Curr Diab Rep (2013) 13:533–549
DOI 10.1007/s11892-013-0387-7

Painful and Painless Diabetic Neuropathy: One Disease or Two?

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Published online: 16 May 2013

Abstract Painful diabetic polyneuropathy (PDPN) is generally considered a variant of diabetic polyneuropathy (DPN) but the identification of distinctive aspects that characterize painful compared with painless DPN has however been addressed in many studies, mainly with the purpose of better understanding the mechanisms of neuropathic pain in the scenario of peripheral nerve damage of DPN, of determining risk markers for pain development, and also of recognizing who might respond to treatments. This review is aimed at examining available literature dealing with the issue of similarities and differences between painful and painless DPN in an attempt to respond to the question of whether painful and painless DPN are the same disease or not and to address the conundrum of why some people develop the insensate variety of DPN whilst others experience distressing pain. Thus, from the perspective of comparing painful with painless forms of DPN, this review considers the clinical correlates of PDPN, its distinctive framework of symptoms, signs, and nerve functional and structural abnormalities, the question of large and small fiber involvement, the peripheral pain mechanisms, the central processing of pain and some new insights into the pathogenesis of pain in peripheral polyneuropathies and PDPN.

Keywords Painful · Painless · Diabetic neuropathy · Neuropathic pain · Risk factors · Biomarkers · Predictors · Autonomic neuropathy · Small fiber neuropathy · Epidemiology · Pain mechanisms · Genetics · Central plasticity · Inflammation · Painful neuropathy · Painless neuropathy

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Introduction

Diabetic polyneuropathy (DPN) has recently been defined by the Toronto Expert Panel on Diabetic Neuropathy as a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure (diabetes) and cardiovascular risk covariates [1•]. The same panel provided a definition of peripheral neuropathic pain in diabetes, adapted from the one recently proposed by the International Association for the Study of Pain (IASP) [2], ie, pain arising as a direct consequence of abnormalities in the peripheral somatosensory system in people with diabetes [1•]. Painful DPN (PDPN) is then generally considered a variant of DPN.

PDPN affects about 18 % of adult diabetic patients [3–8] compared with at least 30 % of patients with overall DPN [9, 10]. Neuropathic pain represents the most problematic symptom of DPN. PDPN is associated with sleep disturbance, depression, anxiety, fatigue, and impaired quality of life [6, 11–16] as all these comorbidities are related - in some cases in a bidirectional way - to chronic pain [17]. The presence of PDPN is also consequently associated with a negative impact on productivity at work and increased health care resource use [12] with excess cost estimated to be almost $6000 per year [18, 19].

All these aspects emphasize the need to effectively manage pain in patients with PDPN. However, the treatment of neuropathic pain is challenging and not completely satisfying in a still relatively high number of patients with rates of responders (defined by a 50 % reduction in pain intensity) not above 50 % and the number-needed-to-treat between 5 and 7.5 for the better-tolerated first line drugs [20•, 21, 22].

The identification of the distinctive aspects that characterize painful compared with painless DPN can help in both understanding the pathogenetic mechanisms of neuropathic pain and addressing still unresolved issues like predicting who responders will be.

Through the examination of available literature regarding the issue of similarities and differences between painful and painless DPN, this review attempts to answer the question of whether painful and painless DPN might be the same disease and why some people develop the insensate variety of DPN but others endure harrowing pain. In making this comparison between painful and painless DPN, this review explores the clinical aspects of PDPN in search of a specific metabolic and/or neurologic phenotype, the peculiar abnormalities of large and small fiber function and structure, and the pain mechanisms (peripheral and central) active in PDPN. Finally, gaps in our knowledge and some of the reasons for future research are highlighted.

Epidemiological Aspects: Is it Possible to Isolate Distinct Clinical Correlates of PDPN?

Epidemiological studies in the field of PDPN have used different population sampling, diagnostic criteria, and methods, ranging from posted questionnaires or telephone interviews to a complete clinical evaluation (Table 1), with varying accuracy in excluding causes of pain and neuropathic pain that differ from PDPN.

The available studies—a few of which are now quite dated—give estimates of PDPN prevalence ranging from 3.3 % to 26.8 % (Table 1). A prevalence of about 17.5 % corresponds to the median of the figures obtained when the diagnosis was based on the presence of both neuropathic pain and DPN [3–8].

Recently, using the validated neuropathic pain screening tool DN4 [23, 24•], prevalence rates of PDPN were provided for Saudi Arabia and Middle East Region [25, 26•] with values (65.3 % and 53.7 %, respectively) higher than in Western populations. There is no sufficient explanation for this finding apart from the possible role of poorer glycemic control in those areas. No data on the prevalence of DPN was provided for comparison (Table 1).

Risk markers or factors for DPN have been well-defined in observational as well as intervention studies. These are age, diabetes duration, glycemic control, microangiopathic complications, hypertension, and smoking (these last 2 mainly in type 1 diabetes) [10, 27]. In addition, new and less strong clinical correlates or predictors of DPN are obesity, body mass index (BMI), waist circumference, hypoinsulinemia in type 2 diabetes, low levels of C peptide in type 1 diabetes, metabolic dyslipidemia, and cardiovascular disease including peripheral arterial disease [5, 6, 10, 27–37]. By contrast, very little data is available thus far on clinical correlates and risk factors for PDPN, and in most studies it has not been possible to derive the differences between patients with PDPN and those with painless DPN.

Table 1 summarizes the data from published epidemiological studies. Among the known risk factors for DPN, diabetes duration was also found to be a correlate or predictor for PDPN in some studies [6, 26•, 29, 38, 39], but not in others [3, 5, 7, 8, 31, 40, 41]. Similarly, age was a predictor of PDPN only in a few studies [5, 6, 25, 26•, 40]. A relation with glycemic control has not been documented apart from the association of painful symptoms with the self-declared frequency of hyperglycemia and glycosuria in the 1989 National Health Interview Survey in the US [38]. However, epidemiological cross-sectional studies consider just the current glycemic control and do not allow the establishment of a longitudinal relationship. Moreover, in the studies listed in Table 1, glycated hemoglobin was associated with DPN in only 3 out of 7 studies addressing this topic [4, 28, 29].

Diabetic retinopathy and nephropathy were not associated with PDPN apart from Van Acker's study [6] that showed microalbuminuria/proteinuria as a predictor of PDPN, in contrast with other studies [5, 39]. In the MONIKA/KORA studies [5, 32], peripheral arterial disease was found to be an independent predictor of PDPN. However, in these studies [5, 32] PDPN was diagnosed on the basis of the Michigan Neuropathy Screening Instrument (MNSI) that also includes foot inspection. Since foot skin abnormalities or lesions can also be ischemic in nature, the use of MNSI might have overestimated the association between peripheral arterial disease and PDPN. In another study that excluded patients with advanced peripheral arterial disease, a relationship between peripheral arterial disease and PDPN was not confirmed [39]. Moreover, Benbow et al. [42] did not document an influence of peripheral arterial disease on the natural history of pain in diabetic patients.

Obesity (ie, weight, BMI, or BMI $\geq$30 Kg/m^2) and abdominal obesity (ie, waist circumference) have been found to be related to PDPN and as such have been suggested as risk markers [5, 6, 26•, 39]. In particular, a cross-sectional clinic based study, characterized by a multilevel approach to PDPN diagnosis and a careful exclusion of non diabetic painful neuropathies, confirmed that BMI was an independent predictor of PDPN in a multiple logistic regression analysis. This included anthropometric, clinical, metabolic and neurologic parameters and explained 43 % of the variance of PDPN [39].

Other associations have been described in isolation between PDPN and hypertension [38], physical inactivity [32] or metabolic dyslipidemia, ie, low HDL cholesterol and high triglycerides [6]. In 2 studies in distant countries, type 2 [7] and type 1 diabetes [26•] were associated with PDPN with double the risk for type 2 and a 50 % increase for type 1 diabetes [7, 26•] (Table 1).

The female gender was associated with PDPN in a few studies [7, 25, 26•, 41] with no association in the others, while an association with the male gender was found in just

Table 1 Epidemiological studies on prevalence and clinical correlates of PDPN: author, study characteristics, number of patients, diagnostic criteria for PDPN, prevalence of PDPN, and correlates of DPN and PDPN (in **Bold** those found in multivariate analysis)

Author (year)	Study design/setting	Number (type)	Diagnostic criteria for PDPN	Prevalence (%)	Correlates and predictors of DPN	Correlates and predictors of PDPN
Chan 1990 [146]	Hospital diabetic clinic; UK	962 (type 1 and 2)	Neuropathic pain in the lower limbs	7.4	Not provided	Not provided
Harris 1993 [38]	Population based study (NHIS); US	124 (type 1) 2268 (type 2)	Painful sensation or tingling in hands and feet (personal household interviews)	26.8	Not provided	Diabetes duration, **hypertension** (OR = 1.58), **hyperglycemia** (OR = 2.51), **glycosuria** (OR = 2.31)
Partanen 1995 [28]	University hospital diabetes center (longitudinal study); Finland	132 (type 2) (aged 45–64, newly diagnosed)	Pain in the limbs + 4 NCS abnormalities	6 at diagnosis, 20 at 10 years	Poorer glycemic control, low serum insulin	Not provided
Sorensen 2002 [29]	Hospital diabetes center; Australia	2610 (type 2)	Bilateral and symmetrical foot pain; criteria for DPN: VPT≥30	3.3	**Age** (OR = 1.09), **diabetes duration** (OR = 1.09), **height** (OR = 1.05), **HbA1c** (OR = 1.2)	**Diabetes duration** (OR = 1.09), **VPT** (OR = 1.06)
Daousi 2004 [3]	Community-based study in 3 urban general practice surgeries; UK	350 (type 1 and 2)	PDPN [typical neuropathic pain >1 year + PSS≥3 + (NDS≥6) or (NDS≥3 + NSS≥5)]	16.2	Not provided	No clinical correlates among sex, age, duration, type, BMI, HbA1c, smoking, alcohol, PAD, CAD, foot ulceration, depression
Davies 2006 [4]	Population-based study in an urban community; UK	353 (type 2) in phase 1; 269 in phase 2	Typical neuropathic pain (phase 1: postal survey; phase 2: clinical neurologic history and examination + TCSS)	26.4 (23.4 and 19 when excluding patients with TCSS<5 and mixed pain)	**Diabetes duration** (OR = 1.06), **HbA1c** (OR = 1.28)	No clinical correlates apart from severity of DPN (TCSS score) (in univariate analysis)
Wu 2007 [40]	Population-based study (random sample of households); France	1023 (type 1 and 2)	Neuropathic symptoms and pain (MNSI-Q ≥7 + average pain on BPI >0); computer-aided telephone interviews;	8	Type 1, age >65 years, gender (female) (only in univariate analysis)	Age >65 years, gender (male) (only in univariate analysis)
Ziegler 2009 [5]	Population-based study (MONICA/KORA); Germany	195 (type 1 and 2)	PDPN (positive answer to question 2 and/or question 6 of MNSI-Q + MNSI score>2)	13.3	Not provided	**Age** (OR = 1.08), **weight** (OR = 1.03), **PAD** (OR = 9.27)
Ziegler 2009 [32]	Population-based study (KORA Myocardial Infarction Registry); Germany	214 (type 1 and 2, post-Myocardial Infarction)	PDPN (positive answer to question 2 and/or question 6 of MNSI-Q + MNSI score >2)	21	Not provided	**Waist circumference** (OR = 1.05), **physical activity** (OR = 0.31), **PAD** (OR = 5.61)
Van Acker 2009 [6]	40 outpatients diabetes clinics; Belgium	344 (type 1); 767 (type 2)	PDPN (DN4 ≥4 + abnormal sensitivity to 10 g monofilament and/or insensitivity to pinprick)	14.1	**Gender** (female) (OR = 0.7), **age** (per 10 years OR = 1.56), **type 2** (OR = 1.65), **diabetes duration** (per 5 years OR = 1.16), **low HDL** (OR = 2.12)	**Age** (OR = 1.47), **diabetes duration** (per 5 years OR = 1.14), **obesity** (OR = 1.62), **low HDL** (OR = 2.17), **high triglycerides** (OR = 1.76), **nephropathy** (OR = 1.69)

Table 1 (continued)

Author (year)	Study design/setting	Number (type)	Diagnostic criteria for PDPN	Prevalence (%)	Correlates and predictors of DPN	Correlates and predictors of PDPN
Miralles-García 2010 [8]	20 hospital outpatient endocrinological clinics; Spain	526 (type 1); 485 (type 2)	PDPN (DN4 ≥4 + abnormal tactile sensitivity to von Frey filaments or VPT or TT or NCS	21.1	Type 2, diabetes duration, BMI, waist circumference, blood pressure, smoking, nephropathy, retinopathy, PAD, CAD, cerebrovascular disease, dyslipidemia (all in univariate analysis)	Less impaired VPT and TT (Vs. painless PND)
Halawa 2010 [25]	100 outpatient diabetes clinics; Saudi Arabia	66 (type 1); 954 (type 2)	PDPN (DN4 ≥4)	65.3	Not provided	Gender (female), diabetes duration, age (in univariate analysis)
Spallone 2011 [39]	University hospital diabetes clinic; Italy	191 (type 1 and type 2)	PDPN (chronic neuropathic pain + MDNS ≥7 and/or abnormal VPT and/or abnormal 10 g monofilament)	–	Not provided	**Diabetes duration** (OR = 1.07), **BMI** (OR = 1.22), **MDNS** (OR = 1.27)
Erbas 2011 [41]	14 university hospital diabetes outpatient clinics; Turkish	91 (type 1); 1022 (type 2)	PDPN (LANSS ≥12); criteria for DPN: MDNS ≥7	14.0	**Age** (OR = 1.03), **diabetes duration** (OR = 1.07)	Gender (female), DPN (in univariate analysis)
Jambart 2011 [26•]	Diabetes outpatient (primarily private) medical settings; Middle East Region (Egypt, Gulf States, Jordan, Lebanon)	378 (type 1); 3611 (type 2)	PDPN (DN4 ≥4)	53.7	Not provided	**Age** ≥65 years (OR = 2.13), **diabetes duration** ≥10 years (OR = 2.43), **type** 1 (OR = 1.59), **gender** (female) (OR = 1.27), **obesity** (OR = 1.35), **living in Gulf States or Lebanon protective** (OR = 0.44 and OR = 0.66)
Abbott 2011 [7]	Community based study (NWDFCS); UK	1338 (type 1); 14,206 (type 2)	NSS≥5 and NDS ≥3	34 for painful symptoms, 21 for PDPN	Not provided	**Type 2 diabetes** (OR = 2.1), **gender** (female) (OR = 1.5), South Asian ethnicity only in absence of clinical neuropathy (OR = 1.5),

BMI Body Mass Index, *BPI* Brief Pain Inventory, *CAD* Coronary Artery Disease, *DN4* Douleur Neuropathique en 4 Questions, *DPN* Diabetic Polyneuropathy, *LANSS* Leeds Assessment of Neuropathic Symptoms and Signs, *MDNS* Michigan Diabetic Neuropathy Score, *MNSI* Michigan Neuropathy Screening Instrument, *MNSI-Q* Michigan Neuropathy Screening Instrument Questionnaire, *NCS* Nerve Conduction Study, *NDS* Neuropathy Disability Score, *NHIS* National Health Interview Survey, *NSS* Neuropathy Symptom Score, *NWDFCS* North-West Diabetes Foot Care Study, *OR* odds ratio, *PAD* Peripheral Arterial Disease, *PDPN* Painful Diabetic Polyneuropathy, *PSS* Pain Symptom Score, *TCSS* Toronto Clinical Scoring System, *TT* Thermal Threshold, *VPT* Vibration Perception Threshold

a single study [40]. Height was associated with DPN and not PDPN in Sorensen's study [29]. In the 1999–2002 NHANES survey in 5229 subjects aged ≥40 years, including 683 with diabetes, height was a risk marker of peripheral insensate neuropathy (foot insensitivity to 10 g monofilament) [43]. The authors proposed that this different relationship between height and painless/painful neuropathy might suggest a different degree of underlying structural changes in peripheral nerves [43].

It is difficult to glean from all these epidemiological findings a clear definition of a clinical phenotype of patient with painful as opposed to painless DPN. In the MONIKA/KORA studies [5, 32] the independent predictors for both overall DPN and neuropathic pain were similar (age, waist circumference, or weight, and PVD) without allowing for a distinction between painful and painless forms. On the other hand, in van Acker's study [6], age, diabetes duration, and low HDL cholesterol were independent predictors of both DPN and PDPN, whereas gender and type 2 diabetes were predictors of DPN, and obesity and nephropathy of PDNP. Although some metabolic variables are related to both painless and painful DPN, it would appear that the relation with weight/obesity/BMI or abdominal obesity is more prominent for the painful form [5, 6, 26•, 39].

Controversial data is available on the presence and nature of a prediabetic neuropathy that seems to appear, in many cases, in the form of a painful small fiber neuropathy [44, 45, 46•]. Moreover, morbid obesity also in absence of hyperglycemia and hyperinsulinemia was associated with an asymptomatic small fiber neuropathy [47]. Thus, obesity as a component of the metabolic syndrome or as the scene for multiple processes also involved in the pathogenesis of DPN (such as increased inflammation or oxidative stress) would appear to represent a particular risk marker for neuropathic pain [48–51]. In a large epidemiological survey in the general population in Germany, chronic neuropathic pain of multiple etiologies was found to be associated with a number of clinical correlates and comorbid conditions including obesity [52].

Neurologic Aspects: Is there a Particular Neurologic Phenotype of Painful vs Painless DPN?

The Association Between Sensorimotor Deficits and PDPN

According to a redefinition and a grading system for neuropathic pain diagnosis [2•], the level of certainty for definite neuropathic pain requires the coexistence of (1) pain with plausible distribution, with (2) a history of peripheral or central neuropathy, (3) an objective demonstration of neurologic signs concordant with the distribution of pain, and finally with (4) the objective confirmation of the diagnosis of the neurologic disease. Thus, to obtain a definite diagnosis of PDPN the presence of clinical evidence of DPN is mandatory. In this sense, the coexistence of neuropathic pain and clinical sensory deficits is unavoidable, with the possible exception of cases where subclinical sensory dysfunction is detected only by instrumental methods, ie, nerve conduction studies (NCS), quantitative sensory testing (QST), and skin biopsy.

Generally, positive sensory symptoms, such as pain and paresthesia, are considered the consequence of fiber neuropathic damage with active degeneration or impaired regeneration, whereas with increasing loss of sensory fibers, negative symptoms occur, ie, sensation loss [53]. According to this view, some preservation of fibers is required to allow the persistence of positive sensory symptoms, and painful symptoms should improve as the severity of deficits increases. In actual fact, data on the natural history of painful symptoms is scarce and conflicting. In 1 study, after 3.6 years of follow-up, an improvement of positive symptoms occurred in 88 % of patients with PDPN concomitantly with a DPN severity progression [42], but in another study no significant change in pain was observed during 4 years of follow-up [54]. In a survey of 105 patients with PDPN, 72 %, 12 %, and 15 % reported worsening, improvement, and no change of pain since PDPN onset [55].

A few studies have addressed the relationship between neuropathic pain and DPN severity [4, 7, 29, 39, 56, 57] (Table 1). Veves et al. [56] showed in 94 diabetic patients that the prevalence of painful symptoms were similar in those with DPN compared with those with neuropathic foot ulceration (43 % vs 33 %) and suggested that neuropathic pain can in fact be present at any stage of DPN, from subclinical to very late neuropathy even with severe Charcot arthropathy and foot ulcers. This finding appeared to give support to the concept of painful-painless leg described by Ward [57]. In a second study by the same authors, in 70 diabetic patients the score of sensory deficits was higher in patients with painful than in those with painless DPN [58]. Sorensen et al. [29] described an association between insensate DPN, defined as a Vibration Perception Threshold (VPT) ≥30 V, and painful DPN, although to a limited degree. Diabetes duration and VPT were the only independent determinants of pain accounting however for only 3 % of the variance. They suggested that these 2 presentations of diabetic neuropathy were not mutually exclusive although they could develop in a dichotomous way with different predictors and imperfect overlapping. Davies et al. [4] showed that the prevalence of patients with neuropathic pain or mixed pain increased from 7.4 % in patients without DPN to 20.1 %, 64.9 %, and 67.9 % in those with mild, moderate, or severe DPN, respectively [4]. Consistent with the last finding, another study found that PDPN patients had worse sensorimotor deficits— assessed by Michigan Diabetic Neuropathy Score (MDNS)— than patients with non painful

DPN and that there was a positive correlation between pain intensity and MDNS score, and finally that MDNS was the major independent determinant of PDPN after adjusting for multiple confounders (odds ratio 1.27 for each point of MDNS) [39] (Fig. 1). Moreover, in 1113 diabetic patients neuropathic pain was present in 14 % and was more common in those with moderate to severe DPN than in those with mild or no DPN (70 % and 30 %, respectively) [41]. Another large population based study in the UK (15,692 patients) found an increasing prevalence of painful symptoms with worsening of clinical neuropathy (60 % with severe DPN, compared with 26 % without DPN) [7]. In 154 patients with DPN recruited consecutively in an electrophysiological laboratory, the Diabetic Neuropathy Index was the only independent predictor of painful form (odds ratio 1.8) [59].

However, a complete overlapping between painful symptoms and neuropathic signs cannot be asserted as in some studies painful symptoms can be present also in the absence of clinical signs of DPN [4, 7, 29]. In Davies' study [4], 7.4 % of subjects with classical pain symptoms had no detectable neuropathy. In Abbott's study [7], approximately 25 % of patients without clinical neuropathy on examination had significant painful neuropathic symptoms whereas only 11.7 % of patients with insensate neuropathy had pain. In Sorensen's study [29], 60.7 % of patients with painful neuropathy had normal VPT (the only sensory measure).

In conclusion, the findings regarding the clinical presentation of neuropathic pain in relation to sensory deficits enable some considerations. First, the clinical manifestations of painful and painless DPN are not mutually exclusive. Second, in most papers there is an association between the 2 forms and even a positive relationship between neuropathic pain intensity and the severity of sensory loss. This consideration remains valid also when taking into account the fact that the requirements to be met for PDPN diagnosis - according to guidelines - include neuropathic signs. In fact, the association between neuropathic pain and sensory deficits persisted also when considering in diagnosing PDPN just the presence of neuropathic pain [4, 41] or painful symptoms [7, 56]. Third, some cases of peripheral neuropathic pain have been described also in the absence of clinically detectable - mostly large fiber - sensory deficits, [4, 7, 29]. Thus, some painful forms could start as prevalent small fiber neuropathy with limited sensory deficits but increasing severity of DPN appears to be associated with an increased risk of developing PDPN.

The Association Between Neuropathic Pain and Small-Fiber Function and Morphology

A number of studies have described in PDPN pain-related sensory dysfunction using QST to assess large (Aβ) and mainly small-fiber (Aδ and C) function [60]. They yielded, however, contradictory results with regard to a predominant or exclusive involvement of small fibers (responsible for nociceptive and thermal sensation) in PDPN. Tsigos et al. [61] compared 19 patients with PDPN to 14 with painless foot ulcers and 19 with no clinical neuropathy and found

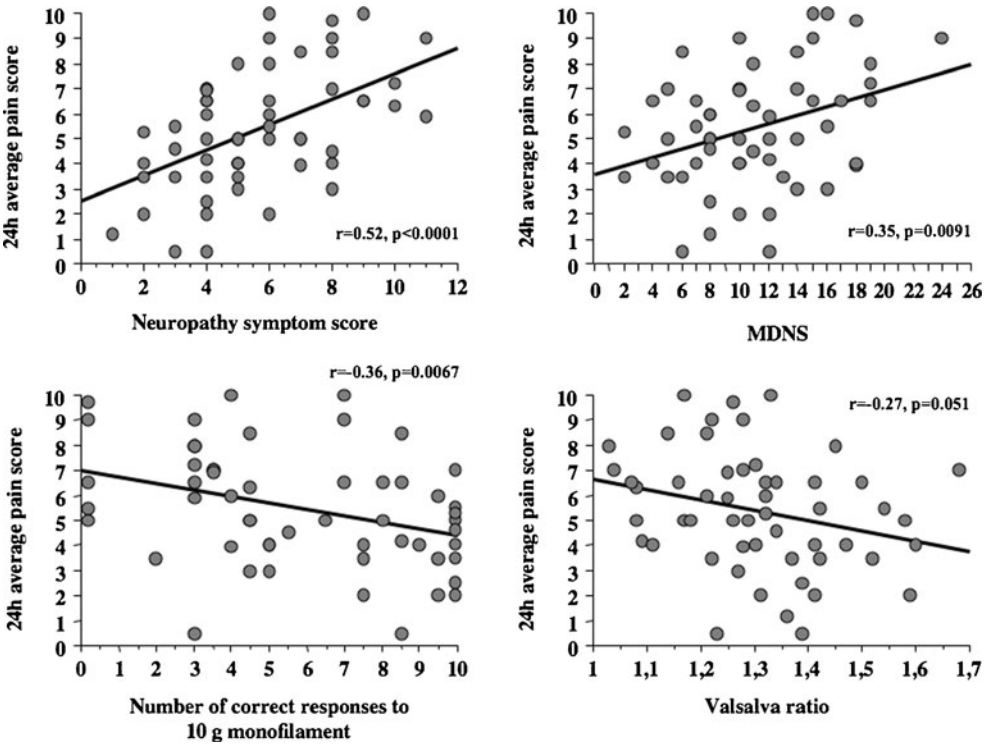

Fig. 1 Correlation between average 24-h pain score and some autonomic and sensorimotor indexes of diabetic neuropathy, ie, neuropathy symptom score, Michigan Diabetic Neuropathy Score (MDNS), number of correct responses to 10 g monofilament, and Valsalva ratio. (With permission from John Wiley and Sons, license number 3092161237906: Spallone V, Morganti R, D'Amato C, Cacciotti L, Fedele T, Maiello MR, et al. Clinical correlates of painful diabetic neuropathy and relationship of neuropathic pain with sensorimotor and autonomic nerve function. Eur J Pain. 2011;15:153–60) [39]

that PDPN was associated with small somatic fiber dysfunction - cooling and warming thresholds - and preserved sympathetic nerve activity (plasma noradrenaline) with a variable range of abnormalities in large somatic fibers - NCS and VPT - and in cardiovascular autonomic tests. By contrast, painless foot ulcers were universally associated with severe dysfunction of all nerve fiber populations. On the other hand, Benbow et al. [42], in 50 patients with PDPN followed for 3.6 years, did not find a significant correlation between the initial or follow-up pain scores and small fiber function, ie, thermal limen, heat-pain threshold, and weighted pinprick threshold. Moreover, although small fiber tests were impaired and further deteriorated during follow-up, they were unhelpful as predictors of the natural history of neuropathic pain. Krämer et al. [62] in 30 patients found that those with PDPN were indistinguishable in NCS, VPT, and thermal thresholds from those with painless DPN, but in the pain group there was a mildly significant correlation between pain intensity ratings and the deterioration over 2 years of cold detection threshold. Vrethem et al. [63] in 55 patients with polyneuropathy of various etiologies, including 20 with DPN, found tactile sensitivity (conveyed by large fibers) and not thermal sensitivity more compromised in those with painful compared with those with painless DPN.

Skin biopsy with quantification of intraepidermal nerve fibers (IENF) has undoubtedly become the most validated and recognized tool for somatic small fiber assessment. It has contributed to the definition of small fiber neuropathy, a condition characterized on clinical and neurophysiologic ground by the exclusive impairment of somatic small fibers [64•], and is recommended in diabetic patients in presence of painful neuropathy symptoms in the feet and normal NCS [1•].

Using skin biopsy in 35 patients with diabetes a slightly greater loss of IENF was documented in those with neuropathic pain compared with those without, but IENF density seemed to discriminate better between patients with and without pain when no or mild signs of neuropathy were present [65]. The authors suggested that abnormalities of small nerve fibers are more likely to play a central role in the genesis of pain mainly in individuals with little objective sign of neuropathy. Slightly reduced IENF and corneal nerve fiber lengths (but not density) were also observed in painful DPN compared with its painless equivalent [66]. However, also using skin biopsy some studies failed to find a close or constant link between the presence of neuropathic pain and IENF morphology [65, 67, 68]. Actually, no significant correlation was found at all between pain intensity and IENF density in some relevant studies [65, 67, 68].

Other observations in diabetic and non-diabetic polyneuropathies support the fact that neuropathic pain is not invariably associated with a pure small fiber neuropathy. In a retrospective analysis of a cohort of 124 patients with sensory neuropathy including 23 diabetic patients, only 54 % fulfilled the diagnostic criteria for small fiber neuropathy [67]. Scherens et al. [68] documented in 42 patients that dysesthesias - defined as an unpleasant abnormal sensation - may occur in pure small fiber neuropathy, mixed small and large fiber neuropathy and even in pure large fiber neuropathy, thus ruling out an exclusive relationship with detectable small fiber damage and at the same time suggesting a heterogeneous pathophysiology of dysesthesias.

Thus, a selective or prevalent small fiber sensory neuropathy might occur in diabetes in isolation or preceding larger fiber involvement [69, 70] and an impairment of small fiber function can be usually encountered in painful forms of DPN [65], but the absence or presence of pain cannot be explained by small nerve fiber dysfunction alone as measured by thermal thresholds [71], and an exclusive or prominent involvement of small fibers has not always been documented.

Furthermore, there is no agreement that the natural history of DPN includes inevitably a first stage of small fiber damage and a subsequent stage of large fiber damage. Ziegler et al. [72] documented in 40 patients with newly diagnosed type 1 diabetes, impaired thermal thresholds and not VPT. Conversely, in the patients of Rochester Diabetic Neuropathy Study cohort, characterized by only mild neuropathy, VPT was more frequently abnormal than the thermal thresholds, which suggested that large fibers are affected in mild neuropathy whereas all sensory fibers are affected in more severe neuropathy [73]. Zinman et al. [74] in 83 diabetic patients failed to find a concordance between thermal thresholds and pain sensation, but detected instead a strong correlation of thermal thresholds with sural amplitude and with clinical indicators of large fiber neuropathy, such as Toronto Clinical Neuropathy Score, monofilament score and VPT. Moreover, IENF density has been reported to progressively decrease with increasing severity of DPN [65, 66]. Similarly, in 30 patients with diabetes or impaired glucose tolerance, although foot pain was almost invariably associated with a reduction in skin innervation, the degree of abnormalities in skin biopsy increased from the group with pure small fiber neuropathy to that with mixed small and large fiber neuropathy [75]. Moreover although early impairment of small fiber function (thermal thresholds, or laser evoked potentials) and morphology (IENF) have been observed in asymptomatic diabetic patients [71, 76, 77] leading to the proposal of some of these measures as biomarkers for early DPN [77], it is also clear that the combination of small and large fiber tests complement each other in the description of DPN [78]. Even the neuropathy of prediabetes does not seem to be exclusively a small fiber neuropathy although small fiber involvement is mostly represented [46•, 79].

All these observations point to the fact that in diabetes small fiber neuropathy and large fiber involvement are not incompatible alternatives and that there is no definite evidence of a preferential link between pain and pure small

fiber neuropathy. Moreover, although pain in PDPN would appear to be mainly associated with the impairment of small afferent fibers, the reverse cannot be sustained, ie, that there is no small fiber impairment in the absence of pain. Thus, from the perspective of preferential small or large fiber damage, the question as to why DPN can be either painful or painless remains unanswered.

The Association Between Diabetic Neuropathic Pain and Autonomic Neuropathy

The relationship between autonomic involvement and PDPN has been evaluated with 2 possible implications: (a) the expected involvement of autonomic fibers inside a spectrum of small fiber damage, and (b) a possible role of autonomic - mainly sympathetic - dysfunction as a pain generating mechanism.

Both a higher density of efferent sympathetic fibers in sural nerve biopsies of painful compared with painless peripheral neuropathies [80] and local sympathetic denervation in PDPN [81] were documented. Clinical forms of autonomic and painful/painless small fiber neuropathies have been described. A subgroup was reported of type 1 diabetic patients - mainly women - with severe autonomic symptoms, selective small fiber sensory, and autonomic impairment but with relatively preserved large fiber sensory modalities [70]. Moreover, acute reversible painful small fiber neuropathies associated with autonomic dysfunction induced by intensive glucose-control were recently well characterized in a large case series [82•]. Peripheral autonomic dysfunction has been documented in painful small fiber neuropathy of different etiologies [67, 83, 84], mostly concerning neural peripheral vascular control and cholinergic sudomotor function.

However, a preferential association of cardiovascular autonomic control abnormalities as expressed by cardiovascular autonomic reflex tests (CARTs) and painful DPN was not documented [39, 57, 85]. Young et al. [85] performed NCS and CARTs in 106 patients without DPN and with acute and chronic painful DPN or severe painless DPN with recurrent foot ulceration. They found a significant overall relationship between peripheral and autonomic dysfunction but subjects with painful DPN, despite the same degree of autonomic impairment, had a lower degree of NCS abnormalities compared with those with painless DPN. Somewhat in contrast, Veves et al. [57] in 122 patients with and without painful and painless DPN failed to show any difference in NCS, VPT, thermal thresholds, current perception thresholds, and CARTs between painful and painless DPN. In a smaller group of 30 patients, Kramer et al. [62] did not find differences in 7 cardiovascular autonomic measures between those with painful and painless DPN.

In another study, the Valsalva ratio was associated with PDPN and negatively related to pain intensity (Fig. 1), but this relation disappeared in multivariate analysis in favor of an index of DPN severity (ie, MDNS) [39]. Gandhi et al. [86] showed in 60 patients with painful or painless DPN that despite no differences in NCS, VPT, cooling detection thresholds, and CARTs, a few time- and frequency-domain indexes of short-term heart rate variability were lower in patients with painful compared with those with painless DPN. However, in interpreting these findings it should be taken into account the confounding effect of a possible sympathetic activation induced by pain itself (acting as a stressor) or by pain-related sleep disturbance [87] leading to an overall reduction of heart rate variability. A preliminary observation of an association between PDPN, sleep disturbance and reduced blood pressure fall during the night (nondipping) was reported that points to a condition of autonomic imbalance linked to chronic neuropathic pain [88]. Moreover, relief of pain may be accompanied by improved HRV indexes [89].

Although an association between autonomic dysfunction, mainly in the peripheral regions, and PDPN is to be expected, also in this case available observations do not allow a definite conclusion about a preferential link between autonomic dysfunction and neuropathic pain.

Morphological and Vascular Issues: Do Distinct Morphological or Vascular Abnormalities of Peripheral Nerves Account for the Development of Neuropathic Pain?

The existence of specific structural abnormalities of peripheral nerves in painful compared with painless peripheral neuropathy has been object of a number of studies, not only in diabetes [90]. Old morphological theories of painful DPN were based on nerve biopsy evidence or experimental findings and documented a number of possible histopathological abnormalities as characteristic of painful DPN and perhaps involved in pain generation such as active axonal degeneration, axonal atrophy (shrinkage), selective loss of small fibers, or increased regeneration with sprouting of small Aδ and C fibers [91, 92]. However, subsequent studies in sural nerve biopsies did not confirm these previous suggestions or provided inconsistent findings on the existence of histopathological markers of painful forms [90, 93, 94].

The availability of skin biopsy, and more recently of corneal confocal microscopy [95], to assess small fiber abnormalities has provided new insights into this issue (see previous sections).

High foot skin temperatures and increased blood flow in the lower limbs are considered characteristic of patients with DPN due to peripheral sympathetic denervation. These abnormalities were observed in a small number of patients with both PDPN and painless DPN [96]. However, patients with PDPN

still retained the ability to constrict their peripheral blood vessels in response to arousal stimuli and reduce peripheral flow whereas patients with painless DPN did not [96].

Using microlight-guided spectrophotometry and fluorescein angiography, higher epineurial intravascular oxygen saturation and higher epineurial blood flow were recorded within the sural nerve in 11 patients with PDPN compared with 8 with painless DPN [97]. This finding appeared to be in contrast with the observations in patients with DPN of sural nerve biopsies that showed microangiopathic alterations in the endoneurial vessels [98] and reduced oxygen tension, and of fluorescein angiography of sural nerves that detected microvascular abnormalities in epineurial arteries and veins, ie, arterial attenuation/tortuosity and arteriovenous shunting. These abnormalities in DPN patients were interpreted as responsible for a steal effect with consequent endoneurial hypoxia and nerve damage [99]. Quattrini et al. [100] found not significantly different results in foot skin vasodilator responses to acetylcholine and sodium nitroprusside but significantly impaired vasoconstrictor responses to sympathetic (deepest possible gasp) stimulation in 8 patients with PDPN compared with 10 with painless DPN, suggesting a role of sympathetic denervation in the development of cutaneous shunting and consequent reduction in dermal nutrition blood flow. Evidence of sympathetic denervation in the feet of diabetic patients with PDPN was also documented using tritiated norepinephrine spillover and Positron Emission Tomography [81]. Moreover, a greater impairment of C fiber mediated nerve axon reflex, ie, vasodilator responses to acetylcholine, was observed by Doupis et al. [101] in 31 patients with painless DPN compared with 46 with PDPN.

Then, inconsistent data exist also on a preferential link between local basal and stimulated vascular responses and the presence of neuropathic pain. However, pain relief was obtained in some PDPN patients by using local nitric oxide (NO) donor vasodilators (isosorbide dinitrate spray and glyceryl trinitrate patches) [102, 103].

Pathophysiology of Neuropathic Pain: Are There Specific Mechanisms of Neuropathic Pain in PDPN?

There is a considerable increase of knowledge of mechanisms of neuropathic pain [104, 105•, 106•]. Table 2 lists the putative pain mechanisms in peripheral neuropathies, most of them have derived by preclinical studies and just a few have been confirmed in human PDPN [107–109] (Table 2).

There are some clear points in this field: (a) a lesion to the somatosensory nervous system is a prerequisite for the development of neuropathic pain and, in the case of peripheral neuropathic pain, damage to peripheral sensory nerves, and subsequent primary afferent activity is widely considered as the initiating event; (b) consequent changes in structure and function of the somatosensory nervous system lead to spontaneous pain and pathological amplification of responses to noxious and innocuous stimuli, ie, allodynia and hyperalgesia; (c) neuropathic pain is expression of a maladaptive plasticity within the nociceptive system; (d) several mechanisms are involved in generation and maintaining of neuropathic pain; (e) pain mechanisms are not disease-specific and the same mechanisms may act in different diseases; (f) pain mechanisms are not symptom-specific and different mechanisms may induce the same symptom; and (g) multiple pain mechanisms may act in 1 individual patient [104, 105•].

Sensory Profile of Neuropathic Pain in PDPN

Given the multiplicity of pain mechanisms potentially acting in a single patient, a challenge in the therapeutic field is to identify the particular neurobiological mechanisms responsible for pain in individual patients.

The recognition of multidimensional nature of neuropathic pain and the availability of assessment tools, aimed at measuring neuropathic pain dimensions, have led to the description of sensory profiles of neuropathic pain in different conditions, including PDPN. Using the pain *DETECT* screening tool, in a large PDPN population, Baron et al. [110] found that the association between burning, prickling, and numbness was the most common pain sensory profile (26 %), followed by the pattern of pain attacks (16 %), burning with both prickling and allodynia without numbness (13 %), and allodynia with pressure hyperalgesia (9 %). Using the assessment tool NPSI, 59 patients with PDPN reported paresthesia/dysesthesia (tingling and pins and needles) and burning as the most frequent sensory descriptors (96 % and 87 %, respectively), followed by paroxysmal pain (electric shock and stabbing), evoked pain (by brushing, pressure and cold), and deep pain (squeezing and pressure) [111].

With regard to the topic of this paper, a possible question to be answered could be whether the sensory profiles identified in PDPN correspond to different underlying pathophysiologic conditions. For example, if the combination of numbness and burning pain without allodynia indicates a severe length-dependent denervation of afferents neurons as the leading mechanism and substrate, whereas burning pain with allodynia and no/mild sensory deficits could suggest peripheral sensitization and irritable nociceptors [112]. These aspects, however, are still under investigation, although in patients with distal symmetrical polyneuropathy, including 46 with PDPN, laser-evoked potentials, which assess nociceptive Aδ fiber function, were more severely affected in presence of ongoing pain, ie, burning pain, than in presence of

Table 2 Mechanisms of neuropathic pain in peripheral polyneuropathies and PDPN

Mechanisms	Somatosensory system level	Consequences	Insights into neurobiological molecular mechanisms
Peripheral sensitization	Nociceptors and sensory nerve endings	• Reduction in thermal and mechanical pain thresholds; • pain is generated in presence of innocuous or noxious stimulus (ie, primary allodynia and hyperalgesia)	• Nociceptor sensitization due to increased membrane excitability without inflammation (irritable nociceptors) (recorded by microneurography in PDPN) [107]; • upregulation of receptor proteins, such as TRPV1, on uninjured C-fibers
Ectopic impulse generation	Afferent nerve fibers: nociceptors and Aβ fibers	• Spontaneous pain or paresthesia/dysesthesia are generated in the absence of stimulus	• Spontaneous ectopic activity recorded by microneurography in PDPN [108, 109]; • changes in sensory neuron ion channel expression, including voltage gated sodium channels (Nav 1.3, Nav 1.6, Nav 1.9) [119, 122••]
Central sensitization	Spinal cord	• Secondary allodynia or hyperalgesia are generated in the presence of innocuous or noxious stimulus	• Spinal cord hyperexcitability and abnormal central sensory processing; • presynaptic changes: alterations in the synthesis of transmitters and neuromodulators and in calcium channel density; • postsynaptic changes: phosphorylation of NMDA subunits and increased receptor density
Centralization	Spinal cord and brain stem	• Pain is maintained independently of any ongoing peripheral input	• Increased excitability; • structural alterations in synaptic circuitry; • degeneration of inhibitory interneurons; • alterations in the brain stem regulation of nociceptive transmission
Ectopic transduction	Spinal cord	• Possible cause of spontaneous pain	• Enhanced sensitivity of injured sensory neurons to endogenous thermal and chemical stimuli
Changes in DRG cells	DRG cells	• Involved in both ectopic activity and central sensitization	• Sympathetic-sensory neuron coupling (with abnormal release of substance P from A fibers); • changes in the expression and phosphorylation of Nav leading to increased DRG neurons excitability; • upregulation of messenger RNA and protein levels for the Nav1.3, Nav1.6, Nav 1.7, Nav 1.8 and Nav1.9 contributing to electrogenesis in DRG neurons
Disinhibition in spinal cord	Spinal cord	• Disinhibition and facilitation of spinal cord horn neurons; • involved also in central sensitization	• Loss of spinal inhibitory interneurons; • reduction in μ opioids receptors; • loss of pre- and postsynaptic GABAergic inhibitions (controversial); • dysfunction of descending pathways that modulate the spinal transmission of nociceptive input
Structural changes	Spinal cord, DRG	• Structural neuroplasticity may form an unremitting source of central sensitization	• Sprouting of the central axon terminals of injured neurons in the spinal cord; • neuroplasticity of CGRP fibers within the spinal nociceptive network
Neurodegeneration	Spinal and brain neurons	• Uncertain role	• Degeneration and loss of spinal and brain neurons after peripheral nerve damage and chronic pain
Neuroimmune interaction	Spinal cord	• It enhances excitability of second-order neurons in the spinal cord dorsal horn and contributes to the induction and maintenance of neuropathic pain	• Activation of microglia and macrophages of CNS via chemokines, such as CCL2; • microglia and astrocytes release neuroactive immune-related modulators (cytokines and growth factors, such as TNFα and BDNF) and increase glutamate concentration [116•]

Table 2 (continued)

Mechanisms	Somatosensory system level	Consequences	Insights into neurobiological molecular mechanisms
Changes in thalamic activity	Thalamus	• Thalamic neurons can act as central generators or amplifiers of pain in diabetes	• Lower thalamic expression of N-acetylaspartate in patients with PDPN [124]; • increased thalamic vascularity in PDPN patients [128]; • hyperexcitability of thalamus in animal models of PDPN [131]

BDNF brain-derived neurotrophic factor, *CCL2* Chemokine (C-C motif) ligand 2, *CGRP* calcitonin gene-related peptide, *CNS* central nervous system, *DRG* Dorsal root ganglia, *GABA* gamma-amino-butyric acid, Na_v voltage-gated sodium channels, *NMDA* N-methyl-D-aspartate, *TNFα* tumor necrosis factor-α, *TRPV1* transient receptor vanilloid 1

provoked pain and correlated with the intensity of ongoing pain [113]. The authors suggested that ongoing pain reflects damage to nociceptive axons whereas provoked pain would relate to the abnormal activity arising from partially spared and sensitized nociceptive terminals [113].

Immune Response, Inflammation, and Pain

Increasing evidence exists in animal and human studies of an association between inflammation and diabetic neuropathy [114] and of a role of cytokines in the induction and maintenance of pain [115, 116•]. After neuronal injury, a robust immune response is elicited at the level of the somatosensory system with bi-directional signalling between the sensory and the immune system that involves injured neurons, glial cells, immune cells, cytokines, and chemokines and affects the generation and transmission of neuropathic pain [116•].

Doupis et al. [101] showed that while DPN was already associated with increased biochemical markers of inflammation and changes in the levels of various growth factors, PDPN was associated with a further increase in markers of inflammation and endothelial dysfunction, as indicated by the higher levels of C-reactive protein and soluble intercellular adhesion molecule, respectively, but with a preservation of the nerve axon reflex. The authors considered these findings as a proof of concept that inflammation and endothelial dysfunction may indeed play a role in the development of painful neuropathy. Moreover, high levels of interleukin-2 (IL-2) [117], tumor necrosis factor alpha (TNF-α) [117, 118], and high inducible NO synthase and TNF-α immunoreactivity of macrophages [118] were associated with painful compared with non painful neuropathy [117] or DPN [118]. Pro-inflammatory cytokines in the plasma were correlated with increasing pain intensity [118]. There is insufficient evidence, however, to affirm that increased inflammation can be considered a discriminant between painful and painless DPN.

Hyperglycemia-Dependent Mechanisms of Pain

Several hyperglycemia-related mechanisms clearly involved in the pathogenesis of DPN have also been implicated in experimental conditions in neuropathic hyperalgesia and abnormal sensation, such as increased aldose reductase activity, oxidative-nitrosative stress, protein kinase C, poly (ADP-ribose) polymerase (PARP), p38-MAP kinase activity, proinflammatory response (increase in TNF-α and COX-2 activity) [119]. Dysregulation of neuronal Ca^{2+} homeostasis, produced by reduced stimulation of insulin receptors, has been proposed as an early mechanism for both nerve degeneration and neuropathic pain of DPN [120].

Recently, new insights into the relation between hyperglycemia and pain generating mechanisms have been provided by the identification of a mechanism of action of methylglyoxal that may account for diabetic hyperalgesia and appears to be independent on structural changes of nerves. Methylglyoxal, also called pyruvaldehyde, is the product of glycolysis, it reacts non-enzymatically with arginine residues of proteins to form the advanced glycation end products (AGEs), such as argpyrimidine that is also contained in heat shock protein 27 (HSP27). Methylglyoxal is increased in patients with type 2 diabetes, enhances in vitro platelet-neutrophil aggregation and has been linked to the development of atherosclerosis and heart failure [121]. Bierhaus et al. [122••] have shown that methylglyoxal plasma levels were increased in 10 type 2 patients with PDPN compared with 10 patients with painless DPN. Moreover, further experiments showed that methylglyoxal induces post-translational modification of the nociceptor-specific sodium channel Nav1.8 and in this way it facilitates nociceptive neuron firing, enhances sensory neuron excitability in animal models, and causes hyperalgesia in diabetic neuropathy, at the same time that it slows myelinated nerve conduction and drives Nav1.7 into slow inactivation. Thus, methylglyoxal-dependent modification in Nav1.8 has a role in diabetes-associated hyperalgesia that is independent of

degenerative or regenerative changes in the nerve [122••]. Glyoxalase 1 (Glo1) and glyoxalase 2 (Glo2) are the enzymes that metabolize methylglyoxal and represent an enzymatic defense system against glycation; altered Glo1 activity is associated with late diabetic complications. Skapare et al. [123] showed that the activity of the Glo1 enzyme was lower in blood samples from type 1 and type 2 patients with PDPN, supporting the hypothesis that Glo1 activity modulates the phenotype of diabetic neuropathy.

Central Mechanisms of Pain

Some evidence exists of involvement of CNS at different levels in DPN and PDPN. Magnetic resonance (MR) documented a significant shrinkage of the spinal cord not only in patients with established DPN [124] but also in type 1 patients with subclinical DPN, with correlations between cord area and neurophysiological parameters of DPN [125]. This would suggest that neuropathic process is not confined to the peripheral nerve but appears to early involve also the spinal cord.

Proton MR spectroscopy showed that thalamic N-acetyl aspartate (NAA), marker for brain neuronal and axonal integrity in vivo, was significantly lower in the group of patients with DPN compared with those without, with an additional correlation between NAA and neurophysiological indexes of DPN [126]. Similarly, Sorensen et al. [127] observed a lower thalamic expression of NAA in patients with PDPN than in those without. Moreover, thalamic relative cerebral blood flow, assessed using MR perfusion imaging, was lower in patients with DPN compared with those without, but it was higher in patients with painful PDPN, suggesting increased thalamic vascularity in painful and greater thalamic microvascular impairment in painless DPN [128].

Cauda et al. [129] used functional MR imaging (fMRI) to explore thalamocortical functional connectivity in a group of 8 patients with PDPN and found decreased resting state functional connectivity between the thalamus and the cortex compared with healthy individuals. They suggested that chronic pain can alter thalamocortical connections causing a disruption of thalamic feedback, and supported the view of chronic pain as a thalamocortical dysrhythmia leaving unanswered, however, the question of the meaning - adaptive or misadaptive - of this plastic change of thalamus in conditions of chronic neuropathic pain. With the same technique but in different experimental conditions (ie, nociceptive heat stimulation applied to both foot and thigh region) a significant increase in neuronal activation within the pain matrix during foot stimulation was observed in healthy volunteers and patients with painful DPN but not in painless DPN [130•]. This is not unexpected because these latter subjects were insensate at this stimulation site. Patients with painful DPN displayed significantly greater neuronal activation within the pain matrix (insula, anterior cingulated cortex, prefrontal cortex, thalamus, primary and secondary somatosensory cortices, and the basal ganglia) compared with both painless DPN and healthy subjects [130•].

Finally, functional observations in experimental diabetes documented enhanced spontaneous neuronal activity and an increase in responsiveness of thalamic neurons to peripheral stimulation indicative of a thalamic hyperexcitability [131]. These data suggest that thalamic neurons might not only amplify pain messages that are sent centrally from peripheral neurons, but also act as intrinsic generators of impulses, projected rostrally, and interpreted by the brain as signalling pain [131, 132•].

Thus, a central plasticity occurs in conditions of chronic pain and also in PDPN. It is not clear if this phenomenon is just consequent to pain per se or whether it can be influenced by the different degree of sensory deficits. Other factors affecting the central processing of neuropathic pain might be cognitive dysfunction and depression/anxiety.

Genetic Susceptibility to Pain

The role of genetic factors in the development of neuropathic pain has been increasingly recognized, starting from the observation that loss-of-function mutation in the gene for Nav1.7 leads to congenital analgesia whereas gain-of-function leads to inherited erythromelalgia [133]. Gain-of-function variants of sodium channel Nav1.7 have recently been found also in 29 % of cases of idiopathic painful small-fiber neuropathy [134]. Mutations of Nav1.8 have been found in 9 subjects within a series of 104 patients with painful predominantly small-fiber neuropathy, 3 of which met the criteria for potential pathogenicity [135]. Other studies have indicated in animal models up-regulation of some genes coding for tetrahydrobiopterin (BH4), including GCH1. BH4 is an essential cofactor for aromatic amine hydroxylases, which synthesize serotonin and catecholamines, and for all NO synthases. NO is a very versatile, tightly controlled molecule that contributes to the functional adaptations of nociceptive synapses in the whole pain pathway with a prevalent nociceptive role but also neuroprotective effects [136]. Increased BH4 synthesis in the injured DRG contributes to increase NO release and produces a large calcium flux in DRG neurons and thus promotes their excitability. Inhibition of GCH1 was found to have analgesic effect in animal models. In humans, an association of a haplotype of GCH1 with the development of pain after surgery for prolapsed disk or with other hyperalgesic conditions has been demonstrated [137].

These findings have pointed to the need for genome-wide association studies in carefully phenotyped cohorts to identify genetic contributions to the risk of developing neuropathic pain and also to develop a gene-therapeutic approach to neuropathic pain [104, 138]. Moreover, the concept of

genomic susceptibility, which in combination with the environment determines the risk for neuropathic pain, may help in understanding the preferential development of neuropathic pain in patients with PDPN.

Pain in RCTs in Diabetic Neuropathy. Why is Pain More Responsive to Disease-Modifying Intervention than Other Neurologic Endpoints?

When considering the long series of RCTs in DPN (the majority of which unsuccessful) it may come to light that neuropathic symptoms (including pain) behaved, at least in some trials, as more sensitive endpoints than other neurologic measures, and as such were able to detect significant changes induced by active treatment. This happened with aldose reductase inhibitors [139], acylcarnitine [140], actovegin [141], VEGF [142], alpha lipoic acid [143, 144], and a combination of L-methylfolate, methylcobalamin, and pyridoxal-5′-phosphate [145]. This could be due to the intrinsically subjective nature of symptoms but it may also suggest that neuropathic pain is more susceptible to dynamic processes and changes and that somehow, different mechanisms may prevent the development of pain and of sensory deficits.

Conclusions

The point of this article was to try to identify which patients are prone to developing PDPN and why. Despite the fact that a clear profile could not be created, some clues can aid ongoing research or more simply may act as cues for reflection.

While painful and painless DPN share most risk markers, the relationship with obesity, however, would appear more prominent for the painful form. Neuropathic pain can develop or persist also at advanced stages of DPN, and an increasing severity of sensory deficits is associated with an increased risk of developing neuropathic pain. Although somatic small fiber damage is considered a prerequisite for neuropathic pain development in diabetes, there is no definite evidence of an exclusive or prominent involvement of small fibers in PDPN. Thus, neurologic — functional and structural — biomarkers for the development of neuropathic pain are still lacking.

At the end of this attempt to answer the question in the title, the overwhelming complexity of neuropathic pain is what comes through most clearly, ie, the multiplicity of pain mechanisms that despite stemming from the common soil of peripheral nerve damage (at the level of small and usually also large nerve fibers) can take different directions, in a dynamic way that might change through the subsequent stages of nerve disease. Some new findings point to a peculiar role in neuropathic pain generation of genetic susceptibility, inflammation, direct hyperalgesic effect of hyperglycemia, and central processing of neuropathic pain. Thus, PDPN probably needs, for its development, the intervention of distinct contributors: gender, genetics, particular nuances of metabolic derangement (greater glycemic oscillations, more dyslipidemia, more oxidative stress, more inflammation), psychological and behavioral interactions, and environment.

Considerations for Future Research

A number of issues have not been fully addressed and remain open for future research, among which the following:

- the need to identify genetic markers for pain development;
- the need to identify pain phenotypes, ie, clusters of symptoms and signs (including measures of nerve fibre function and structure);
- the need to clarify the role of central mechanisms and the interfering factors on pain transmission and generation, such as psychological factors;
- the need to better define the natural history of PDPN in type 1 and type 2 diabetes (and possibly since prediabetes) in order to detect risk markers and turning points that become potential targets for intervention;
- the need for a more accurate diagnosis of neuropathic pain and of PDPN in clinical research to obtain well-selected PDPN patients and to avoid the inclusion of those with mixed pain or non-PDPN conditions.

Acknowledgment Carla Greco is a trainee of the Specialization School for Nutritional Sciences of Tor Vergata University, Rome, Italy.

Conflict of Interest Vincenza Spallone has board membership with Wörwag Pharma, TRIGOcare International, Daichii Sankyo Europe, and Ely Lilly Italy. She also has been a consultant for AWP srl, Wörwag Pharma Group. She has received grant support from Biocure SrL. She has received payment for development of educational presentations including service on speakers' bureaus for continuing medical education from Ely Lilly Italy, Sanofi Aventis, and Pfizer Italy.

Carla Greco declares that she has no conflict of interest.

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