy has been regarded as the cause of disordered gut motility in diabetes, recent evidence indicates a heterogeneous picture with a range of fixed pathology and reversible functional abnormalities (41). Acute hyperglycemia slows gastric emptying (GE), while insulin-induced hypoglycemia accelerates it.

Clinical features. Disordered GI motility may be associated with GI symptoms, impaired oral drug absorption, poor glycemic control, malnutrition, abnormal postprandial regulation of BP, poor QoL, and a high rate of hospitalization. The re-

lationships with symptoms and CAN are relatively weak (42). Esophageal transit is delayed in ~50% of patients with longstanding diabetes and may be associated with regurgitation, dysphagia, and a propensity for pill-induced esophageal erosions and strictures. Gastroparesis affects ~40% of patients with longstanding diabetes. Symptoms are variable and more common in patients with worse chronic glycemic control and psychological disorders (43).

The rate of GE is a major determinant of postprandial blood glucose changes. In insulin-treated patients, nutrient delivery needs to be matched to the action of the exogenous insulin, and delayed GE is a cause of otherwise unexplained hypoglycemia (44).

Postprandial hypotension occurs frequently in diabetes, and its magnitude is related directly to GE rate. The prevalence of disordered small and large intestinal and anorectal motility is high. Diarrhea may result from rapid or slow transit, which is complicated by bacterial overgrowth and/or disordered secretion. Constipation frequently occurs. Fecal incontinence is not uncommon and is related to reduced and unstable internal anal sphincter tone and impaired rectal compliance and sensation.

Assessment. Studies of GI autonomic neuropathy, whether performed for clinical, epidemiological, or research purposes, may potentially be focused on GI symptoms, QoL, GI motility/transit, glycemic control, and/or postprandial BP. A number of instruments are available to quantify GI symptoms, including the Diabetes Bowel Symptom Questionnaire. Objective GE measurement is advocated for the diagnosis of gastroparesis. Evaluation of solid emptying is probably more sensitive than that of low-nutrient liquid or semi-solid meals. Medications that may influence GE should ideally be withdrawn, glycemia should ideally be <10 mmol/l throughout the test, and other causes of gastroparesis must be excluded. Failure to demonstrate delayed GE does not necessarily imply that symptoms are not due to "diabetic gastropathy," but it does help guide drug therapy. Scintigraphy is still regarded as the gold standard technique for GE measurement. Standardization of the meal technique has been improved by the recommendation of a low-fat, egg white meal labeled with technetium-99 (99mTc) sulfur colloid (45). Breath tests using nonradioactive 13 C-acetate or -octanoic acid as a label are appealing options, at least as a screening tool. They are safe, easy to perform, inexpensive, and correlate well with scintigraphy. Ultrasonography (two-dimensional and three-dimensional) is noninvasive and two-dimensional ultrasound has been validated for measuring emptying of liquids and semi-solids. However, obesity and abdominal gas, together with the necessity for an experienced operator, have limited its widespread use. Surface electrogastrography, used to detect abdominal gastric slow-wave activity, should be regarded as a research tool. A barium meal has no role in quantifying GE.

In the investigation of "diabetic diarrhea" celiac disease, exocrine pancreatic insufficiency and small intestinal bacterial overgrowth must be excluded. Tests of anorectal motor and sensory function are well developed for clinical use.

Erectile dysfunction

The prevalence of erectile dysfunction (ED) among diabetic men varies from 35 to 90%, depending mainly on the various methods applied (46). Neuropathy is one of the leading causes of ED, along with glycation of elastic fibers, peripheral vasculopathy, endothelial dysfunction, psychological factors, drugs, and hormonal changes (47). ED seems to be associated with a higher rate of abnormal sensory and autonomic tests. ED is a predictor of cardiovascular events and is associated with silent myocardial ischemia in type 2 diabetes (48). Alteration of QoL and depressive symptoms seem to precede ED. In clinical trials, ED was more severe and more resistant to treatment in diabetic than in nondiabetic individuals.

Key diagnostic procedures of ED include comprehensive patient history (sexual, medical, drugs, alcohol, tobacco, and psychosocial). The use of validated questionnaires, such as the International Index of Erectile Function and the Sexual Encounter Profile, is the most appropriate method to characterize the frequency and severity of ED symptoms. Other explorations, including evaluation of nocturnal penile tumescence, penile Doppler ultrasound, sacral response, bulbo-cavernosus reflex, dorsal sensory nerve conduction of the penis, amplitude and latency of penile sympathetic skin response, and pudendal nerve somatosensory-evoked potentials (49), may be useful in patients who do not respond to phosphodiesterase (PDE)-5 inhibitors. Due to the potential risks of adverse or unanticipated drug interactions, cardiac risk factors should be evaluated and managed in all patients with ED and cardiovascular disease. Although ED is a part of autonomic dysfunction, ED prevalence in patients with DAN and the prevalence of DAN among patients with ED have not been analyzed in large epidemiological studies.

Bladder dysfunction

Bladder complications can be due to an alteration of the detrusor smooth muscle, neuronal dysfunction, and urothelial dysfunction. Estimates of the prevalence of bladder dysfunction are 43 to 87% of type 1 diabetic patients and 25% of type 2 diabetic patients. Diabetes duration is significantly associated with severe incontinence. The correlation between diabetic cystopathy and peripheral neuropathy ranges from 75 to 100%.

Common symptoms include dysuria, frequency, urgency, nocturia, and incomplete bladder emptying. Other symptoms include infrequent voiding, poor stream, hesitancy in initiating micturition, recurrent cystitis, and stress and urgency urinary incontinence. Since urological conditions such as benign prostatic hypertrophy in men or gynecological disorders in women may share the same symptoms, these causes must be excluded by appropriate testing.

Diagnosis should use a validated questionnaire for lower urinary tract symptoms (LUTS). The type of bladder dysfunction is most readily characterized with complete urodynamic testing. Measurement of peak urinary flow rate and postvoid residual volume (PVR) should be considered in diabetic patients with LUTS when diagnosis remains doubtful (50). PVR is ideally measured by portable ultrasound (51). Urodynamic findings include impaired bladder sensation, increased cystometric capacity, decreased (or sometimes unexplained increased) detrusor contractility, and increased PVR (52). Microscopic urinalysis and culture are essential in assessing patients complaining of LUTS. Bladder dysfunction has not been assessed up to now in epidemiological and longitudinal studies or in RCTs.

Sudomotor dysfunction

Sweat glands are innervated by the sudomotor, postganglionic, unmyelinated cholinergic sympathetic C-fibers. Sudomotor dysfunction may result in dryness of foot skin and has been associated with foot ulceration (53). Assessment of sudo-

motor dysfunction contributes to the detection of autonomic dysfunction in DPN.

The quantitative sudomotor axon reflex test (QSART) is capable of detecting distal small fiber polyneuropathy with a sensitivity of >75% (54). QSART may be considered the reference method for the detection of sudomotor dysfunction and is used for clinical and research purposes. Other available techniques for assessment of sudomotor function include the thermoregulatory sweat test, silastic imprint method, the indicator plaster method (55), and the quantitative direct and indirect reflex test (QDIRT) (56). Comparative studies of the sensitivity and specificity of these diagnostic techniques are necessary. Sudomotor function has not yet been assessed in epidemiological and longitudinal studies or in RCTs.

EMERGING MARKERS OF DPN: FOCUS ON SMALL FIBERS

— It was proposed earlier in this article that if NC is normal, a validated measure (with class 1 evidence) of SFN may be used. We have therefore assessed the validity of established and emerging measures of SFN and propose a definition.

Nerve biopsy

Nerve biopsy detects unmyelinated fiber damage while myelinated nerve fiber morphology is still normal in patients with early DPN (57). However, nerve biopsy is an invasive and highly specialized procedure that requires electron-microscopy and cannot be advocated for routine use.

Skin biopsy

Skin punch biopsy, a minimally invasive procedure, allows morphometric quantification of intraepidermal nerve fibers (IENF) most commonly expressed as the number of IENF per length of section (IENF/mm). Intra- and inter-observer variability for the assessment of IENF density is good, declines with age, is lower in males than in females, and is not influenced by weight or height (58). The blister technique is a less invasive procedure that assesses innervation of the epidermis alone and shows good agreement with punch biopsy (58).

Diagnostic yield of IENF quantification. No study assessing sensitivity and specificity in DPN alone is available. However, several studies in SFN, which included patients with DPN, have been published. In a study of 58 patients with pure SFN (59), a cut-off IENF density of ≤8.8/mm at the ankle was associated with a sensitivity of 77.2% and a specificity of 79.6%. In a study of 210 patients with SFN (60), which included 65 diabetic patients, the *Z*-scores and 5th percentile provided the highest specificity (98 and 95%, respectively) but the lowest sensitivity (31 and 35%, respectively) compared with the receiver operating characteristic analysis (specificity 64%, sensitivity 78%). Thus, the diagnostic yield of skin biopsy may depend on the reference and cut-off values selected and the definition of SFN. IENF density correlates inversely with both cold and heat detection thresholds (61).

The AAN, AAEM, and AAPM&R provide a level C recommendation for the use of skin biopsy to diagnose DSPN, particularly SFN (36). The European Federation of the Neurological Societies and the Peripheral Nerve Society revised guidelines on the use of skin biopsy in the diagnosis of SFN and have concluded that IENF density is a reliable and efficient technique to confirm the clinical diagnosis of SFN with a level A recommendation (58). The presence of diffuse IENF swellings, especially if large, may predict a decline in IENF density (58)

DPN. IENF density is significantly reduced in patients with normal NC, suggesting early damage to small nerve fibers (62,63), and there is an inverse correlation with the Neurological Disability Score (63). Additionally, IENF density is lower in diabetic patients with painful—compared with painless—early neuropathy (64). A 1-year diet and exercise intervention program for patients with SFN and IGT led to increased IENF density (65). These data suggest that IENF loss is an early feature of diabetes, progresses with increasing neuropathic severity, and may repair with early intervention.

Sudomotor innervations. Recently, a skin biopsy study has shown a correlation between sweat gland nerve fiber density, neuropathic symptoms, neurological deficits, and sweat production in diabetic patients (66).

Corneal confocal microscopy

Corneal confocal microscopy is a noninvasive technique that can detect small sensory corneal nerve fiber loss in diabetic neuropathy (63), idiopathic SFN, and Fabry disease. Corneal nerve fiber damage correlates with IENF loss and the severity of neuropathy in diabetic patients (63), was more prominent in painful neuropathy (63), and improved 6 months after combined pancreas/kidney transplantation (67). Its quantification may be a surrogate marker of diabetic neuropathy.

Nerve axon reflex/flare response

Stimulation of C-nociceptive fibers by acetylcholine iontophoresis induces vasodilation, which can be quantitatively measured and serve as a measure of small fiber function (68). This technique correlates with other measurements of small fiber function and may be considered for the diagnosis of SFN in diabetic patients. The laser Doppler imaging flare test evaluates 44°C heat-induced vasodilation and is reduced in subjects with IGT and type 2 diabetic patients with and without neuropathy (69). Further studies are required to validate these tests as diagnostic tools or as outcome measures in clinical trials.

Definition of SFN

In diabetic patients, we propose to grade SFN as follows: *1*) possible: the presence of length-dependent symptoms and/or clinical signs of small fiber damage; *2*) probable: the presence of length-dependent symptoms, clinical signs of small fiber damage, and normal sural NC study; and *3*) definite: the presence of length-dependent symptoms, clinical signs of small fiber damage, normal sural NC study, and altered IENF density at the ankle and/or abnormal quantitative sensory testing thermal thresholds at the foot. At present, it is not possible to suggest criteria to define the severity of SFN in DPN.

CONCLUSIONS

— Diabetic polyneuropathy is one of the most common long-term complications of diabetes affecting ~50% of all diabetic people. This review by an international panel of experts examines recent literature regarding diagnostic criteria for DPN, painful DPN, and autonomic neuropathy and makes diagnostic recommendations in the context of clinical practice and research. The review also discusses emerging markers of DPN. Finally, the diagnostic criteria for DPN are likely to evolve with developments in the field, and there is clearly a need for experts in the field to provide periodic updates.

Acknowledgments— S.T. has received honoraria from Eli Lilly, Boehringer Ingelheim,

Pfizer, Shwartz Pharma, and UCB. V.S. has received research support, consulting fees, or honoraria from Boehringer Ingelheim, Daiichi Sankyo Europe, Eli Lilly, Laborest, miro Verbandstoffe, Pfizer, and Schwarz. A.V. has received research grants from the National Institutes of Health/National Institute on Aging, American Diabetes Association, Abbott, GlaxoSmithKline, sanofi-aventis, Arcion Therapeutics, Eli Lilly, and Merck Research Labs. A.V. has served as a consultant for Ansar, AstraZeneca, Eli Lilly, KV Pharmaceuticals, Merck, Novartis Pharmaceuticals, R.W. Johnson Pharmaceutical Research Institute, sanofi-aventis, Takeda, and Tercica and also has served on the speaker's bureau for Abbott, Ansar, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline Beecham, Merck, Novartis Pharmaceuticals, Pfizer, sanofi-aventis, and Takeda. No other potential conflicts of interest relevant to this article were reported.

S.T. contributed to the discussion and wrote, reviewed, and edited the manuscript. A.J.M.B. researched data, contributed to the discussion, wrote the manuscript, and reviewed and edited the manuscript. P.J.D. researched data, contributed to the discussion, and reviewed and edited the manuscript. R.F. contributed to the discussion, wrote the manuscript, and reviewed and edited the manuscript. M.H. contributed to the discussion and wrote the manuscript. P.K. wrote the manuscript. G.L. researched data, contributed to the discussion, and reviewed and edited the manuscript. R.A.M. researched data, contributed to the discussion, and wrote, reviewed, and edited the manuscript. V.S. researched data, contributed to the discussion, and wrote, reviewed, and edited the manuscript. A.V. contributed to the discussion and reviewed and edited the manuscript. L.B. contributed to the discussion and reviewed and edited the manuscript. P.V. wrote the manuscript.

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