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Mediators of diabetic neuropathy - is hyperglycemia the only culprit?

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Abstract

Purpose of this review—Diabetic peripheral neuropathy (DPN) is a disabling, highly prevalent complication of both type 1 and type 2 diabetes mellitus (T1DM, T2DM). Large clinical studies support the concept that, in addition to hyperglycemia, components of the metabolic syndrome (MetS) may underlie the pathogenesis of DPN, especially in T2DM. This review will present the evidence supporting the MetS and its individual components as potential causal factors for the development of neuropathy.

Recent findings—In addition to poor glycemic control and duration of diabetes, components of MetS such as dyslipidemia, obesity, and hypertension, may have an important impact on the prevalence of DPN. Obesity and prediabetes have the most data to support their role in neuropathy, whereas hypertension and dyslipidemia have more mixed results. Non-metabolic factors, such as genetic susceptibility, age, height, gender, smoking, and alcohol, have also been highlighted as potential risk factors in peripheral neuropathy, although the exact contribution of these factors to DPN remains unknown.

Summary—DPN is a chronic and disabling disease, and the accurate identification and modification of DPN risk factors is important for clinical management. Recent data support a role for components of the MetS and other risk factors in the development of DPN, offering novel targets beyond hyperglycemia for therapeutic development.

Keywords

diabetic peripheral neuropathy; hyperlipidemia; obesity; hypertension; metabolic syndrome; risk factors

Introduction

Diabetes mellitus (DM) is one of the most common diseases worldwide, affecting 420 million people in 2014 at a prevalence of 8.5% in adults. The prevalence of diabetes is

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Conflicts of interest

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increasing in middle and low-income countries throughout Asia and Africa, as more calorie dense Western diets are adopted throughout the world (1).

Diabetic peripheral neuropathy (DPN) is the most common complication of both type 1 and type 2 diabetes mellitus (T1DM, T2DM) and occurs in over half of all individuals with T1DM and T2DM (2). DPN is associated with pain, falls, disability, and a reduced quality of life (3, 4). Patients present with distal symmetric polyneuropathy, a slowly progressing and length-dependent, axonal neuropathy. Symptoms present in a stocking and glove-like pattern, beginning in the feet and progressing proximally, with either positive (tingling, pain) or negative (numbness, insensate) symptoms. Neuropathic pain is common, with sharp, burning, and electrical sensations in the feet. Another typical clinical presentation, especially in prediabetes or new-onset T2DM, is small-fiber neuropathy (SFN). Subjects report extreme shooting pain, tingling, and dysesthesias in the feet. In DPN, clinical examination most commonly reveals decreased perception of all sensory modalities in the feet with decreased or absent Achilles reflexes. In SFN, there is poor pinprick and temperature discrimination, while vibratory sensation, position sense, and reflexes are normal. Other neuropathies that can occur with T1DM and T2DM include autonomic neuropathy, treatment-induced neuropathy, polyradiculoplexus neuropathy, mononeuropathies, and cranial neuropathies (5).

The development of DPN is complex, with multifactorial pathologic mechanisms, some not fully understood. While hyperglycemia and the duration of DM play an important role in DPN in T1DM and T2DM patients, other potentially causal factors have been identified, especially in T2DM. In this review, we will discuss the evidence supporting metabolic risk factors for the development of DPN.

Effect of DM on peripheral neuropathy

T1DM is most common in children and adolescents and is the result of autoimmune damage to the pancreas and subsequent failure of insulin production. T2DM, on the other hand, occurs most commonly in adults and is secondary to inflammation and insulin resistance in multiple tissues, including muscle, fat depots, and liver. Several perturbations in biochemical pathways leading to damage are present in the peripheral nervous system of patients with T2DM. For example, abnormalities in nerve polyol, hexosamine, and protein kinase C pathways are reported, in parallel with changes in advanced glycation endproducts and Poly (ADP-ribose) polymerase. Separately and in concert, these changes produce nervous system oxidative stress and apoptosis of both neurons and supporting glia (6, 7).

Clinical studies support the concept that DPN in T1DM and T2DM share both common and divergent mechanisms. Studies in T1DM populations show that enhanced glucose control can substantially reduce the incidence of DPN (8–12), while long-term poor glycemic control can be a determining factor in rapid DPN development (13). In contrast, in patients with T2DM, intensive glucose control was only marginally effective at reducing DPN incidence (14), a finding illustrated by the ACCORD study which followed 10,251 patients with T2DM for 3.7 years. This study used the Michigan Neuropathy Screening Instrument (MNSI) to clinically measure DPN and found no significant difference, only a small risk

reduction in T2DM subjects receiving intensive glucose therapy (15). Likewise, the UKPDS study involving 3,867 patients showed only a modest risk reduction in the intensive treatment group (measured with vibration threshold >25V) after follow-up at 15 years (16), and two additional studies further demonstrated no significant difference in DPN in subjects in the intensive glucose control group (17, 18). Cumulatively, these data indicate that factors in addition to hyperglycemia itself and duration of disease (19, 20) must be considered when evaluating the prevalence, development, and treatment of DPN in subjects with T2DM.

Prediabetes and peripheral neuropathy

Prediabetes, a precursor to DM, is characterized by increased blood sugar levels due to impaired fasting glucose or impaired glucose tolerance as demonstrated on a 2-hour glucose tolerance test. Multiple large, population-based studies report a higher prevalence of peripheral neuropathy in patients with prediabetes compared to those with normoglycemia (21–24). In contrast, other studies revealed a comparable prevalence of symptomatic DPN in subjects with prediabetes and those with normoglycemia (25–27). Table 1 summarizes the positive and negative findings of these aforementioned studies. Reasons for the discrepancies in the studies described above include the likely low effect size of prediabetes on neuropathy in comparison to diabetes, as well as the fact that the negative studies may not have been adequately powered to detect such a small, yet important, effect. Furthermore, the populations studied were diverse, including different countries, different ages, and different proportions of patients with diabetes, prediabetes, and normoglycemia. For example, one of the negative studies was performed in an elderly population where prediabetes may have less importance. Finally, the definitions of neuropathy were very different in these studies. Studies that were more likely to detect a small fiber predominant neuropathy were more likely to demonstrate an association between prediabetes and neuropathy.

In addition to evaluating the prevalence of DPN, some studies further suggest that individuals with prediabetes or early stages of diabetes often present clinically with SFN (28, 29). Interestingly, physical exercise and life-style intervention can reverse components of the MetS in prediabetic patients (30, 31). In a trial of patients with prediabetes and SFN, life-style intervention led to reversal of SFN, cutaneous re-innervation, and improvement of pain (31). Nonetheless, due to the persisting uncertainty regarding the role of prediabetes and DPN, further studies to clarify whether treatment of prediabetes improves neuropathy outcomes are needed.

The MetS and DPN

The MetS by definition comprises obesity, insulin resistance, hypertension, hypertriglyceridemia, and dyslipidemia, and its coexistence with diabetes has been described to be associated with the development of DPN (25, 32–36). The main findings of the conducted studies are presented in Table 2. The exact impact of metabolic factors in DPN, however, is still unclear. In patients with T1DM, the duration of DM, height of HbA1c, age, and sex seem independently associated with neuropathy (39). The EURODIAB study further indicated that elevated triglycerides, body mass index (BMI), smoking, and hypertension play a major role in T1DM and DPN (40).

Across studies with T2DM subjects, an even stronger association of the prevalence of DPN with the MetS (33, 35–37), especially in obese patients (22, 38, 41), has been reported. Of note, the prevalence seems to progressively increase as the number of MetS components increases (34). We recently reported that obese patients with normal glucose levels have a higher prevalence of neuropathy compared to lean controls, with an even higher prevalence in those with prediabetes and diabetes (24). Prediabetes, waist circumference, and T2DM represent the major metabolic factors, whereas systolic blood pressure, high density lipoprotein (HDL), and triglyceride levels do not appear to have a significant impact on the development of DPN (24). Although normal BMI levels are uncommon in patients with T2DM, this population still shows a two-fold higher prevalence of micro- or macrovascular complications when compared to the normal population (42).

Overall, the MetS has a major influence on the development of peripheral neuropathy in patients with prediabetes and on the presence of DPN in both T1DM and, to an even greater extent, T2DM. However, to elucidate the exact impact of the MetS on peripheral neuropathy, further trials with larger cohorts are required.

Individual MetS components and DPN

Obesity

Previous studies suggest that obesity is associated with DPN in both T1DM (39, 40) and T2DM (38, 41). Similarly, a recent study showed that the prevalence of DPN was higher in obese patients compared to lean controls, even in those individuals with normoglycemia, and the neuropathy prevalence was even higher in obese participants with prediabetes and diabetes (24). In this study, obese subjects also showed abnormalities in intraepidermal nerve fiber density and nerve conduction studies, confirming the severity of the neuropathy in this population. The obese subjects with neuropathy also had worse neuropathy specific quality of life and higher pain scores, which suggests that the neuropathy is clinically impactful in this population as well. This study also demonstrated an independent association of waist circumference with DPN after adjusting for demographics and other metabolic components. Similar results have been demonstrated by two others studies performed in China and Germany (22, 36). Moreover, low physical activity is associated with DPN (22), as patients with T2DM and DPN seem to be less active compared to T2DM subjects without DPN (43). Therefore, weight loss and/or exercise are both potential interventions to prevent and/or improve neuropathy, but future studies are needed to determine which intervention leads to the best patient outcomes.

Dyslipidemia

Dyslipidemia may have a strong impact on DPN due to its contribution to oxidative stress in dorsal root ganglion sensory neurons and endothelial dysfunction (44). In T1DM, elevated levels of low density lipoprotein (LDL) (20, 40), total cholesterol, and triglycerides (40) have been shown to be associated with DPN. In T2DM, low HDL levels (22, 41, 45) have also been reported to influence the development of DPN. Additional support for the link between dyslipidemia and DPN is seen in the observational Fremantle Diabetes Study (FDS), where therapy with statins and fibrates were both associated with a reduced

development of DPN in a longitudinal analysis (46). On the other hand, three other studies have not demonstrated an association between LDL or HDL and neuropathy (24, 25, 36). In contrast to obesity, the evidence supporting dyslipidemia and neuropathy is less definitive.

Hypertriglyceridemia

The association of elevated levels of triglycerides with DPN has also been evaluated in subjects with T1DM (40) and T2DM (41, 45, 47, 48). In a study of patients with mild to moderate diabetes, a correlation between the loss of myelinated fiber density and hypertriglyceridemia was observed, independent of disease duration, age, diabetes control, or other variables (49), suggesting an important influence of elevated triglycerides on the progression of DPN. Likewise, another study demonstrated that lower extremity amputations were more frequent in diabetic subjects with elevated triglyceride levels (50), and lower extremity amputations are known to be highly associated with neuropathy. In contrast to these positive findings, however, Kwai et al. showed that serum triglyceride levels did not influence axonal function in T2DM patients (51), and other recent studies also did not find an association between elevated triglycerides and DPN (24, 25, 36). Similar to the evidence for HDL and LDL and neuropathy, the data supporting hypertriglyceridemia and neuropathy is mixed.

Hypertension

The role of hypertension and DPN is uncertain (19). In individuals with T1DM, studies have shown an association between high blood-pressure and DPN (20, 40). In T2DM, however, most previous studies have been negative (24, 25, 52–54) with one exception (22). Hence, current evidence supports an association between hypertension and neuropathy in T1DM but not in T2DM.

Other potential risk factors for DPN

In addition to hyperglycemia and the MetS, there are other risk factors that potentially contribute to the development of DPN. Gender appears to influence DPN in T2DM, with male gender being associated with neuropathy (25, 35), although no association was observed in a T1DM population (40). Age, on the other hand, has long been known to be a risk factor for DPN (19, 22, 40, 55, 56); the prevalence of DPN increases with every decade of life (53, 55). Potentially due to the length-dependent presentation of DPN, height is also associated with neuropathy (20, 25, 40, 56, 57).

Substance abuse has also been linked to DPN risk, with a specific focus on smoking and alcohol use. In T2DM patients, smoking may also be a risk factor (58); in a recent study smoking was an independent risk factor, as heavy smokers exhibited worse nerve conduction studies (59). Likewise, smoking was also significantly associated with DPN in T1DM (40, 60), or exhibited a trend for association (20). The influence of alcohol consumption, on the other hand, remains uncertain. While some studies support a link between alcohol consumption and DPN (55, 56), others show no association (22, 58). One study, however, did report an association between increased ulcerations in diabetic feet and alcohol consumption (61).

Potential genetic susceptibility to DPN is also suggested through studies reporting an association with several genes, such as ACE, MTHFR, GST, GLO 1, APOE, TCF7L2, VEGF, IL4, GPX1, eNOS, ADRA2B, MIR146A, and MIR128A (62). Of particular interest are ApoE and TCF7L2, two genes involved in lipid metabolism. Apo E is polymorphic, consisting of ApoE2, ApoE3, and ApoE4, and it is a lipoprotein involved in the metabolism of plasma cholesterol and triglycerides. In a multivariate analysis, the E4-carrier status conferred a more than 5-fold increased risk of severe neuropathy in T2DM (63). Also involved in glucose and lipid metabolism, the TCF7L2 gene encodes a nuclear receptor for B-catenin, which interferes with the Wnt signaling pathway (44). Studies indicate that variants of the TCF7L2 gene are associated with insulin resistance, reduced insulin secretion, and increased risk of T2DM (64). In addition, consanguinity and hereditary gene-environment interactions have also recently been determined to have an impact on DPN in an Arabic study (65).

Conclusion

New research has recently increased the available knowledge about possible causes of DPN. While hyperglycemia clearly plays an important and devastating role in developing DPN in patients with DM, recent literature has also shown that prediabetes and other components of the MetS, particularly obesity, likely play an important role in damaging nerve fibers. In addition, other risk factors, such as genes, age, gender, height, alcohol, and smoking, may also contribute to DPN pathogenesis. These studies highlight the importance and impact of metabolic components and additional risk factors, other than hyperglycemia, on DPN. Given that the current established therapies for DPN only target hyperglycemia, further studies regarding the impact of novel therapies on DPN outcomes, such as weight loss and exercise, are warranted.

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Abbreviations

BMI	body mass index
DM	diabetes mellitus
DPN	diabetic peripheral neuropathy
HDL	high density lipoprotein

LDL	low density lipoprotein
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
MetS	metabolic syndrome
SFN	small fiber neuropathy

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Key points

- The prevalence of DPN is high in T1DM and T2DM, but the mechanisms of nerve injury are likely quite different
- The metabolic syndrome is associated with neuropathy, and its individual components have also been demonstrated to be associated with this disabling condition. Hyperglycemia is the most established risk factor for neuropathy, but other metabolic components, particularly obesity, are also likely risk factors.
- Age, gender, height, smoking, alcohol use, genetic susceptibility and gene-environment interactions are also discussed to have an influence on DPN.

Table 1

Prediabetes and its association with DPN

Study	Population	Number	Neuropathy measurement	Main findings	Study design
Increased prevalence of peripheral neuropathy in prediabetes					
Franklin <i>et al.</i> , Am J Epidemiol, 1990 (San Louis Valley Diabetes Study) (21)	<ul style="list-style-type: none"> • 279 T2DM • 89 IGT • 488 NG • 20–74 yrs 	n=856	<ul style="list-style-type: none"> • symptom questionnaire and examination 	<ul style="list-style-type: none"> • higher prevalence of DPN in prediabetes and diabetes compared to NG (11.2% vs. 27.8% vs. 3.5%) 	<ul style="list-style-type: none"> • case-control
Ziegler <i>et al.</i> , Diabetes Care 2008 (MONICA/KORA study) (22)	<ul style="list-style-type: none"> • NG (n=81, 63.6±9.3 yrs) • IFG (n=71, 66.6±8.1 yrs) • IGT (n=46, 69.3 ±7.8 yrs) • T2DM (n=195, 66.8 ±9.4 yrs) 	n=393	<ul style="list-style-type: none"> • MNSI>2 	<ul style="list-style-type: none"> • higher prevalence of DPN in IFG and IGT subjects compared to NG (11.3% vs. 13.0% vs. 7.4%; p<0.05 for T2DM vs. NG, IFG and IGT) 	<ul style="list-style-type: none"> • cross-sectional
Lee <i>et al.</i> , Diabetes Care 2015 (PROMISE) (23)	<ul style="list-style-type: none"> • individuals with high risk for T2DM • mean age 53 yrs 	n=467	<ul style="list-style-type: none"> • MNSI>2 	<ul style="list-style-type: none"> • higher prevalence of DPN in new-onset diabetes and prediabetes compared to NG (50.0% vs. 49.0% vs. 29.0%, p<0.001 for trend) 	<ul style="list-style-type: none"> • prospective examination after 3yrs
Callaghan <i>et al.</i> , JAMA Neurol. 2016 (24)	<ul style="list-style-type: none"> • obese patients -(52.9±10.2 yrs) • with NG (n=45) • with prediabetes (n=31) • with T2DM (n=26) 	n=102	<ul style="list-style-type: none"> • Toronto Consensus definition of probable neuropathy 	<ul style="list-style-type: none"> • prevalence of DPN higher in prediabetes and diabetes compared to NG (29.0% vs. 34.6% vs. 11.1%, p<0.01 for trend) 	<ul style="list-style-type: none"> • cross-sectional
No association of prediabetes and increased prevalence of peripheral neuropathy					
Gregg <i>et al.</i> , Diabetes Research and Clinical Practice, 2007 (NANHES) (26)	<ul style="list-style-type: none"> • NG • IFG • newly diagnosed T2DM • T2DM 	n=3607	<ul style="list-style-type: none"> • heavy monofilament 	<ul style="list-style-type: none"> • prevalence between NG and prediabetes comparable (10.5% vs. 11.9%) 	<ul style="list-style-type: none"> • cross-sectional

Study	Population	Number	Neuropathy measurement	Main findings	Study design
	• mean age 56.7 yrs				
Dyck <i>et al.</i> , Diabetes Care 2012 (The OC IG Survey) (27)	<ul style="list-style-type: none"> • NG (n=150) • impaired glycemia (n=174) • new-onset T2DM (n=218) 	n=542	<ul style="list-style-type: none"> • sum of 2 NCV abnormalities • Neuropathy Impairment Score • Neuropathy Symptoms and Change Score 	<ul style="list-style-type: none"> • prevalence of DPN increased only in new-onset diabetes, not in prediabetes (7.8% vs. 1.7%, p<0.01) 	<ul style="list-style-type: none"> • cross-sectional
Callaghan <i>et al.</i> , Diabetes Care 2016 (Health ABC) (25)	<ul style="list-style-type: none"> • NG (n=1145, 73.4 ±2.8 yrs) • prediabetes (n=699, 73.6 ±3 yrs) • diabetes (n=490, 73.6 ±2.7 yrs) • MetS present in 52.8% 	n=2382	<ul style="list-style-type: none"> • 1 of 2 neuropathic symptom questionnaire items plus one of three confirmatory tests (vibration perception threshold, peroneal conduction velocity, heavy monofilament) 	<ul style="list-style-type: none"> • comparable prevalence of symptomatic DPN in prediabetes compared to NG (9.3% vs. 9.7%) • no association of prediabetes with neuropathy outcome in adjusted model 	<ul style="list-style-type: none"> • cross-sectional

Abbreviations: DPN: Diabetic Peripheral Neuropathy, IFG: Impaired Fasting Glucose, IGT: Impaired Glucose Tolerance, NCV: Nerve Conduction Velocity, NG: Normoglycemia, MNSI: Michigan Neuropathy Severity Scale, T2DM: Type 2 Diabetes Mellitus

Table 2

The association of the MetS and its individual components with DPN.

Study	Population	Number	Neuropathy assessment	Main findings	Study design
The MetS and DPN					
Isomaa <i>et al.</i> , Diabetologia 2001 (35)	<ul style="list-style-type: none"> T2DM with MetS (n=85; 59.5±8.8 yrs) T2DM without MetS (n=85; 61.2±7.5 yrs) 	n=170	<ul style="list-style-type: none"> NDS 3–5 or NSS 5 or NDS 6 	<ul style="list-style-type: none"> higher prevalence of DPN in MetS (5.0% vs. 21.0%, p<0.001) no association between components of MetS and DPN HbA1C and LDL particle size as independent risk factors 	<ul style="list-style-type: none"> cross-sectional
Costa <i>et al.</i> , Diabet Med. 2004 (34)	T2DM - <ul style="list-style-type: none"> without MetS (58±10 yrs) with 2 MetS components (58 ± 10 yrs) with 3 MetS components (59 ± 10 yrs) with 4 MetS components (60 ± 10 yrs) 	n=548	<ul style="list-style-type: none"> Achilles reflex and either vibration or monofilament 	<ul style="list-style-type: none"> distal sensory neuropathy more frequent in patients with MetS higher prevalence of DPN with increasing number of metabolic abnormalities (24.0%, 32.0%, 49.0% and 57.0%; p< 0.05 for trend). 	<ul style="list-style-type: none"> cross-sectional
The Metascreen Writing Committee, Diabetes Care 2006 (Metascreen) (33)	<ul style="list-style-type: none"> T1DM (n=638, 48±17 yrs) T2DM (n=7859, 65 ±11) 	n=8497	<ul style="list-style-type: none"> clinical assessment 	<ul style="list-style-type: none"> MetS independently associated with clinical neuropathy (p<0.01) 	<ul style="list-style-type: none"> cross-sectional
Smith <i>et al.</i> , J Neurol Sci. 2008 (37)	<ul style="list-style-type: none"> NG (n=77, 62.9 ±12 yrs) IGT (n=77, 61.2 ±8.7 yrs) 	n=154	<ul style="list-style-type: none"> abnormality of 2 measures (clinical assessment, NCV, cold and vibration sensory tests, sudomotor axon reflex tests, skin biopsy) 	<ul style="list-style-type: none"> equivalent prevalence of MetS in NG and IGT more components (apart from hyperglycemia) in NG group than in diabetics (p<0.001) 	<ul style="list-style-type: none"> cross-sectional
Han <i>et al.</i> , Diabetol Metab Syndr. 2015 (SH- DREAMS) (36)	<ul style="list-style-type: none"> NG (n=458) IGT (n=1043) T2DM (n=534) median age 61.5 ±10.1 	n=2035	<ul style="list-style-type: none"> NDS 3, NSS 5 	<ul style="list-style-type: none"> rate of peripheral neuropathy higher in MetS group (5.5% vs. 2.6%, p = 0.001) waist circumference, fasting blood glucose, HbA1c, treatment for T2DM and hypertension significantly 	<ul style="list-style-type: none"> cross-sectional

Study	Population	Number	Neuropathy assessment	Main findings	Study design
Callaghan <i>et al.</i> , JAMA Neurol. 2016 (24)	obese patients -(52.9±10.2 yrs) • with NG (n=45) • with prediabetes (n=31) • with T2DM (n=26)	n=102	• Toronto Consensus definition of probable neuropathy	• prevalence of DPN is high in obese patients with NG compared to lean controls (p<0.1 for trend) • diabetes, prediabetes and obesity are the likely metabolic drivers for DPN	• cross-sectional
Individual components of the MetS and DPN					
Straub <i>et al.</i> , Diabetes Care 1994 (38)	• T2DM BMI < 26.5 (n = 41; 58.6 ± 1.7 yrs) • T2DM BMI > 26.5 (n=50, 61.9 ± 1.2 yrs)	n=91	• clinical assessment 0–100 points (vibration, temperature, discrimination perception, reflexes, muscular force)	• worse clinical neuropathy examination in obese patients (BMI>26.5) (p<0.05)	• cross-sectional
De Block <i>et al.</i> , Diabetes Care 2005 (39)	T1DM (41±12 yrs) • BMI<25 (n=314) • BMI>25 (n=278)	n=592	• NCS (motor peroneal and tibial; sensory sural; H-reflexes, F-waves)	• prevalence of DPN more often in overweight (BMI > or=25kg/m ²) than normal-weight T1DM subjects (49% vs. 38%, p=0.008) • duration of diabetes age, and sex independently associated with neuropathy (p<0.0001)	• cross-sectional
Tesfaye <i>et al.</i> , N Engl J Med. 2005 (EURODIAB) (40)	• T1DM (30.7±8.8 yrs)	n=1172	• 2 measures of the following: symptoms, absence of knee/ankle reflexes, abnormal vibration perception, abnormal autonomic function	• incidence of DPN associated with HbA1C, disease duration, BMI, hypertension, smoking, hypertriglyceridemia	• prospective, longitudinal follow-up 7.3±0.6 yrs
Ziegler <i>et al.</i> , Diabetes Care 2008 (MONICA/KORA study) (22)	• NG (n=81, 63.6 ±9.3 yrs) • IFG (n=71, 66.6±8.1 yrs) • IGT (n=46, 69.3 ±7.8 yrs) • T2DM (n=195, 66.8 ±9.4 yrs)	n=393	• MNSI>2	• age, waist circumference and peripheral arterial disease associated with DPN (p<0.05)	• cross-sectional
Van Acker <i>et al.</i> , Diabetes Metab. 2009 (41)	• T1DM (n=344, 45.9 ±15)	n=1111	• Neuropen	• obesity, low HDL, high triglycerides levels	• cross-sectional

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Study	Population	Number	Neuropathy assessment	Main findings	Study design
	T2DM (n=767, 63.6 ±11) •			independently associated with DPN	

Abbreviations: BMI: Body Mass Index, DPN: Diabetic Peripheral Neuropathy, HDL: High Density Lipoprotein, IGT: Impaired Glucose Tolerance, LDL: Low Density Lipoprotein, NCS: Nerve Conduction Study, NDS: Neuropathy Disability Score, NG: Normoglycemia, NSS: Neuropathy Symptom Score, MeS: Metabolic Syndrome, MNSI: Michigan Neuropathy Severity Index, T1DM: Type 1 Diabetes Mellitus, T2DM: Type 2 Diabetes Mellitus