

Risk Factors and Comorbidities in Diabetic Neuropathy: An Update 2015

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■ Abstract

Distal symmetric sensorimotor polyneuropathy (DSPN) is the most common neurological manifestation in diabetes. Major risk factors of DSPN include diabetes duration, hyperglycemia, and age, followed by prediabetes, hypertension, dyslipidemia, and obesity. Height, smoking, insulin resistance, hypoinsulinemia, and others represent an additional risk. Importantly, hyperglycemia, hypertension, dyslipidemia, obesity, and smoking are modifiable. Stringent glycemic control has been shown to be effective in type 1, but not to the same extent in type 2 diabetes. Antilipidemic treatment, especially with fenofibrate, and multi-factorial in-

tervention have produced encouraging results, but more experience is necessary. The major comorbidities of DSPN are depression, autonomic neuropathy, peripheral artery disease, cardiovascular disease, nephropathy, retinopathy, and medial arterial calcification. Knowledge of risk factors and comorbidities has the potential to enrich the therapeutic strategy in clinical practice as part of the overall medical care for patients with neuropathy. This article provides an updated overview of DSPN risk factors and comorbidities.

Keywords: diabetic neuropathy · hyperglycemia · prevalence · prediabetes · risk factor · glucose variability · hypertension · dyslipidemia

1. Introduction

In diabetes, the most common neurological complication is distal symmetric sensorimotor polyneuropathy (DSPN), often simply referred to as diabetic polyneuropathy [1, 2]. Its prevalence is approximately 30% in hospitalized diabetes patients and 20-30% in community-based patients [1]. It is now increasingly accepted that it starts to develop earlier than previously considered, namely as early as prediabetes [3]. The main clinical features of DSPN include symmetrical, predominantly sensory deficits in the distal lower extremities, and neuropathic pain [1, 2]. Moreover, DSPN is a pivotal risk factor for diabetic foot ulceration due to the loss of protective sensation [2, 4, 5]. Due to its important clinical impact, there has been

considerable effort to ensure and improve its early diagnosis, including the development of new screening tests [6-9]. At the same time, research has been aimed at a deeper understanding of the pathogenesis and risk factors, since this knowledge may help towards preventing DSPN [1]. Therefore, the aim of the present review was to provide an update on these developments, with a focus on the risk factors of DSPN.

2. Search strategy

The electronic search for relevant literature was based on PubMed, Embase, and Google scholar databases up to March 2015 using combinations of the following keywords: age, cardiovascular, comorbidities, depression, diabetes, diabetic

neuropathy, height, hyperglycemia, insulin, platelets, polyneuropathy, risk factors, smoking. All types of articles written in the English language were included, whereas those written in other languages were studied in abstract form only.

3. Risk factors of distal symmetric sensorimotor polyneuropathy

The risk factors of DSPN, including its degree of association with DSPN, are summarized in **Table 1**.

3.1 Duration of diabetes

Diabetes duration is a major and well-recognized risk factor of DSPN [1, 10]. In both diabetes types, the association of DSPN with diabetes duration is independent of patients' age [1, 11-15]. Although the exact prevalence of DSPN differs according to the diagnostic methodology used and the population selected (for example, hospital-based vs. outpatient-based vs. community-based) [1], its association with diabetes duration remains significant [1, 11-18]. However, the following two important observations should not escape our notice:

1. Long-term stringent metabolic control may reduce the prevalence of DSPN, despite longer diabetes duration, especially in type 1 diabetes (T1D) [19, 20]. In a 24-year follow-up of patients with T1D, the development of confirmed clinical DSPN in inadequately controlled patients was 64%, as opposed to 0% in stringently controlled patients [20].
2. The distribution in age of onset is broad, with some patients developing DSPN after long diabetes duration, while others exhibit this complication as early as the prediabetic stage [3, 21].

Interestingly, Delcourt *et al.* have reported that the correlation of DSPN with diabetes duration in France was strong until the age of 54 only, but this finding has never been replicated [22].

3.2 Hyperglycemia

Hyperglycemia is the other major risk factor of DSPN [1, 23-26]. Its paramount importance has been documented in both T1D and type 2 diabetes (T2D) [12, 24-29]. It has been calculated that every 1% increment in HbA1c is connected with approximately 10-15% higher frequency of DSPN [1].

Abbreviations:

ABI – ankle-brachial index
CAN – diabetic cardiovascular autonomic neuropathy
CGM – continuous glucose monitoring
DAN – diabetic autonomic neuropathy
CI – confidence interval
DCCT – diabetes control and complications trial
DNA – deoxyribonucleic acid
DSPN – distal symmetric sensorimotor polyneuropathy
HDLc – high-density lipoprotein cholesterol
HR – hazard ratio
HRV – heart rate variability
IFG – impaired fasting glucose
IGF1 – insulin-like growth factor 1
IGT – impaired glucose tolerance
IL – interleukin
KORA – co-operative research in the region of Augsburg
LDLc – low-density lipoprotein cholesterol
MAC – medial arterial calcification
MDA – malondialdehyde
MPV – mean platelet volume
NCV – nerve conduction velocity
NGF – nerve growth factor
NGT – normal glucose tolerance
OR – odds ratio
OSA – obstructive sleep apnea
PAD – peripheral artery disease
sICAM-1 – soluble intercellular adhesion molecule-1
T1D – type 1 diabetes mellitus
T2D – type 2 diabetes mellitus
UKPDS – United Kingdom prospective diabetes study
VPT – vibration perception threshold

Therefore, the effectiveness of strict glycemic control in reducing the incidence and progression of DSPN has been the object of several ambitious studies in both types of diabetes [16, 19, 20, 29-33]. However, an important difference has emerged between T1D and T2D. As detected in a meta-analysis, optimized glycemic control in T1D exerts significantly beneficial effects in preventing the development of clinical DSPN and reducing neurological deficits, while in T2D this effect was not (wholly) significant ($p = 0.06$) [34]. Another meta-analysis concluded that intensive glucose-lowering treatment was not successful in reducing DSPN in patients with T2D [35]. These findings point to a potential difference in terms of the pathogenesis of DSPN between the two types of diabetes. However, the data are far from being conclusive, because the trials in T2D have only secondarily looked at DSPN, and included only clinical evaluation measures. Therefore, the identification of a beneficial treatment effect was more difficult [1].

3.3 Glycemic variability

Patients with similar HbA1c and mean blood glucose levels can have markedly different daily

Table 1. Risk factors of distal symmetric sensorimotor polyneuropathy

Risk factor	Degree of association	References
Diabetes duration	+++	1, 11-18
Hyperglycemia	+++	1, 23-29
Glycemic variability	+	39, 42
Prediabetes	++	43-47
Age	+++	1, 10-12, 26, 27, 43-45, 50, 51
Height	++	11-14, 26
Hypertension	++	1, 12, 13, 24, 25, 51, 53
Dyslipidemia	+	11, 13, 25, 26, 55-57
Smoking	+	11, 13, 15, 48, 59
Obesity	++	43-45, 60, 61
Metabolic syndrome	++	60, 62, 63
Insulin resistance	+	58, 64
Alcohol consumption	+	1, 12, 50
Hypoinsulinemia	+	14, 15, 24
Oxidative stress	++	65-77
Platelet activation	+	78, 79, 81, 82
Vitamin D deficiency	++	83, 84, 86, 87
Genetic factors	++	95-100, 102-112
Subclin. inflammation	++	89-92
Low physical activity	++	43-45
Growth factor depletion	+	114-117

Legend: Moderate association (+), stronger association (++), very strong association (+++).

glucose excursions. The role of glucose variability in pathophysiological pathways is a subject of debate [36]. Recent observational studies suggest an association between high HbA1c variability and all-cause mortality in T2D subjects, particularly in individuals with low mean HbA1c levels of <7.3% [37] or <8% [38]. There is little information on the role of glycemic variability as a risk factor for the development of DSPN. While one study concluded that blood glucose variability may constitute an important risk factor in the development of neuropathy in patients with T1D [39], the Diabetes Control and Complications Trial (DCCT) failed to confirm this association for DSPN and cardiac autonomic neuropathy (CAN) [40]. In a recent smaller study from Korea, variability in continuous glucose monitoring (CGM) and all parameters of HbA1c variability were independently associated with the presence of CAN in T2D subjects [41]. Another small study from China reported a close relationship between glycemic variability and DSPN in T2D patients with HbA1c levels <7% [42].

It has been reasoned that there is no “gold standard” for determining glucose variability and that the only way to determine the utility of targeting glycemic variability would be to conduct

studies specifically aimed at lowering glucose variability to assess its influence on the development of diabetic neural and vascular complications [36]. In summary, the role of glucose variability in causing neuropathy remains unclear. Reducing glucose variability could become an important part of diabetes management, should the association with diabetic complications be established. At present, there is little supportive evidence for targeting glucose variability separately from mean glucose and/or HbA1c values [36]. More research is necessary to clarify this important question.

3.4 Prediabetes

There is accumulating evidence suggesting that the combined prevalence of DSPN and CAN is increased in individuals with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) as compared to those with normal glucose tolerance (NGT) [21]. In the KORA (Cooperative Research in the Region of Augsburg) study, the prevalence of DSPN was 13% in IGT, lying between diabetes (28%) and NGT (7.4%) [43]. Neuropathic pain was as frequent as 8.7% in IGT vs. 1.2% in NGT [44]. In subjects with prior acute myocardial infarction, the rate of neuropathic pain was 14.8% in IGT vs. 21% in diabetes and 3.7% in NGT [45]. This pattern was confirmed by the KORA F4 Survey using an alternative definition for DSPN [46]. Among prediabetes subgroups, IFG+IGT, but not isolated IFG or IGT, was associated with a higher risk of DSPN, compared with normal glucose tolerance [46]. A J-shaped relationship was shown between DSPN and quartiles of 2-h post-challenge glucose, but not with fasting glucose and HbA1c levels [46]. Moreover, in the KORA S4 survey, the prevalence of CAN was increased in individuals with diabetes and in those with IFG+IGT and, to a lesser degree, in those with isolated IFG [47]. Thus, combined IFG+IGT in particular is associated with an increased risk of DSPN and CAN, almost reaching the rates seen in patients with known diabetes. However, some authors argue against an increased prevalence of DSPN and small fiber neuropathy in prediabetes [48, 49].

3.5 Age

Age has long been regarded as a risk factor of DSPN [1, 10-12, 26, 27, 43-45, 50, 51]. Several groups have shown that age exerts an independent effect on DSPN, leading to a progressive increase in its prevalence for approximately every decade of

life [10, 27, 50, 51]. The independent effect of age has also been shown for prediabetes in epidemiological surveys [43-45]. However, there is an important caveat in these observations. As age *per se* causes a progressive deterioration in neurological functions, independent of diabetes, the symptoms call for a differentiated interpretation [14, 52]. Delcourt *et al.* carried out an adjustment for age and found that DSPN no longer correlated with age [22]. On the other hand, it is conceivable that the impact of age on nerve function outweighs the influence of diabetes in the elderly population in which the prevalence of DSPN in milder degrees of hyperglycemia (prediabetes) may approach that of known diabetes [43-45]. Regrettably, no age-adjusted normal values have been used in the vast majority of studies.

3.6 Height

Height has been implicated in its pathogenesis of DSPN because of the length-dependent pattern of the disease, as a measure of nerve fiber length. Evidence for an association of DSPN with height comes from studies in both diabetes types [11-14, 26]. In a population study in Mauritius, height was a significant ($p < 0.001$) independent risk factor of DSPN, increasing its prevalence by 36% for every 5 cm increment (odds ratio (OR): 1.36, 95% confidence interval (CI): 1.19-1.57) in the cross-sectional analysis [14]. In the same study, prospective data confirmed this association (OR: 1.23, 95% CI: 1.03-1.45 per 5 cm, $p = 0.02$) [14]. By contrast, Franklin *et al.* found no association between height and prevalence of DSPN in a population study in Southern Colorado [51].

3.7 Hypertension

Hypertension is another risk factor for DSPN [1, 12, 13, 24, 25, 51, 53], but there appears to be a difference between the two diabetes types. In T1D, the data is affirmative [13, 25]. Forrest *et al.* have identified hypertension as the strongest predictor of DSPN, as it increased the relative risk approximately four times in a 6-year period [13]. Similarly, Tesfaye *et al.* have reported that systolic hypertension was an independent predictor after adjustment for age, duration of diabetes, and metabolic control [25]. In contrast, studies in T2D have been negative [12, 24, 51, 53]. Of note, tight blood pressure control in the United Kingdom Prospective Diabetes Study did not reduce deterioration of DSPN [54].

3.8 Dyslipidemia

Dyslipidemia is an additional risk factor, according to some studies. After adjustment for metabolic control, age, and other covariates, DSPN has been shown to correlate with high cholesterol [26] and triglycerides [11]. In T1D, increased low-density lipoprotein cholesterol (LDLc) [13] and triglycerides [25] have been identified as predictors of DSPN. However, in the first study, LDLc lost significance as a risk factor following adjustment for metabolic control and other covariates [13]. In T2D, fibrate use (hazard ratio (HR): 0.52, 95% CI: 0.27-0.98) and statin use (HR: 0.65, 95% CI: 0.46-0.93) significantly reduced the incidence of DSPN over 5 years [26]. Similarly, Keech *et al.* have reported improvement of protective sensation in DSPN following fenofibrate treatment [55]. More impressively, the same group has shown a significant ($p = 0.027$) reduction in minor lower-extremity amputations associated with DSPN (HR: 0.53, 95% CI: 0.30-0.94) [56].

Wiggin *et al.* have reanalyzed data from two randomized, placebo-controlled, clinical trials of patients with mild/moderate DSPN, and found that reduction of sural nerve myelinated fibre density at 52 weeks was independently correlated with high serum triglycerides ($p = 0.04$) [57]. More recently, a 6-year follow-up study of 48 Korean patients revealed that reduced high-density lipoprotein cholesterol (HDLc) (OR: 5.292, 95% CI: 1.001-27.989, $p = 0.05$) and high triglycerides (OR: 6.129, 95% CI: 1.057-35.528, $p = 0.043$) significantly increased the risk of DSPN, after adjusting for age and gender [58]. On the other hand, there is also some evidence against the association of DSPN with serum lipids [14, 24].

3.9 Smoking

There is some evidence that smoking is an independent risk factor of DSPN in T1D [11, 13]. In T2D, smoking may also be a risk factor [15], but its contribution may be weak and not independent [14]. Surprisingly, a protective effect of smoking has been reported in US veterans [12]. More recently, a meta-analysis including 10 prospective and 28 cross-sectional studies has found that smoking had an unadjusted OR of 1.26 for prospectively developing DSPN (95% CI: 0.86-1.85) [59]. In the cross-sectional studies, the pooled OR for DSPN due to smoking was 1.42 (95% CI: 1.21-1.65) [48]. For both analyses, evidence was graded as low-strength [59].

3.10 Obesity

In the Southern German population, obesity has been identified as a risk factor of DSPN [43-45]. In the general US population ≥ 40 years, obesity and the presence of at least 2 cardiovascular risk factors (triglycerides or plasma glucose, reduced HDLc, increased waist circumference, hypertension) increases the likelihood of peripheral neuropathy (OR: 2.20, 95% CI: 1.43-3.39) [60]. Subjects with morbid obesity have been found to exhibit features of small nerve fiber dysfunction (impaired pain perception and diminished reflex vasodilatation) [61].

3.11 Metabolic syndrome

With or without obesity, presence of the metabolic syndrome has been found to increase the likelihood of peripheral neuropathy (OR: 2.20 and 1.5, respectively) in the general population [60]. Among patients with idiopathic neuropathy, more frequent and more prominent features of the metabolic syndrome other than hyperglycemia have been found to influence the disease, as compared with those free from neuropathy [62, 63].

3.12 Insulin resistance

A study in 86 T2D patients has identified insulin resistance as a major independent risk factor of DSPN ($p < 0.001$) [64]. Of these patients, 48 were followed for 6 years [58]. It was found that initial insulin resistance was positively associated with impairment of sural sensory nerve action potential at 6 years ($r = 0.629$, $p = 0.001$), after adjustment for age, gender, and height [58].

3.13 Alcohol

Some studies [12, 50] have reported an association between DSPN and alcohol consumption, but others have not [15, 43-45]. In general, it may be difficult to differentiate between DSPN with alcohol as a risk factor and alcoholic neuropathy in a person with diabetes [1]. It would be useful to address this differentiation by careful patient selection in a prospective cohort study.

3.14 Hypoinsulinemia

In Finnish male patients recently diagnosed with T2D, low insulin in the fasting state and at 2 hours after oral glucose administration was associated ($p = 0.03$) with incident DSPN, irrespective of glycemic control (evaluated as fasting glucose

and glycated hemoglobin) [24]. Likewise, Sands *et al.* have found an association between low C-peptide and DSPN, but this association lost significance after adjustment for diabetes duration [15]. A similar but weak association has also been found in the Mauritius population [14]. Generally, the data on hypoinsulinemia are interesting, but it is important to remind that long diabetes duration *per se* is an important confounder, and needs to be taken into account when interpreting study results.

3.15 Oxidative stress

Experimental evidence suggests that oxidative stress is connected with DSPN [65-68]. Numerous studies have reported associations between systemic markers of oxidative stress and DSPN in diabetic patients. For example, lower values of reduced glutathione and reduced glutathione/oxidized glutathione ratio in association with DSPN have been reported [69]. Lower plasma concentrations of nitric oxide and higher endogenous oxidative DNA damage in T2D patients with DSPN have also been observed [70]. Bierhaus *et al.* have reported increased plasma methylglyoxal concentrations in association with painful DSPN [71]. Migdalis *et al.* have found reduced thiobarbituric acid-reacting substances in T2D patients with DSPN [72]. An overexpression of cutaneous mitochondrial superoxide dismutase was described in skin biopsies from recent-onset T2D subjects, suggesting enhanced local compensatory antioxidative defense at an early stage of T2D [73].

However, little information is available from prospective studies. In a 6-year study, Ziegler *et al.* found that increased plasma superoxide generation was associated with a decline in median sensory nerve conduction velocity (NCV) and a deterioration in heart rate variability (HRV) at rest [74]. Low vitamin E/lipid ratio tended to predict a decrease in peroneal motor NCV and an increase in malleolar VPT. Hoeldtke *et al.* showed that malondialdehyde (MDA) excretion in urine, a marker of lipid peroxidation, and plasma nitrite and nitrate, markers of nitrosative stress, were associated with sweating abnormalities, while sensory function tests correlated inconsistently with MDA excretion [75-77]. Further studies are required to determine whether optimized patient selection strategies showing increased levels of oxidative stress biomarkers such as superoxide generation could be of value in identifying those patients who may respond better to antioxidant treatment.

3.16 Platelet activation

Patients with DSPN and retinopathy may suffer from increased platelet aggregation [78]. This is even more pronounced in the setting of marked chronic hyperglycemia [79]. Mean platelet volume (MPV) is a marker of platelet activation, and may be increased in diabetes patients, especially in the context of microvascular complications [80]. Elevated MPV has indeed been reported in T2D patients with DSPN [81, 82].

Accumulating evidence indicates that platelet activation plays a contributory role in impaired microcirculation and peripheral nerve function [1, 2]. However, there are no prospective data to confirm or refute the role of increased MPV and/or other platelet activation markers in the development of DSPN. Similarly, there is no information on potential cut-off levels of these platelet markers, which may quantitatively express increased risk of DSPN development.

3.17 Low vitamin D

In T2D, the level of vitamin D was found to be significantly lower in those patients with DSPN [83]. Of patients with DSPN, 81.5% had vitamin D deficiency compared with 60.4% of those without DSPN [83]. DSPN was significantly associated with vitamin D deficiency after adjustment for diabetes duration, glycated hemoglobin, and LDLc (OR: 3.47, 95% CI: 1.04-11.56, $p = 0.043$) [83]. In a short, 8-week prospective study, the same authors demonstrated a significant ($p < 0.001$) improvement of neuropathic symptoms with oral vitamin D supplementation vs. placebo [84]. There is also recent evidence of a significant association between low vitamin D and impaired heart rate variability [85]. At present, there is growing interest in the contribution of vitamin D to the prevention of DSPN [86, 87] and peripheral artery disease [88].

3.18 Inflammation

Several population-based studies conducted in different KORA cohorts have documented associations between markers of systemic subclinical inflammation and the presence of DSPN [89-92]. In the KORA F3 cohort, high levels of C-reactive protein (CRP) and interleukin 6 (IL-6) were positively associated with the presence and severity of DSPN [92]. In the KORA F4 cohort, serum concentrations of the anti-inflammatory IL-1 receptor antagonist (IL-1RA), IL-6, IL-18, and soluble intercellular adhesion molecule-1 (sICAM-1) were positively asso-

ciated with the severity of neuropathic deficits, suggesting that DSPN is linked to pro-inflammatory and anti-inflammatory, possibly compensatory, processes in the older general population [91].

It was also reported that serum concentrations of IL-6 and sICAM-1 are positively associated with painful DSPN [90]. Moreover, serum levels of omentin, an adipokine with anti-inflammatory, insulin-sensitizing, and cardioprotective properties, were reduced in T2D individuals with DSPN, independently of established risk factors of polyneuropathy [89]. In T2D, there is also evidence of increased serum uric acid in the presence of DSPN [93, 94]. Future studies should clarify the temporal sequence and causality of these associations.

3.19 Genetic factors

Genetic factors have been implicated in the pathogenesis of DSPN, to account for the clinical observation that DSPN may, occasionally, be encountered in subjects with short diabetes duration and adequate glycemic control [1]. In this context, reduced/impaired Na^+/K^+ -ATPase activity and increased aldose reductase activity may play a supplementary role [97-100]. Na^+/K^+ -ATPase may be influenced by metabolic control and C-peptide secretion [101]. Some single nucleotide polymorphisms (SNPs) have been studied in Russian T1D patients with DSPN: these relate to the poly(ADP-ribose)polymerase-1 gene, the catalase gene, and genes encoding the enzymes superoxide dismutase extracellular superoxide dismutase [102-104]. In Greek T2D patients, the D allele of the Alpha2B adrenoceptor has been found to be associated with presence and severity of DSPN [105]. In German T1D and T2D patients, 2 single nucleotide polymorphisms (Asp299Gly and Thr399Ile) of the toll-like receptor 4 gene were found to be related with reduced DSPN in T2D, but (importantly) not in T1D [106].

Apolipoprotein E polymorphisms have been studied in a number of trials [107-110]. Results regarding the role of the $\epsilon 4$ allele as a risk factor have been conflicting, but some studies may be criticized because of insufficient patient homogeneity, inconsistent DSPN definition, and small sample size [111]. Monastiriotis *et al.* have reported a 5-fold increased risk of severe DSPN in the presence the $\epsilon 4$ allele (adjusted OR: 5.26, 95% CI: 2.24-12.31, $p = 0.0001$) in Greek T2D patients [112]. However, the exact supplementary role of these SNPs in the development and progression of DSPN remains obscure until confirmatory prospective

Table 2. Comorbidities of distal symmetric sensorimotor polyneuropathy

Comorbidities	Degree of association	References
Depression	++	118-122
Cognitive dysfunction	+	123-128
Autonomic neuropathy	+++	64, 129-134
Peripheral artery disease	+++	60, 135, 136
Medial arterial calcification	+++	139-142
Cardiovascular disease	++	143, 144
Nephropathy	+++	145-147
Retinopathy	++	146, 148, 149
Obstructive sleep apnea	++	152-154

Legend: Moderate association (+), stronger association (++), very strong association (+++).

studies in sufficiently large representative cohorts are available.

3.20 Low physical activity

Low physical activity has been linked with DSPN in the Southern German population [43-45]. In this context, a recent systematic review has examined the therapeutic importance of physical activity for treating pain in DSPN [113]. The evidence of improvement is insufficient; this may be due to limited data (2 studies), but also methodological limitations and risk of bias [113].

3.21 Growth factor depletion

There has been some discussion about reduced levels and impaired function of nerve growth factor (NGF) and insulin-like growth factor 1 (IGF-1) in patients with DSPN [114-116]. NGF induces neuronal growth and differentiation, and protects neural cells from apoptosis [114]. In DSPN, preliminary clinical evidence with NGF has been encouraging [114]. However, a large randomized prospective phase 3 clinical trial failed to show a significant beneficial effect of recombinant NGF on neuropathic deficits [117]. It demonstrated some symptomatic improvement only [117]. As this trial has been criticized for NGF formulation and dosage and for a strong placebo effect, further progress with this agent was discouraged [114].

In DSPN, Migdalis *et al.* have found a negative correlation of DSPN severity with IGF-1 ($r = -0.39$, $p < 0.01$) and IGF-1 receptors ($r = -0.34$, $p < 0.01$) [115]. Guo *et al.* have also reported significantly diminished IGF-1 levels in DSPN ($p < 0.05$) as compared with diabetes patients free from this complication [116]. These studies point out the

need for prospective data on the role of IGF-1 depletion and its potential therapeutic effectiveness in the onset and progression of DSPN.

4. Comorbidities of DSPN

The comorbidities of DSPN are summarized in **Table 2**.

4.1 Depression

Depression is an important comorbidity of DSPN [118-121]. Among neuropathic symptoms, it is pain and, primarily, postural instability (leading to gait uncertainty) that are associated with depression [119, 120]. In the same context, DSPN may be associated with poor quality of life [121], and painful symptoms may be linked with a reduced well-being index [122].

4.2 Cognitive dysfunction

Cognitive dysfunction is a further comorbidity that is being increasingly analyzed [123-128]. In the experimental model of DSPN, reduced pain perception may be associated with memory dysfunction [123]. Patients with DSPN may suffer from cognitive dysfunction [125-127], which affects verbal, visuospatial, and multitasking measures of executive function [124], and this may result in gait disturbances [125, 126] and increased risk of falls [126].

4.3 Autonomic neuropathy

Patients with DSPN frequently suffer from diabetic autonomic neuropathy (DAN) as well; approximately 50% have concomitant CAN [1, 64, 129-132]. The co-existence of DSPN and DAN increases with progressive diabetes duration and poor metabolic control, although this varies with the cohort studied and method of assessment [132]. In an Italian study, the majority of subjects with DAN exhibited DSPN [133]. The presence of concomitant DAN is important for prognosis, given that it is a risk factor of mortality via cardiovascular disease [134].

4.4 Peripheral artery disease

Patients with DSPN may also have concomitant peripheral artery disease (PAD) [60, 135]. US subjects ≥ 40 years with obesity and ≥ 2 cardiovascular risk factors exhibited a 2.4% frequency of simultaneous DSPN and PAD [60]. Obesity increased the likelihood of the presence of both complications

(OR: 6.91, 95% CI: 2.64-18.06) [60]. In the general diabetic population of Augsburg, Germany, there was a significant association between DSPN and PAD ($p < 0.05$) [43]. In the same population, PAD was associated with painful DSPN [44, 45]. In Sweden, T2D patients had a three-fold higher frequency of PAD than those without diabetes (52% vs. 16%, $p = 0.001$) [118]. DSPN was independently associated with PAD (OR: 2.31, 95% CI: 1.25-4.25, $p = 0.007$) [136]. In a Greek clinic-based study, ankle-brachial index (ABI) was significantly lower in T2D patients with DSPN than in those without this complication ($p = 0.001$) [137]. ABI < 0.9 exhibited 47% sensitivity and 90.7% specificity for DSPN [137].

4.5 Medial arterial calcification

Medial arterial calcification (MAC), or Mönckeberg's sclerosis, represents calcification of the tunica media. It is a well-known cause of spurious ABI elevation and mainly observed in the infrapopliteal arteries of diabetes patients [137, 138]. In a case series, Edmonds *et al.* showed that MAC was seen almost exclusively in patients with DSPN [139]. The same group reported that MAC was more common and severe in DSPN patients with neuropathy than in those without this complication ($p < 0.001$); there was a significant association between MAC and DSPN ($p < 0.001$) [140]. Other studies have confirmed the association of MAC with DSPN [141, 142]. Young *et al.* observed that MAC correlated with vibration perception threshold ($r = 0.35$, $p < 0.01$) [142]. Vibration perception threshold and diabetes duration were identified as independent predictors of MAC [142].

4.6 Cardiovascular disease

DSPN is frequently associated with cardiovascular disease [134, 135, 143]. Interestingly, a prospective, primary care study found that incident DSPN was significantly more frequent in subjects with cardiovascular disease at baseline ($p = 0.01$) [144]. Cardiovascular disease was an independent predictor of DSPN development after 10 years (OR: 2.32, 95% CI: 1.03-5.22) [144].

4.7 Nephropathy

Nephropathy may be more frequent in the presence of DSPN [145, 146]. Conversely, patients with diabetic nephropathy may exhibit more pronounced DSPN, and may therefore be at increased risk of severe diabetic foot lesions [147]. This in-

formation is important for the organization of an overall strategy for detecting, monitoring, and treating chronic microvascular complications.

4.8 Retinopathy

Similarly to nephropathy, retinopathy may also be regarded as a comorbidity of DSPN [146, 148, 149]. A study has shown progressive deterioration of corneal nerve fiber pathology with increasing severity of retinopathy [149]. Another group has shown progression of corneal nerve fiber pathology in parallel with diabetic retinopathy and DSPN [150].

4.9 Obstructive sleep apnea

Obstructive sleep apnea (OSA) has recently been recognized as a comorbidity of DSPN [151, 152]. A significantly higher frequency of DSPN in T2D patients with OSA than in those without OSA has been reported ($p < 0.001$) [151]. In a meta-analysis, DSPN was linked with a pooled OR 1.95 (95% CI: 1.03-3.70) for OSA [152]. A very recent, small case study series has suggested that severe OSA may be responsible for the failure to heal diabetic foot ulcers [153]. Therefore, OSA should be considered in the differential diagnoses of non-healing foot ulcers. More experience in this area is awaited [154]. In the light of these considerations, it may be useful to screen for OSA in patients with DSPN and neuropathic foot ulceration [155].

5. Discussion

Obviously, knowledge of risk factors for DSPN is clinically useful, because it offers the opportunity for delay and prevention of this complication. Some risk factors are modifiable and should receive the clinician's attention. These factors include primarily hyperglycemia, hypertension, dyslipidemia, and obesity [1, 13, 23-29, 51, 55, 56, 60]. Secondary risk factors are smoking and pre-diabetes [1, 21, 60, 63]. Platelet activation [79-82], oxidative stress [65-74], low vitamin D [83, 84], insulin resistance [58], and genetic factors [100-106] play another supplementary role, but, for the time being, there are limited options for intervention. A suggestion for targeting insulin resistance originates from the study by Pop-Busui *et al.*, showing that reduced incident DSPN is less frequent in T2D patients receiving insulin-sensitizing oral agents (66%) than in those receiving insulin-providing treatment (66% vs. 72%, respectively, $p = 0.02$) [155]. This effect was more pronounced in men (HR: 0.75, 99% CI: 0.58-0.99, $p < 0.01$).

Obviously, the greatest challenge is to improve outcomes with long-term consistent, stringent glycemic control [1]. The beneficial effect of this strategy is undeniable in T1D [19, 20, 29, 156], but has hitherto not proved significant in T2D [33-35]. This may reflect differences in etiology, but may also be used to motivate further improvements in anti-diabetic regimens and screening for DSPN in T2D. Of note, antilipidemic treatment, especially fenofibrate, has shown encouraging results [26, 55, 56], but these benefits have not yet been realized and confirmed in everyday reality.

Probably, the most ambitious approach involves multi-factorial intervention, addressing several major risk factors [157-159]. In T2D, Gaede *et al.* have employed an intensified approach, including strict metabolic control, aspirin, statins, angiotensin-converting enzyme inhibitors, antioxidants, and cessation of smoking [157]. They managed to demonstrate significant improvements in cardiovascular disease, retinopathy, nephropathy, and CAN, but not in DSPN [157]. In screen-detected diabetes, early intensive, multi-factorial therapy did not reduce incident DSPN and prevalent CAN compared with routine care [158, 159]. However, the feasibility of such studies is questionable. If participants have once been allocated to the routine clinical care arm of the trial, their degree of CVD risk factor control approaches that of the intensively treated group. Indeed, routine clinical care in expert centers is so effective nowadays that the randomization procedure leaves only marginal differences between the groups regarding blood pressure, HbA1c, and serum lipids. Therefore, this procedure minimizes the likelihood to detect differences in clinical neuropathy outcomes.

6. Conclusions

The major risk factors of DSPN include diabetes duration, hyperglycemia, and age, followed by hypertension, dyslipidemia, obesity, and metabolic syndrome [1, 11-15, 24, 25, 29-35, 36, 43-45, 50, 51, 55, 60]. Additional risk factors include height, smoking, insulin resistance, hypoinsulinemia, prediabetes, and several others [1, 15, 21, 64]. Of these, hyperglycemia, hypertension, dyslipidemia, obesity, prediabetes, and metabolic syndrome are modifiable, providing some opportunity to prevent and/or reduce the progression of DSPN. Stringent glycemic control has been shown to be effective in T1D [20, 29], but not or only marginally so in T2D [33-35].

Antilipidemic treatment, especially fenofibrate, has shown encouraging results [26, 55, 56], but more knowledge is needed. Multi-factorial intervention also appeared very promising initially, but this optimism has not been confirmed [157-159]. Emerging risk factors, notably vitamin D deficiency, inflammation, and oxidative stress also need to be therapeutically addressed, but we are currently at the very beginning of our knowledge in this area.

The major comorbidities of DSPN are depression, autonomic neuropathy, peripheral artery disease, cardiovascular disease, nephropathy, retinopathy, and medial arterial calcification [1, 60, 113-122, 129-131, 135, 137, 139-142, 146]. Given that these conditions increase morbidity and mortality, it is advisable for the clinician to screen for and monitor them as part of the overall management plan for DSPN.

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