Risk factors for neuropathic pain in diabetes mellitus.

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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. 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. 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). 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.” 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 including depression, anxiety, and sleep disturbance. In addition, an association has been described with reduced productivity and employability at work compared with nonpainful DN. The combination of these factors places a large economic burden on patients and health care services, 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. 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, body mass index, hypertension, smoking, and waist circumference. 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 relationship and to identify confounding between variables. 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 and in others they are diabetic participants without neuropathy. 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 or the Leeds assessment of neuropathic symptoms and signs) 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.
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.\(^ {51}\)

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)\(^ {3}\) 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,\(^ {2,16,36}\) hypertension,\(^ {2,17}\) 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\(^ 2\)),\(^ {21,32,38}\) 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.\(^ {7,15}\)
| Reference | Study type | Population | Criteria for NP | Sample size | Analysis | Variables analysed | Predictors | OR (95% CI) | P |
|-----------|------------|------------|-----------------|-------------|----------|-------------------|------------|-------------|---|
| Abbott et al., 2011 | 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) |  |
| AlQuliti, 2015 | 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) |  |
| Benbow et al., 1997 | 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 |  |
| Cheng et al., 2010 | 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) |  |
| Cortez et al., 2014 | Cross sectional | Brazil | DN4 ≥ 4 | 12 T2D with PDN | Multivariate analysis | Age, depressive symptoms, diabetes duration, drug adherence, sex, and glycaemic control | Diabetes duration | P = 0.031 |  |
| D’Amato et al., 2016 | Cross sectional | Italy | DN4 ≥ 4 (DN4 interview ≥ 3) | 25 DN with NP | Multivariate analysis | Depression | Depression (BDI-II) | 4.56 (1.09-19.1) |  |
| Reference            | Study type  | Population          | Criteria for NP | Sample size | Analysis                        | Variables analysed                                                                 | Predictors               | OR (95% CI)/P             |
|----------------------|-------------|---------------------|-----------------|-------------|---------------------------------|-------------------------------------------------------------------------------------|--------------------------|---------------------------|
| Daousi et al., 2004  | Cross sectional | UK                | Typical NP symptoms in legs ≥1 y, PSS ≥ 3 and NDS ≥ 6 or NDS ≥ 3 and NSS ≥ 5 | 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  | 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 | 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   | Cross sectional | Turkey            | LANSS ≥ 12      | 975 DM without PDN | Univariate analysis | Age, blood urea BMI, BUN, creatinine, diabetes duration, diabetes type, FPG, HbA1c, PPG, and sex | Duration of diabetes | P = 0.001                |
| Gore et al., 2005    | Cross sectional | USA               | Physician diagnosed | 255 with PDN | Univariate analysis | Anxiety, depression, enjoyment of life, mental health, mood, and relationship with others | Anxiety (HADS) | All P < 0.05               |
|                      |             |                    |                 |             |                                 | Depression (HADS) Enjoyment of life (BPI-DPN) Mental health (SF-12v2) Mood (BPI-DPN) Relationship with others (BPI-DPN) |                       |                           |
| Halawa et al., 2010  | Cross sectional | Saudi Arabia       | DN4 ≥ 4         | 361 DM without PDN | Univariate analysis | Age, BMI, diabetes duration, diabetes type, ethnicity, smoking, and sex | Age                      | P < 0.001                |
|                      |             |                    |                 |             |                                 | Diabetes duration | Women | P < 0.001 | P = 0.024 |
| Harris et al., 1993  | Cross sectional | USA              | Positive response to, “During the past 3 mo, have you had a painful sensation or tingling in your hands or 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 | 2.31 (1.54-3.47) |
|                      |             |                    |                 |             |                                 |                        | Hypertension | 2.51 (1.81-3.49) | 1.58 (1.31-1.90) |
| Reference | Study type | Population | Criteria for NP | Sample size | Analysis | Variables analysed | Predictors | OR (95% CI)/P |
|-----------|------------|------------|----------------|-------------|----------|-------------------|------------|----------------|
| Jambart et al., 2011 | 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 | | | | |
| Li et al., 2015 | Genetic case control | USA/Canada | NCT00501202: lower extremity pain ≥3 mo NCT00870454: as above and NRS-11 ≥11 NCT00993018: Symmetrical pain beginning in feet ≥6 mo and NRS-11 ≥5 but <10 over 7 d. NCT00455520: clinical diagnosis with signs and symptoms ≥6 mo and at screening NCT01041859: As NCT00455520 and pain must include reduction/absence of pin sensibility NCT01063868: As for NCT00455520 and NCT01041859 plus baseline NRS-11 ≥4 | 887 DM with PDN | Univariate analysis | SNPs across SCN9A gene region | rs74449889 (SCN9A) | 2.6 |
| | | | | 1029 without DM and PDN | | | | rs3750904 (SCN9A) | 2.2 |
| Meng et al., 2015 | 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 | 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[37]  | Cross sectional | Australia  | Bilateral and symmetrical foot pain—patient specifically asked about foot pain | 2610 T2D (3.3% with PDS) | 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[31]  | 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, HbA1c, HDL, hypertension, LDL, nephropathy, PAD, physical activity, retinopathy, sex, smoking, triglyceride, and waist circumference | BMI (kg/m²) | 1.22 (1.08-1.37) |
|                            |            |            |                 | 57 DN without NP |          | severity of neuropathy | Severity of neuropathy | 1.27 (1.11-1.44) |
|                            |            |            | 56 without DN or NP |              |          |                     |            |               |
| 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 |              |          |                      |            |               |
| Van Acker et al., 2009[39] | 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 | Diabetes duration (per 5 y) | 1.47 (1.20-1.81) |
|                            |            |            |                 | 321 DN without NP |          |                        |            | 1.14 (1.02-1.28) |
|                            |            |            |                 |              |          |                    |            | 2.17 (1.38-3.41) |
|                            |            |            |                 |              |          |                        |            | 1.69 (1.10-2.59) |
|                            |            |            |                 |              |          |                        |            | 1.62 (1.05-2.49) |
|                            |            |            |                 |              |          |                        |            | 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 |
|                            |            |            |                 |              |          |                      |            | 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 | 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 | 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; BMI, body mass index; BP, blood pressure; BPI, brief pain inventory; BUN, blood urea nitrogen; C, confidence interval; CVA, cerebrovascular accident; CVD, cardiovascular disease; DM, diabetes mellitus; DN, diabetic neurathy; DLQI, Dermatology Life Quality Index; GAD-7, Generalized Anxiety Disorder-7; GDS, Geriatric Depression Scale; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; IL-6, interleukin-6; IASP, International Association for the Study of Pain; MNSI, Michigan Neuropathy Screening Instrument; NA, not applicable; NDS, Neuropathy Disability Score; NG, neuropathic pain; NRS-11, numeric rating scale-11; Q2, question 2; Q6, question 6; R, ratio; ROC, receiver operating characteristic curve; R2, coefficient of determination; R2.4, regression coefficient of determination; SF-36, Short Form-36; SNP, single nucleotide polymorphism; T1D, type 1 diabetes; T2D, type 2 diabetes; TSS, taranto clinic scoring system; TURF, tumour necrosis factor alpha; UK, United Kingdom; USA, United States of America; VAS, visual analogue scale.

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 body mass index, diabetes type and duration and lifestyle factors such as physical activity and smoking. Furthermore, genetic factors also play a role in the development of PDN, as suggested by the findings of several genome-wide association studies in PDN, which have identified genetic variants associated with PDN.

PDN is a heterogeneous condition, and future studies are required to establish the specific risk of PDN and the mechanism of this contribution. For this purpose, larger, multicentre studies with standardized diagnostic criteria and comprehensive evaluation are needed. Additionally, the role of genetic factors in PDN needs further investigation, as the available evidence is inconclusive.

PDN is a common complication of diabetes, and its impact on quality of life and healthcare costs is substantial. Therefore, the development of effective preventive strategies and interventions to manage PDN is crucial.

Future research should focus on identifying specific PDN risk factors in T1D and T2D, and the role of genetics, including the influence of environment. This will require longitudinal studies and the use of advanced statistical methods to account for confounding factors.

The development of effective preventive strategies and interventions for PDN is crucial, and further research is required to identify specific risk factors and the role of genetics in this condition. This will require collaboration between clinician and basic researcher,

2.4 Genetics

Numerous published studies have found that both T1D and T2D have a heritable component, although heritability studies have yet to be conducted. A heritable component to PDN has been hinted at, but the extent to which this is true is currently unknown. Future studies need to be conducted in both groups, particularly with a greater focus on PDN, with and without DN.

In the past, PDN has been studied in terms of its association with specific conditions such as diabetes and its complications. However, the role of genetics in PDN is not well understood, and future studies are required to identify specific PDN risk factors and the role of genetics in this condition.
running Mendelian randomization studies, something that has been used in DM.\textsuperscript{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.\textsuperscript{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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