Topical Review

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Risk factors for neuropathic pain in diabetes mellitus

Harry L. Hébert*, Abirami Veluchamy, Nicola Torrance, Blair H. Smith

1. Introduction

According to the International Diabetes Federation, diabetes mellitus (DM) is estimated to affect around 415 million adults worldwide, roughly 8.8% of the adult population, with the figure projected to rise to over 600 million by 2040.[20] Regional prevalence varies from 3.2% in Africa to 12.9% in North America. Diabetes mellitus is associated with a number of chronic sequelae and around 50% of people with DM go on to develop polyneuropathy.[35] This condition has a variety of clinical manifestations, which are grouped into positive symptoms including dysesthesia (abnormal sense of touch), tingling and itching, and negative symptoms including numbness, muscle weakness, and trouble with balance. Up to 25% of people with diabetic neuropathy (DN) also develop neuropathic pain (NP).[39] Neuropathic pain is defined by the International Association for The Study of Pain as "pain directly caused by a lesion or disease affecting the somatosensory system."[12,22] Symptoms of painful diabetic neuropathy (PDN) include those described above for nonpainful DN with additional "burning," "electric shocks," "stabbing," and "pins and needles" symptoms all being described. Painful diabetic neuropathy is associated with increased distress and poor quality of life compared with nonpainful DN, DM, and the general population[38] including depression, anxiety, and sleep disturbance.[15] In addition, an association has been described with reduced productivity and employability at work compared with nonpainful DN.[37] The combination of these factors places a large economic burden on patients and health care services,[10] a situation likely to grow steadily worse with the aforementioned projected rise in DM prevalence. This situation is further exacerbated by the fact that 13% of patients with PDN do not report their symptoms to primary care, and 39% of patients with PDN have never received treatment.[8] Even for those patients who do attend primary and secondary care for their diabetes, pain is not a symptom that is always included in clinical assessments. Furthermore, not all patients with DN develop PDN, and the reasons for this are unclear.

Understanding the risk factors for PDN will go some way to resolving this and will also help to inform management and prevention of this painful condition by health care services. Any factor that increases the risk of DM or DN is likely to be a risk factor for PDN. However, it is the specific nature and magnitude of the risk that remains unclear and is the focus of this topical review.

2. Risk factors

There have been relatively few published studies examining risk factors specifically for PDN in DM. Clinical, environmental, and genetic factors have been shown to be predictive of developing DM and some of these have also been implicated in the development of DN, including age,[11] body mass index,[25,28] hypertension,[13] smoking, and waist circumference[28] (**Fig. 1**). Given the likely overlap of risk factors between DM and DN, it seems reasonable to hypothesize that some of these factors will also influence the development of PDN.

We conducted a literature search using relevant key words and terms aiming to identify a wide range of studies that investigated risk factors for PDN and to include all the important studies (**Table 1**). A number of limitations can be identified with these studies as a whole. Most of these studies are cross sectional in nature and therefore unable to establish temporal relationship between patient characteristics/factors and PDN. Some studies report only univariate analysis and are therefore unable to assess intervariable relationships and to identify confounding between variables.[2,6,8,9,17,23,30] In addition, it is not always clear in the methods and statistical analyses whether PDN or nonpainful DN is being analysed and what control group the PDN subjects are being compared with. In some studies, those in the control group are diabetic participants with nonpainful neuropathy[30,38,41] and in others they are diabetic participants without neuropathy of any form.[1,2,6,8,11,17] In other studies, it is not possible to determine the nature of the control group from the description of the methods. There was considerable heterogeneity in PDN case ascertainment, with only 6 studies using a validated NP screening questionnaire (the DN4[6,7,17,21,38] or the Leeds assessment of neuropathic symptoms and signs[11]) with the remainder using nonvalidated questionnaires or clinical examinations. This makes it difficult to assess the sensitivity and specificity of each study to identify PDN cases and to make direct comparisons between studies as effect size estimations and associations are likely to be different. Despite these limitations, some potential risk factors have emerged, including environment, clinical, lifestyle, and genetic factors.

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Chronic Pain Research Group, Division of Population Health Sciences, Ninewells Hospital and Medical School, Mackenzie Building, University of Dundee, Dundee, Scotland, United Kingdom

**Corresponding author. Address: Chronic Pain Research Group, Division of Population Health Sciences, Ninewells Hospital and Medical School, Mackenzie Building, University of Dundee, Dundee DD2 4BF, Scotland, United Kingdom. Tel.: +(44) 01382 383191. E-mail address: h.hebert@dundee.ac.uk (H. L. Hébert).*

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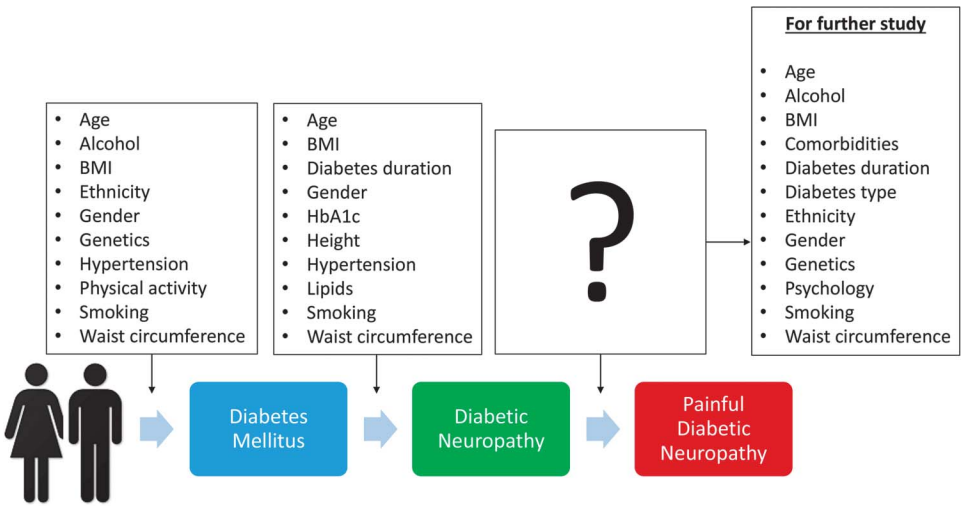

Figure 1. Schematic of the process from diabetes mellitus to diabetic neuropathy and finally painful diabetic neuropathy. Both diabetes mellitus and diabetic neuropathy have their own set of risk factors, both of which could provide important clues as to the risk factors that contribute to painful diabetic neuropathy.

2.1. Demographic

Two nonmodifiable factors—age[2,17,21,38,42] and sex[1,11,17,21,41]—have been specifically associated with PDN, in addition to their known roles as risk factors for DM. Although these are of limited use to clinicians in terms of intervention, they could provide useful clues as to the underlying biological pathways involved and increased awareness of at-risk patients. In particular, the association of PDN with older age (>50 years) is likely to be related to the time it takes for nerve damage and painful symptoms to develop after the onset of DM and the decreased ability of the body to deal with this. Similarly, gender associations may indicate possible subtle differences in biology and psychosocial factors that affect the risk of PDN, something that requires further investigation. It is interesting to note that while 4 of the studies report greater risk in women,[1,11,17,21] 1 study reports greater risk in men.[41] This discrepancy in the latter study could be related to the limited statistical analysis, which did not adjust for potential confounding factors. Despite the prevalence of DM varying according to ethnicity, this has not been found as a risk factor so far for PDN.[1,17,18,21,32,36] One study reported that South Asians were more likely to report painful symptoms than people in other ethnic groups in the absence of clinical neuropathy.[1] Another found an association with pain among people with DM residing in a Gulf state and Lebanon compared with Egypt, but did not analyse ethnic origin.[21]

2.2. Clinical

Clinical and physiological factors associated with PDN are important for clinicians and primary care as they may indicate possibilities for targeted treatment or primary prevention strategies. The clinical diagnosis of the type of DM and the duration since onset of the disease may be particularly relevant. Two studies found an association with DM type in multivariate analysis, with 1 identifying type 1 diabetes (T1D)[21] and the other type 2 diabetes (T2D)[1] as conferring greater risk of PDN. Differences in case definition and study populations could have contributed to the heterogeneity in these results. A clearer consensus is apparent for DM duration with risk increasing over time since diagnosis.[2,6,17,21,32,38] Severity of preceding neuropathy has been found to be associated with PDN, but associations with neuropathy duration and comparison with type of (peripheral or sensory) neuropathy have not been found.[9,11,33,36] Most studies included only 1 type of neuropathy in their analysis. A number of clinical factors and comorbidities have been found to be associated with PDN. These include poor glycaemic control and high HbA1c levels,[2,18,36] hypertension,[2,18] retinopathy,[2] nephropathy,[2,38] cardiovascular disease,[2,42,43] and glycosuria.[18] However, as these conditions are all known complications of DM, it is uncertain from cross-sectional analysis whether these factors are contributing to PDN risk and onset, or simply coexisting factors, perhaps confounded by other factors or with shared aetiology. Biomarkers for the development of PDN can be exploited by providing preventative or diagnostic tests. In this respect, tumour necrosis factor alpha and inducible nitric oxide synthase expression,[30] triglycerides, and low high-density lipoprotein cholesterol[38] all show promising associations but require replication to be confident in their role in disease pathogenesis.

2.3. Lifestyle

Behavioural and social circumstances are important lifestyle aspects that patients can theoretically influence and act on, with greater or less practical difficulty. In particular, some physical characteristics known to be associated with DM and DN are also implicated in PDN. Body mass index has been clearly linked to PDN, particularly in the form of obesity (≥30 kg/m^2),[21,33,38] while in another study, weight was reported independently of height and found to be significantly associated with PDN, although this was attenuated in multivariate analysis.[42] A related study also found a positive correlation with increased waist circumference and high levels of physical activity and risk of PDN.[43] Despite being included in the analyses in most of the studies,[1,2,4,8,17,18,21,32,33,38,42,43] smoking and alcohol consumption have not been specifically associated with PDN. Psychological factors have also been widely reported in the context of general chronic pain, but its relationship with PDN is less clear. Increased depression, anxiety, enjoyment of life, and social relationships are associated with PDN, but without prospective studies and longitudinal analysis, the temporal relationship cannot be established.[7,15]

Table 1

List of studies conducted on predictors of painful diabetic neuropathy and their characteristics.

Reference	Study type	Population	Criteria for NP	Sample size	Analysis	Variables analysed	Predictors	OR (95% CI)/*P*
Abbott et al., 2011[1]	Cross sectional	UK	NSS ≥ 5 and NDS ≥ 3	3242 DM with NP	Multivariate logistic regression	Age, alcohol, diabetes duration, diabetes treatment, diabetes type, ethnicity, foot ulcer, foot deformities, impaired vision, lower limb amputation, nephropathy, PAD, sex, and smoking	T2D	2.1 (1.7-2.4)
				12,372 DM without PDN			Women	1.5 (1.4-1.6)
AlQuliti, 2015[2]	Case control	Saudi Arabia	Foot examination and NSS ≥3	99 T2D with PDN	Univariate analysis	Age, CVD, diabetes duration, glycaemic control, HbA1c, hypertension, insulin use, nephropathy, oral antidiabetic drugs, PVD, retinopathy, sex, smoking, stroke, and working status	Age (>50 y)	1.93 (1.09-3.41)
				99 T2D without PDN			CVD	3.37 (1.28-8.89)
							Diabetes duration (>10 y)	3.38 (1.88-6.07)
							Glycaemic control	0.42 (0.12-0.96)
							Hypertension	2.85 (1.57-5.17)
							Nephropathy	8.93 (2.58-30.95)
							Retinopathy	13.22 (4.49-38.95)
Benbow et al., 1997[4]	Cross sectional	UK	Clinical history and examination; burning/shooting pain/ hyperesthesia ≥6 mo and at least 1 abnormal neurological sign from decrease in light touch, vibration, or pinprick sensation	49 DN with NP	Univariate analysis	Age, diabetes duration, diabetes type, HbA1c, sex, and smoking	NA	NA
				23 DN without NP				
Cheng et al., 2010[5]	Genetic case–control/ cross sectional	Taiwan	Pain VAS ≥4 and grade 3-5 of occurrence of pain in daily activities	15 DFU (and DN) with NP	Univariate analysis/ Fisher exact	Age, albumin, amputation, BMI, diabetes duration, diabetes type, haemoglobin, HbA1c, hyperlipidemia, hypertension, rs1799971 of *OPRM1,* and sex	rs1799971	0.24 (0.07-0.8)
				50 DFU (and DN) without NP				
Cortez et al., 2014[6]	Cross sectional	Brazil	DN4 ≥ 4	12 T2D with PDN	Multivariate analysis	Age, depressive symptoms, diabetes duration, drug adhesion, sex, and glycaemic control	Diabetes duration	$P = 0.031$
				60 T2D without PDN				
D'Amato et al., 2016[7]	Cross sectional	Italy	DN4 ≥ 4 (DN4 interview ≥ 3)	25 DN with NP 46 DN without NP 110 without DN	Multivariate analysis	Depression	Depression (BDI-II)	4.56 (1.09-19.1)

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Table 1 (*continued*)

Reference	Study type	Population	Criteria for NP	Sample size	Analysis	Variables analysed	Predictors	OR (95% CI)/*P*
Daousi et al., 2004[8]	Cross sectional	UK	Typical NP symptoms in legs ≥1 y, PSS ≥ 3 and NDS ≥ 6 or NDS ≥ 3 and NSS ≥ 5	56 DM with PDN 289 DM without PDN	Univariate analysis	Age, alcohol, angina, BMI, BP, CVA, depression, diabetes duration, diabetes type, foot ulceration, HbA1c, hypertension, MI, PVD, sex, and smoking	NA	NA
Davies et al., 2006[9]	Cross sectional	UK	Positive response to "Do you have a burning, aching or tenderness in your legs or feet?" from DNSS and TCSS score >5	71 T2D with PDN (51 with NP and 20 with mixed NP and non-NP) 99 T2D with non-NP 99 T2D with no pain	Univariate analysis	Age, diabetes duration, HbA1c, neuropathy severity, and sex	Severity of neuropathy	$P < 0.0001$
Erbas et al., 2011[11]	Cross sectional	Turkey	LANSS ≥ 12	156 DM with PDN 975 DM without PDN	Univariate analysis	Age, blood urea BMI, BUN, creatinine, diabetes duration, diabetes type, FPG, HbA1c, PPG, and sex	Duration of diabetes T1D Women	$P = 0.001$ $P = 0.039$ $P = 0.001$
Gore et al., 2005[15]	Cross sectional	USA	Physician diagnosed	255 with PDN	Univariate analysis	Anxiety, depression, enjoyment of life, mental health, mood, and relationship with others	Anxiety (HADS) Depression (HADS) Enjoyment of life (BPI-DPN) Mental health (SF-12v2) Mood (BPI-DPN) Relationship with others (BPI-DPN)	All $P < 0.05$
Halawa et al., 2010[17]	Cross sectional	Saudi Arabia	DN4 ≥ 4	678 DM with PDN 361 DM without PDN	Univariate analysis	Age, BMI, diabetes duration, diabetes type, ethnicity, smoking, and sex	Age Diabetes duration Women	$P < 0.001$ $P < 0.001$ $P = 0.024$
Harris et al., 1993[18]	Cross sectional	USA	Positive response to, "During the past 3 mo, have you had a painful sensation or tingling in your hands or feet?"	2392 with DM (26.8% of whom had pain/tingling in hands/feet?) 20,037 without DM	Multivariate logistic regression	Age, amputation, angina, diabetes age, diabetes duration, ethnicity, family income, foot sores, height, higher education, hypertension, insulin, nephropathy, obesity, periodontal disease, proteinuria, retinopathy, sex, smoking, and stroke	Glycosuria Hyperglycaemia Hypertension	2.31 (1.54-3.47) 2.51 (1.81-3.49) 1.58 (1.31-1.90)

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Table 1 (*continued*)

Reference	Study type	Population	Criteria for NP	Sample size	Analysis	Variables analysed	Predictors	OR (95% CI)/*P*
Jambart et al., 2011[21]	Cross sectional	Middle East Region	DN4 ≥ 4	2144 DM with PDN	Multivariate regression	Age, BMI, diabetes duration, diabetes type, ethnicity, sex, and smoking	Age (50-64 y)	1.75 (1.48-2.08)
				1845 DM without PDN			Age (≥65 y)	2.13 (1.72-2.62)
							BMI (≥30 kg/m^2)	1.35 (1.17-1.56)
							Diabetes duration (≥10 y)	2.43 (2.10-2.81)
							Living in a Gulf State (compared with Egypt)	0.44 (0.35-0.56)
							Living in Lebanon (compared with Egypt)	0.66 (0.54-0.81)
							T1D	1.59 (1.24-2.05)
							Women	1.27 (1.11-1.46)
Li et al., 2015[23]	Genetic case control	USA/ Canada	NCT00501202: lower extremity pain ≥3 mo	887 DM with PDN	Univariate analysis	SNPs across *SCN9A* gene region	rs74449889 (*SCN9A*)	2.6
			NCT00870454: as above and NRS-11 ≥11	1029 without DM and PDN			rs3750904 (*SCN9A*)	2.2
			NCT00993018: Symmetrical pain beginning in feet >6 mo and NRS-11 ≥5 but <10 over 7 d.				rs4369876 (*SCN9A*)	2.1
			NCT00455520: clinical diagnosis with signs and symptoms >6 mo and at screening				rs12478318 (*SCN9A*)	2.1
			NCT01041859: As NCT00455520 and pain must include reduction/absence of pin sensibility					
			NCT01063868: As for NCT00455520 and NCT01041859 plus baseline NRS-11 ≥4					
Meng et al., 2015[27]	GWAS	UK	Prescription of at least one from duloxetine, gabapentin, pregabalin, capsaicin cream/ patch, and lidocaine patch. And positive monofilament test in at least 1 foot	572 DM with PDN	Fisher exact	SNPs across whole genome	rs17428041 (Chr8p21.3)	0.67 (0.57-0.78)
				2491 DM without PDN				
Meng et al., 2015[26]	GWAS	UK	Multiple usage of at least 1 from duloxetine, gabapentin, pregabalin, capsaicin cream/ patch, lidocaine patch	961 DM with PDN	Logistic regression	SNPs across whole genome	rs71647933 (Chr1p35.1)	2.31 (1.68-3.17)
				3260 DM without PDN			rs6986153 (Chr8p23.1)	1.67 (1.34-2.08)

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Table 1 (*continued*)

Reference	Study type	Population	Criteria for NP	Sample size	Analysis	Variables analysed	Predictors	OR (95% CI)/*P*
Purwata, 2011[30]	Case control	Indonesia	Pain intensity VAS >0 (representing no pain)	59 DN with NP	Univariate analysis	Age, diabetes duration, FG, HbA1c, iNOS expression, plasma TNF-α, TNF-α expression, and 2h-G	iNOS expression	3.546 (1.613-7.795)
				51 DN without NP			Plasma TNF-α	5.053 (2.241-11.392)
							TNF-α expression	4.125 (1.805-9.425)
Sorensen et al., 2002[32]	Cross sectional	Australia	Bilateral and symmetrical foot pain—patient specifically asked about foot pain	2610 T2D (3.3% with PDN)	Multivariate logistic regression	Age, alcohol, diabetes duration, diabetes treatment, ethnicity, HbA1c, height, sex, and smoking	Diabetes Duration	1.09 (1.06-1.1)
Spallone et al., 2011[33]	Cross sectional	Italy	Clinical examination and history	78 DN with NP	Multivariate logistic regression	Age, alcohol, BMI, BP, creatinine, CVD, diabetes duration, diabetes type, HbA1c, HDL, hypertension, LDL, nephropathy, PAD, physical activity, retinopathy, sex, smoking, triglyceride, and waist circumference	BMI (kg/m^2)	1.22 (1.08-1.37)
				57 DN without NP 56 without DN or NP			Severity of neuropathy	1.27 (1.11-1.44)
Themistocleous et al., 2016[36]	Cross sectional	UK	IASP/NeuPSIG grading system	70 DPN with moderate/severe NP	Univariate analysis	Age, BMI, diabetes duration, diabetes type, ethnicity, HbA1c, neuropathy severity, orthostatic hypotension, ratio, sex, standing and lying BP, and waist–hip circumference	HbA1c and neuropathy severity	$P < 0.01$
				41 DPN with mild NP 80 DPN without NP				$P < 0.01$
Van Acker et al., 2009[38]	Cross sectional	Belgium	DN4 ≥ 4 and positive Neuropen test	157 DN with NP	Multivariate logistic regression	Age, BMI, BP, diabetes duration, foot lesions, HbA1c, HDL, insulin, LDL, nephropathy, retinopathy, sex, triglycerides, and waist circumference	Age (per 10 y)	1.47 (1.20-1.81)
				321 DN without NP			Diabetes duration (per 5 y)	1.14 (1.02-1.28)
							HDL cholesterol (≤1 mmol/L for men, ≤1.3 mmol/L for women)	2.17 (1.38-3.41)
							Nephropathy	1.69 (1.10-2.59)
							Obesity (≥30 kg/m^2)	1.62 (1.05-2.49)
							Triglycerides (≥1.7 mmol/L)	1.76 (1.13-2.75)
Wu et al., 2007[41]	Cross sectional	France	MNSI ≥ 7 and Q5 of BPI ≥ 1	72 DN with NP	No statistical analysis	Age, diabetes age, diabetes duration, diabetes type, education, employment, region, and sex	Age (over 65 y)	NA
				12 DN without NP			Men	

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Table 1 (*continued*)

Reference	Study type	Population	Criteria for NP	Sample size	Analysis	Variables analysed	Predictors	OR (95% CI)/*P*
Ziegler et al., 2009[42]	Cross sectional	Germany	MNSI > 2 and positive answer to Q2 and Q6	195 DM (13.3% with NP)	Multivariate logistic regression	Age, albuminuria, BMI, creatinine, FG, HbA1c, HDL, height, LDL, PAD, physical activity, sex, smoking, alcohol, stroke, systolic BP, waist circumference, and 2h-G	Age	1.08 (1.00-1.16)
							PAD	9.27 (3.44-25.0)
							Weight*	1.03 (1.00-1.06)*
Ziegler et al., 2009[43]	Cross sectional	Germany	MNSI > 2 and positive answer to Q2 and/or Q6	214 DM (21.0% with NP)	Multivariate logistic regression	Age, albuminuria, BMI, creatinine, FG, HbA1c, HDL, height, LDL, PAD, physical activity, sex, smoking, alcohol, stroke, systolic BP, waist circumference, and 2h-G	PAD	5.61 (2.43-12.96)
							Physical activity	0.31 (0.10-0.99)
							Waist circumference	1.05 (1.01-1.09)

* Reported association, but $P > 0.05$.

2h-G, 2 hours glucose; BDI-II, Beck Depression Inventory II; BMI, body mass index; BP, blood pressure; BPI, brief pain inventory; BUN, blood urea nitrogen; CI, confidence interval; CVA, cerebrovascular accident; CVD, cardiovascular disease; DFU, diabetic foot ulcer; DM, diabetes mellitus; DN, diabetic neuropathy; DN4, Douleur Neuropathique en 4 Questions; DNSS, Diabetic Neuropathy Symptom Score; DPN, diabetic peripheral neuropathy; FG, fasting plasma glucose; FPG, fasting plasma glucose; GWAS, genome-wide association study; HADS, Hospital Anxiety and Depression Scale; HDL, high-density lipoprotein; IASP, International Association for the Study of Pain; iNOS, inducible nitric oxide synthase; LANSS, Leeds assessment of neuropathic symptoms and signs; LDL, low-density lipoprotein; MI, myocardial infarction; MNSI, Michigan Neuropathy Screening Instrument; NA, not applicable; NDS, Neuropathy Disability Score; NeuPSIG, neuropathic pain special interest group; NP, neuropathic pain; NRS-11, numeric rating scale-11; NSS, Neuropathy Symptom Score; OR, odds ratio; PAD, peripheral arterial disease; PDN, painful diabetic neuropathy; PPG, postprandial plasma glucose; PVD, peripheral vascular disease; SCN9A, sodium voltage-gated channel alpha subunit 9; SF-12v2, Short-Form 12 version 2; SNP, single-nucleotide polymorphism; T1D, type 1 diabetes; T2D, type 2 diabetes; TCSS, toronto clinical scoring system; TNF-α, tumour necrosis factor alpha; UK, United Kingdom; USA, United States of America, VAS, visual analogue scale.

2.4. Genetics

Numerous published studies have found that both T1D and T2D have a heritable component[3,19,29,31] and genetic studies have been conducted in DN,[24,34] although heritability studies have yet to be conducted. A heritable component to PDN has been hinted at in 1 study, which found that 56% of participants also reported a family member with the condition.[14] Two PDN genome-wide association studies have been conducted, both in the same Scottish diabetic cohort, but with slightly differing phenotype definitions. The first used a positive monofilament test combined with a prescription history of at least 1 from 5 recommended NP medicines. This yielded an association at chromosome 8p21.3 near the gene *GFRA2* and estimated the narrow-sense heritability (proportion of phenotypic variance explained by additive genetic variance) to be 11%.[27] The second used the same definition but without the monofilament test and aimed to capture associations that may have been missed in the previous study, using a less specific cohort. This found sex-specific associations at chromosome 1p35.1 in the *ZSCAN20/TLR12P* gene regions in females and chromosome 8p23.1 next to *HMGB1P46* in males.[26] The narrow-sense heritability was 30% in males and 14.7% in females. In both of these studies, controls were defined as patients who had not previously been prescribed any of the 5 NP medicines or other medicines which are predominantly prescribed for other conditions but are also known to be prescribed for NP. Two separate candidate-gene studies have been conducted and have reported associations with PDN. The first was in the sodium channel gene *SCN9A*, which is expressed in dorsal root ganglia, using a combination of numerical rating scales and clinical examinations to compare PDN with healthy controls.[23] The second was in the opioid receptor gene *OPRM1* using a visual analogue scale for pain intensity and a grading system for pain occurrence during daily activities.[5] All 4 of these studies require independent replication, and further studies are required to establish the extent to which genetics contribute specific risk of PDN and the mechanism of this contribution.

3. Conclusions

Despite the limited number of studies reporting specific predictors for PDN, clear similarities are emerging with the known general risk factors for both DM and DN. These include clinical factors such as diabetes type and duration and lifestyle factors such as body mass index and waist circumference, some of which are not easily or not at all modifiable. Although further work is needed, this suggests that PDN is a manifestation of longer-lasting and more severe diabetes and certainly that it requires specific testing and diagnosis in routine diabetic care. However, there are likely to be factors, among those with DM (with and without DN) that confer a greater risk of PDN, and these require further exploration. It should be noted that while the published literature (and this topical review) has mainly explored NP arising from DN, NP can also arise in the diabetic population through other causes, for example, sciatic neuralgia and carpal tunnel syndrome. The influence of diabetes on the development of NP in these conditions is an area that requires further investigation. There is clear evidence to suggest PDN has a negative impact on quality of life; however, the extent to which the reverse is true—bidirectional aetiology—is currently unknown. Future studies need to be conducted in a longitudinal manner or as clinical trials to establish the temporal relationship between variable and disease, particularly with respect to identifying specific PDN risk factors in T1D and T2D patients. The previous point can be further strengthened by

running Mendelian randomization studies, something that has been used in DM.[16] Mendelian randomization studies establish causal relationship by comparing 2 groups of individuals with and without a genetic marker known to influence the variable being studied. As genotype assignment is random and not subject to confounding typically found in epidemiological studies, a higher prevalence of disease in the group with the marker implies causality. However, we would first need clearer evidence to identify genetic factors associated with PDN. Finally, greater clarity is needed in specifying whether painful or nonpainful DN is being analysed. This can be enhanced by forming a consensus on PDN phenotype definition, to enable studies to be more comparable with one another. This is something that has been addressed for NP generally and could also be applied to PDN.[40] This would make replication of results more likely and brings the added potential of being able to perform meta-analyses in the future. All these limitations will be addressed in the DOLORisk study (http://dolorisk.eu/), a European consortium which aims to identify risk factors for NP.

Conflict of interest statement

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