Pathogenesis, diagnosis and clinical management of diabetic sensorimotor peripheral neuropathy

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Abstract | Diabetic sensorimotor peripheral neuropathy (DSPN) is a serious complication of diabetes mellitus and is associated with increased mortality, lower-limb amputations and distressing painful neuropathic symptoms (painful DSPN). Our understanding of the pathophysiology of the disease has largely been derived from animal models, which have identified key potential mechanisms. However, effective therapies in preclinical models have not translated into clinical trials and we have no universally accepted disease-modifying treatments. Moreover, the condition is generally diagnosed late when irreversible nerve damage has already taken place. Innovative point-of-care devices have great potential to enable the early diagnosis of DSPN when the condition might be more amenable to treatment. The management of painful DSPN remains less than optimal; however, studies suggest that a mechanism-based approach might offer an enhanced benefit in certain pain phenotypes. The management of patients with DSPN involves the control of individualized cardiometabolic targets, a multidisciplinary approach aimed at the prevention and management of foot complications, and the timely diagnosis and management of neuropathic pain. Here, we discuss the latest advances in the mechanisms of DSPN and painful DSPN, originating both from the periphery and the central nervous system, as well as the emerging diagnostics and treatments.

The worldwide diabetes mellitus pandemic is escalating at a startling rate with the prevalence of all types of diabetes mellitus nearly doubling between 1980 (4.7%) and 2014 (8.5%)[1]. It is anticipated that a staggering 700 million people globally will have diabetes mellitus by the year 2045, a one-third increase from the current figure[2]. The annual global health expenditure on diabetes mellitus is currently estimated at US$760 billion, with a projected increase to US$825 billion by 2030 (REF.[2]). These costs are challenging to developed countries, let alone to resource-limited countries, which are likely to experience the greatest increase in the prevalence of diabetes mellitus[3].

Diabetic sensorimotor peripheral neuropathy (DSPN) is a major complication of diabetes mellitus. It is the main precipitating factor for diabetic foot complications, including ulceration and Charcot neuroarthopathy, which frequently result in lower-limb amputation. Although foot protection services reduce amputation rates[4], the overall number of diabetic foot complications, including amputations, continues to increase globally[5]. Other clinical sequelae of DSPN include distressing peripheral neuropathic pain (painful DSPN) and an increased risk of falls. Most troublingly, DSPN[6], foot ulceration[7] and lower-limb amputation are independently associated with an increased risk of mortality[8]. Within 2 years of having a healed diabetic foot ulcer, mortality is 23%[7], which increases to 71% at 10 years following an incident ulcer[8]. The cost of DSPN is considerable; for example, in the UK, diabetic foot disease costs more than breast, lung and prostate cancer combined[9].

A number of important reviews in the field of DSPN have been published in the past few years with different foci, including disease mechanisms[10–12], screening strategies[13], biomarkers and diagnostic tools[14], the pharmacological treatment of neuropathic pain[15], the management of foot complications[16] and the management of diabetic neuropathies[17]. The aim of this Review is to encapsulate all aspects of DSPN in a cogent and contemporary article. In this Review, the term 'diabetes mellitus' refers to all types of the condition and we will specify when referring to individual types, for example, type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM).

Classification and definition

The diabetic neuropathies encompass a heterogeneous group of clinical syndromes. Typically, these syndromes are categorized according to their pattern of neurological

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https://doi.org/10.1038/s41574-021-00496-z

Key points

- Diabetic sensorimotor peripheral neuropathy (DSPN) is a common complication of diabetes mellitus that is associated with increased mortality, neuropathic pain, foot ulceration and lower-limb amputation.
- The mechanisms of DSPN are not fully understood but involve downstream injurious pathways associated with hyperglycaemia, dyslipidaemia and microvascular disease leading to neuronal inflammation, oxidative stress, mitochondrial dysfunction and cell death.
- There are no universally accepted disease-modifying treatments for DSPN; management is focused on optimizing glycaemic control, the achievement of cardiometabolic targets, and the prevention and/or treatment of diabetic foot complications.
- The reasons why some patients develop painless rather than painful DSPN are unknown; however, alterations in the peripheral and central nervous system have emerged as potential explanations.
- New compounds for the treatment of painful DSPN are being developed and the concept of stratifying patients according to various pain characteristics to improve analgesic response is being explored.

involvement (BOX 1). BOX 2 provides a brief description of these neuropathic syndromes, with the exception of DSPN, which is the main subject of this Review and is discussed in greater detail.

Features of DSPN

DSPN is the most prevalent neuropathic syndrome in diabetes mellitus. It is defined as a symmetrical, length-dependent sensorimotor polyneuropathy that results from metabolic and microvascular alterations secondary to chronic hyperglycaemia and other cardiovascular risk factors[18]. It begins in the toes bilaterally, progressing to involve the feet and legs in a 'stocking distribution'. Once it is well established in the lower limbs, the upper limbs can be affected. Motor manifestations follow sensory loss, initially involving the muscles of the foot and legs, and the hands and upper limb in advanced cases.

DSPN develops insidiously and patients might be asymptomatic. However, some patients experience varying combinations of symptoms, including numbness ('dead feeling'), paraesthesia and neuropathic pain. A curious feature of DSPN is that severe sensory loss in the presence of painful neuropathic symptoms might occur, the so-called painful–painless leg[19]. Painful symptoms include a burning, 'electric shock-type', sharp, cold and aching pain, hyperalgesia (increased pain from a stimulus that normally provokes pain) and allodynia (pain due to a stimulus that does not normally provoke pain)[20]. The intensity of neuropathic pain is typically worse at night, frequently causing insomnia. Some patients report pain on weight bearing (likened to walking on pebbles or hot sand). As a result of painful DSPN, patients are often profoundly disabled, experience mood disorders, have a reduced quality of life and might struggle to maintain full employment[21].

It is critically important to regularly examine the feet of patients with diabetes mellitus as loss of protective sensation is the strongest risk factor for diabetic foot ulceration. All patients with diabetes mellitus should have an annual foot examination[17]. Patients with DSPN are recommended to undergo more frequent foot examinations (for example, every 4–12 weeks) and should also be encouraged to check their feet on a daily basis.

On examination, there might be a reduction or absence of all modalities of sensation (pain or temperature (small-nerve fibres) and vibration, light touch or proprioception (large nerve fibres)), which begins in the toes. These changes then spread in a stocking distribution in the lower limbs and then in a glove distribution in the upper limbs as the disease progresses. An absence or reduction in ankle tendon reflexes is an early sign but this feature might occur with advancing age in the absence of DSPN. With advancing neuropathy, motor findings, including muscle weakness, wasting of small muscles of the foot and extensor hallucis longus, high arching of the foot and abnormal knee reflexes, become apparent. Clawing of the toes leading to prominent metatarsal heads is a common feature, increasing the risk of ulceration. During a clinical assessment of the neuropathic foot, a thorough assessment of the patient's footwear is mandatory. Trauma resulting from a poor fit or abnormal wear from internal pressure areas and foreign objects are common causes of foot ulceration[22]. Upper-limb motor nerve features, such as weakness and wasting of the muscles of the hand, are a late finding. In patients with advanced neuropathy, sensory ataxia, foot deformity and muscle weakness put patients at risk of falling.

Peripheral autonomic neuropathy causes foot skin dryness and hence the skin can become prone to cracks, infection and ulceration. The purely neuropathic foot

Box 1 | **Classification of the diabetic neuropathies**[17]

Generalized symmetrical polyneuropathies

Diabetic sensorimotor polyneuropathy

- Mixed sensorimotor neuropathy
- Predominantly large-fibre neuropathy
- Predominantly small-fibre neuropathy
- Pure small-fibre neuropathy

Acute painful–distal sensorimotor polyneuropathies

- Treatment-induced neuropathy of diabetes mellitus
- Hyperglycaemia-induced neuropathy

Autonomic neuropathy

- Cardiovascular autonomic neuropathy
  - Reduced heart rate variability
  - Resting tachycardia
  - Orthostatic hypotension
  - Exercise intolerance
  - Silent myocardial ischaemia
  - Sudden cardiac death
- Gastrointestinal autonomic neuropathy
  - Oesophageal dysmotility
  - Gastroparesis
  - Diabetic diarrhoea
  - Constipation
  - Faecal incontinence
- Urogenital
  - Neurogenic bladder
  - Sexual dysfunction (erectile and female sexual dysfunction; retrograde ejaculation)
- Sudomotor dysfunction
  - Peripheral anhidrosis
  - Hyperhidrosis
  - Gustatory sweating

Metabolic (that is, hypoglycaemia unawareness)
Pupillary dysfunction

Focal or multifocal neuropathies

Mononeuropathy

- Mononeuropathies
  - Cranial nerve (for example, oculomotor nerve palsy or facial nerve palsy)
  - Peripheral nerve (for example, peroneal nerve palsy)

Mononeuritis multiplex
Radiculoplexus neuropathy

- Radiculopathy
  - Thoracic
  - Abdominal
  - Thoraco–abdominal
- Radiculoplexopathy
  - Lumbosacral radiculoplexopathy
  - Cervical radiculoplexopathy

Entrapment neuropathies

- For example, carpal tunnel syndrome, ulnar neuropathy

Box 2 | **Neuropathic syndromes occurring in diabetes, other than diabetic sensorimotor peripheral neuropathy**

Acute painful–distal sensory polyneuropathies
These acute painful polyneuropathies are induced by hyperglycaemia or treatment. Two distinct presentations exist, which occur either in the context of poor diabetes mellitus control, often associated with weight loss, or following rapid improvements in glucose control (treatment-induced neuropathy of diabetes). An acute 'stocking and glove' pattern of painful sensory neuropathy presents within weeks, with small-fibre neuropathic deficits. Management is focused on relieving pain and on the maintenance of optimal glycaemic control.

Autonomic neuropathies
Abnormalities of autonomic function are very common in patients with longstanding diabetes mellitus. Several systems might be affected (BOX 1), with cardiac autonomic neuropathy being the most prevalent. The cornerstone for the prevention or delay of progression of cardiac autonomic neuropathy is early achievement of tight glycaemic control and multifactorial cardiometabolic risk reduction[207,292]. For greater detail of the diagnosis and management of diabetic autonomic neuropathy please refer to REFS[293–299].

Focal or multifocal neuropathies
Focal neuropathies are secondary to nerve compression or microvasculitis. The latter mainly affect middle-aged or older patients, are more common in men than in women and have a fairly rapid onset.

Mononeuropathy and mononeuritis multiplex
Cranial nerve palsies (for example, third cranial nerve palsy) are the most common mononeuropathies[300]. Mononeuritis multiplex has also been described in diabetes mellitus, but this is rare.

Radiculoplexus neuropathy
The most common disorder is lumbosacral radiculoplexopathy. Patients present with subacute, painful, unilateral lower-limb neuropathy associated with weight loss[301]. Proximal muscle weakness, often affecting the lower limbs (amyotrophy) is associated with neuropathic pain and can be profoundly disabling.

Truncal radiculopathy causes neuropathic pain in a radicular distribution and might be associated with pain and muscular weakness, classically causing out-pouching of the abdominal wall[302].

Entrapment neuropathies
Entrapment neuropathies most commonly involve the median, ulnar and peroneal nerves[303]. Diagnosis requires nerve conduction studies, although this might be challenging when there is concurrent diabetic sensorimotor peripheral neuropathy.

without vascular disease is warm with a bounding arterial pulse. In this scenario, nutritive capillary circulation is often impaired owing to arteriovenous shunting[19].

Charcot neuroarthropathy is a rare but well-recognized limb-threatening complication of DSPN[23]. It is now considered an inflammatory syndrome characterized by varying degrees of bone and joint disorganization secondary to underlying neuropathy, trauma and perturbations of bone metabolism[23]. In the acute presentation, the foot is often swollen, warm and erythematous with varying degrees of pain. If the condition is not rapidly recognized and joint immobilization instituted, chronic deformities can develop that subsequently put the foot at very high risk of ulceration. Pathways to Charcot neuroarthropathy and to foot ulceration and/or amputation are shown in FIG. 1.

Assessment of DSPN

Bedside assessment and foot screening

DSPN can be diagnosed by the bedside with careful examination of the feet and legs using simple instruments and within a few minutes. The assessment of temperature or pinprick sensation (small-fibre function), a 128-Hz tuning fork test to assess vibration sense (large-fibre function) and a 10 g monofilament test (foot ulcer risk) are a minimum requirement[17]. It is recommended that these tests are done at the point of diagnosis of T2DM, 5 years after diagnosis of T1DM, and annually thereafter for patients with either T1DM or T2DM[17]. Where resources are extremely limited, a simple sensory test can be performed by lightly touching the tips of the first, third and fifth toes (the Ipswich Touch Test)[24]. Moreover, the 3-minute foot exam can help to detect major foot risks and prompt early referral to a specialist. This brief assessment outlines a 1-minute history, 1-minute physical examination and 1-minute patient education and is discussed in more detail by Miller et al.[25]. The diagnosis of painful DSPN is made based on the presence of typical painful neuropathic symptoms and a clinical diagnosis of DSPN after the exclusion of other neuropathies.

Scored clinical assessments

Scored clinical assessments provide a standardized, quantitative, objective and reproducible measure. These instruments are used for the screening, diagnosis and grading of severity of DSPN[17]. They can be used in a clinical scenario but they are particularly useful for clinical and epidemiological research. However, care must be taken to standardize the assessments (by the careful training of practitioners who perform the assessments). The limitations of these tests include the provision of only a probable diagnosis (BOX 3) and that they might be time-consuming to perform in the context of a busy clinical practice. The most widely used instruments include the Michigan Neuropathy Screening Instrument Questionnaire (MNSIQ; 15-item self-administered questionnaire)[26], the Michigan Neuropathy Screening Instrument (MNSIQ plus a structured clinical examination), Michigan Diabetic Neuropathy Score (neurological assessment coupled with nerve conduction studies)[26], Toronto Clinical Neuropathy Score (composite score of neuropathy symptoms sensory exam and reflexes)[27], modified Toronto Clinical Neuropathy Score (composite score of neuropathy symptoms and signs)[28], Neuropathy Disability Score (neuropathy signs, including reflexes)[29], Neurological Disability Score (neurological examination of cranial nerves and upper and lower limbs)[30], the Utah Early Neuropathy Scale (examination scale targeted to early sensory neuropathy)[31] and the Neuropathy Symptom Score (assessment of sensory, motor and autonomic neuropathy symptoms)[30].

A number of instruments have also been used to assess neuropathic pain, including the Neuropathy Total Symptom Score-6 (measures frequency and intensity of neuropathic symptoms)[32], PainDETECT (patient-administered 10-item questionnaire)[33], DN4 (Doleur Neuropathique en 4; composite score of seven sensory descriptors and three clinical signs)[34] and the Neuropathic Pain Symptom Inventory (self-administered 12-item questionnaire evaluating different symptoms of neuropathic pain)[35].

Point-of-care testing devices

In the past few years, a number of bedside point-of-care testing devices have been developed for the assessment of DSPN in the context of busy clinical practice[13,14]. These include those that rely on patients' subjective

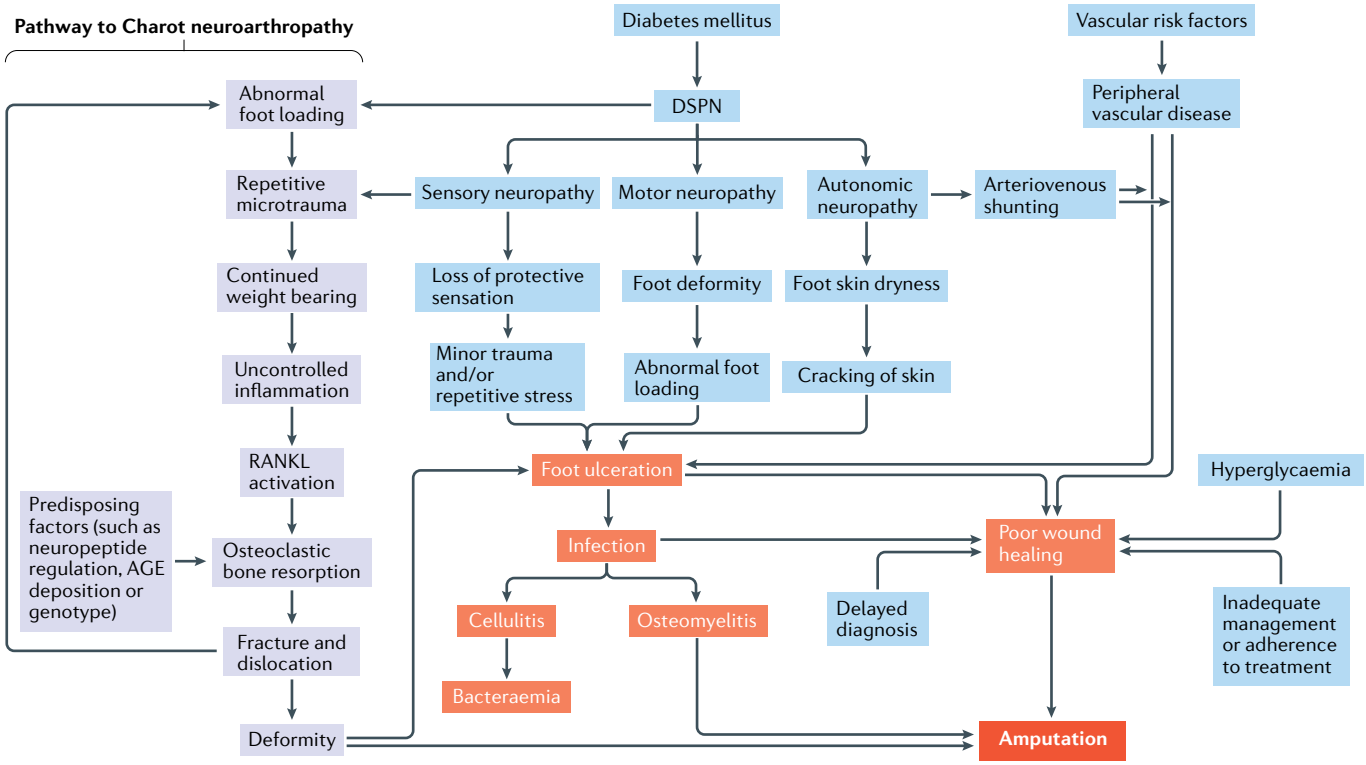

Fig. 1 | **The pathways to foot ulceration and amputation.** Diabetic sensorimotor peripheral neuropathy (DSPN), vascular disease and foot deformity might result in foot ulceration. In Charcot neuroarthropathy, minor trauma of the foot or ankle triggers an inflammatory cascade with a subsequent imbalance of the receptor activator of NF-κB ligand (RANKL)–osteoprotegerin axis, promoting osteoclastic bone resorption[288,289]. A cycle of fracture and dislocation develops, which is further compounded by weight bearing[289]. Blue boxes signify risk factors to foot ulceration and poor wound healing. Orange boxes represent the pathway to amputation of the ulcerated foot. The grey boxes indicate the pathway to Charcot neuropathy. AGE, advanced glycation end-product.

responses (for example, assessment of the vibration perception threshold using the biothesiometer or Vibratip)[14] and others that provide an objective assessment. The devices that enable an objective assessment are gaining popularity as they provide rapid, quantitative and sensitive measures of DSPN. These include DPNCheck[36] (a hand-held device that measures sural sensory conduction velocity and amplitude within 5 minutes), SUDOSCAN[37] (a test of sudomotor function of the feet and hands) and corneal confocal microscopy[38] (measuring corneal nerve fibre morphometric parameters). These devices could also be used to detect early or subclinical DSPN and monitor disease progression[13]. A feasibility study using a one-stop approach with combined eye, renal and DSPN screening using point-of-care testing devices (measuring both small-fibre and large-fibre function) demonstrated that this approach was an effective model for the early diagnosis of DSPN[39]. However, before such point-of-care testing devices can be recommended for routine screening they must be validated (including their use to predict hard clinical endpoints such as the development and progression of clinical DSPN[40] and foot ulceration) and shown to be cost-effective[13].

Assessment of DSPN in research

For clinical research, including longitudinal studies measuring disease progression and randomized controlled trials for the treatment of DSPN, a more accurate measure of neuropathy (confirmed DSPN with electrodiagnostic studies or small-fibre measure with class 1 evidence (as defined by REF.[41])) is required[18] (BOX 3). The use of electrodiagnostic studies is also recommended by the American Academy of Neurology[41]. A number of composite scoring systems have also been used in longitudinal studies and randomized controlled trials[42]. These systems include the Neuropathy Impairment Score of the Lower Limb plus 7 Neurophysiological Tests (deriving a score from sensory and motor signs and vibration perception threshold, heart rate variability to breathing and nerve conduction measures)[42] and Total Neuropathy Score (deriving a score from sensory and motor symptoms and signs, vibration perception threshold, and sural and peroneal amplitude)[43].

DSPN has a profound effect on quality of life and psychosocial well-being. A number of specific instruments for assessing these factors in patients with DSPN have been developed, including NeuroQol[44] and Norfolk Quality of Life Questionnaire-Diabetic Neuropathy[45], and have also been used in randomized controlled trials.

Diagnosis of DSPN

A consensus definition of DSPN has been proposed by the Toronto Diabetic Neuropathy Expert Group[18] (BOX 3). The diagnosis of possible or probable DSPN is normally sufficient in a clinical context without the need for specialist investigations. Atypical symptoms or signs

or diagnostic uncertainty should prompt the referral for specialist opinion and neurophysiological testing[18]. Nerve conduction studies remain the gold-standard investigation for the diagnosis and estimation of the severity of DSPN[18,41]. However, to be reliable, they must be done rigorously using appropriate reference values corrected for applicable variables[18]. Nerve conduction studies measure large-fibre function and hence measures of small-fibre function (quantitative sensory testing (QST), thermal threshold testing, skin biopsy with intra-epidermal nerve fibre density quantification or corneal confocal microscopy) are necessary to detect small-fibre neuropathy[18,46].

Before attributing a neuropathy to diabetes mellitus, a careful clinical history and investigation should be performed to exclude other potential causes (for example, thyroid disease, vasculitis, vitamin B_{12} deficiency, alcohol neuropathy or uraemia). The absence of other microvascular complications of diabetes mellitus (for example, retinopathy and nephropathy), rapid weight loss and atypical features in the history or clinical examination (for example, asymmetry, rapid progression, predominantly motor involvement or early upper-limb involvement) should direct the physician to search for other causes of neuropathy and perhaps the referral to a specialist.

Epidemiology

DSPN

The global prevalence of clinically diagnosed DSPN is estimated at around 30% in people with diabetes mellitus, and ranging between 6% and 51%, in people with diabetes mellitus or pre-diabetes[47]. The considerable variability in the reported prevalence of DSPN is due to a number of factors, including patient selection bias and the use of different diagnostic criteria and assessment methods[47]. This variability is clearly illustrated when comparing reports that estimate the prevalence of DSPN at 11–13% in patients with T1DM using a questionnaire-based approach (MNSIQ)[48,49] versus a much higher prevalence (28%) when a structured clinical examination plus vibration perception threshold is used[50]. Moreover, when more sensitive tests (such as nerve conduction studies) are used, the reported prevalence increases to above 50%[51,52].

In contrast to patients with T1DM, patients with T2DM might present with DSPN at diagnosis or even in the pre-diabetes state[53]. In the MONICA/KORA Augsburg Survey, the prevalence of peripheral neuropathy was 7.4% in those with normal glucose tolerance, 11.3% in those with impaired fasting glucose, 13.0% in those with impaired glucose tolerance and 28.0% in the T2DM group[53]. Clearly, therefore, future studies need to ensure that the population under study is carefully defined (including the duration of diabetes mellitus) and should avoid volunteer and selection bias. The prevalence of DSPN in patients with T2DM ranges from 13% to 18% if assessed using the MNSIQ[54,55], from 23% to 51% when a structured clinical examination or vibration detection thresholds are used[56,57], and from 42% to 44% when nerve conduction is used[52,58]. The past few years have seen a concerning increase in the number of young people diagnosed with T2DM, which is associated with a premature onset of complications, including a 22% prevalence of DSPN (mean age 22 ± 3.5 years)[59].

Painful DSPN

Epidemiological studies of painful DSPN have similar limitations to those studying DSPN, with the added complexity of diagnosing and quantifying neuropathic pain. Studies from the past few years have used a widely adopted definition of neuropathic pain[60] and used validated screening tools, including DN4 and PainDETECT, that have high sensitivities. Most reports estimate the prevalence of painful DSPN at between 13% and 35% of patients with diabetes mellitus[61–64]. In the MONICA/KORA study, the overall prevalence of neuropathic pain was 13.3% in patients with diabetes mellitus (6% T1DM, 69% T2DM, 3% secondary diabetes mellitus and 22% unknown type of diabetes mellitus), 8.7% in those with impaired glucose tolerance, 4.2% in those with impaired fasting glucose and 1.2% in those with a normal glucose tolerance[63].

Risk factors

DSPN

The risk factors for DSPN are well recognized and are based on several large, well-conducted cross-sectional and prospective studies. The most notable risk factor for DSPN is poor glycaemic control[47,49,51]. A 1% increase in HbA_{1c} results in an estimated 10% higher prevalence of DSPN[47]. A longer duration of diabetes mellitus and increasing age are also associated with a higher risk of DSPN[47,48,51,65,66]. Beyond glucose burden, risk factors classically associated with cardiovascular disease have also been linked to DSPN. For instance, several studies have shown that obesity, an increased waist-to-hip ratio, hypertension, dyslipidaemia, hypertriglyceridaemia and smoking are independent risk factors for incident DSPN[47–49,59,65,67]. Preliminary evidence also indicates that certain genetic polymorphisms, including *ACE* and *MTHFR* gene variants, might predispose individuals to DSPN[68]. A novel genetic locus of chromosome 2q24, which is associated with increased tibial nerve expression of the nearby gene

Box 3 | **The minimal diagnostic criteria for DSPN**[a]

- Possible diabetic sensorimotor peripheral neuropathy (DSPN): the presence of symptoms or signs of DSPN.
- Probable DSPN: the presence of symptoms and signs of DSPN, including any two or more of the following: neuropathic symptoms, reduced distal sensation or abnormal ankle reflexes.
- Confirmed DSPN: the presence of abnormal nerve conduction studies and/or abnormal validated measures of small-fibre neuropathy with class 1 evidence (for example, from skin biopsy samples or thermal threshold testing) and symptoms and/or signs of DSPN.
- Subclinical DSPN: the presence of no symptoms or signs with confirmed abnormal nerve conduction studies or a validated measure of small-fibre neuropathy with class 1 evidence.

[a]Criteria recommended by the Toronto Expert Panel[18]. Adapted with permission from REF.[18], ADA.

SCN2A (encoding the α-subunit of Nav1.2, a human voltage-gated sodium channel (VGSC)), has a protective effect on the development of DSPN in T2DM[69].

Painful DSPN

The risk factors for painful DSPN are poorly understood[70]. An increasing severity of neuropathy[71,72], the duration of diabetes mellitus[73], HbA_{1c} (REF.[72]) and body weight[73,74] have all been reported to be associated with painful DSPN[70]. Women also appear to be at greater risk than men[62], a finding in agreement with sex differences in other chronic pain conditions[75]. In addition, gain-of-function variants in genes encoding VGSCs, which are associated with an increase in neuronal excitability, have been found in patients with painful DSPN[76,77]. Furthermore, two genome-wide association studies found single-point nucleotide polymorphism clusters in Chr8p21.3 (next to the *GFRA2* gene), Chr8p23.1 (next to *HMGB1P46*) and Chr1p35.1 (spanning the *ZSCAN20–TLR12P* area) in patients with painful DSPN[78,79]. However, although these were large studies, detailed neuropathy phenotyping was unfortunately not undertaken.

Pathophysiological mechanisms of DSPN

The peripheral neurons supplying the feet are the longest cells in the body and require an adequately functioning vascular supply, mitochondria, and glucose and lipid metabolism, all of which can be disturbed in diabetes mellitus. The pattern of peripheral nerve injury in DSPN matches the clinical presentation, with the distal terminals of the sensory nerve fibres affected first. Ultimately, however, the whole peripheral nervous system is affected in DSPN, including the myelinated and unmyelinated nerve axons, perikaryon, nerve vasculature and glial cells (FIG. 2).

Clinical and preclinical studies have identified several mechanistic pathways believed to be involved in the pathophysiology of DSPN (FIG. 3). Animal models have been widely used to investigate the pathophysiology of DSPN; however, no single model fully mimics the human condition[80]. This divide between experimental and clinical DSPN is probably the main factor explaining why disease-modifying treatments that are successful in rodent models have failed to translate into successful treatments for patients. Experimental and clinical evidence suggests that hyperglycaemia-mediated cellular injury is probably the most important factor in DSPN[47,49,51,81,82]. Alongside hyperglycaemia, other factors, such as obesity, dyslipidaemia, impaired neurotrophic support and insulin signalling, and microvascular disease, induce downstream oxidative stress, mitochondrial dysfunction and inflammation, ultimately causing cellular dysfunction and death[81]. We consider the pathophysiology of DSPN first and then discuss the mechanisms of neuropathic pain in diabetes mellitus.

Different types of diabetes mellitus

DSPN in T1DM is primarily induced through hyperglycaemia whilst, in T2DM, obesity, insulin resistance and dyslipidaemia might be additional key factors[67,81]. This observation is consistent with glycaemic control having a substantial effect in reducing the incidence of DSPN in T1DM but only a modest effect in T2DM[82]. A detailed review is beyond the scope of this article but studies have found differences between T1DM and T2DM in several aspects, including experimental sural nerve gene expression[83,84], inflammatory biomarkers[85], the extent of small-fibre impairment[86], and nerve ultrasound[87] and MR neurography features of the peripheral nerve[88].

Hyperglycaemia

The most extensively studied metabolic pathway in DSPN is the polyol pathway, in which glucose is converted into sorbitol and sorbitol into fructose. Excessive flux through this pathway results in oxidative stress and dysfunction of Na^+/K^+ ATPase activity, resulting in impaired nerve conduction[89]. Additionally, the glycolytic intermediate fructose-6-phosphate is shunted into the hexosamine pathway, increasing the production of uridine diphosphate *N*-acetylglucosamine (UDP-GlcNAc). The increased flux of fructose-6-phosphate to UDP-GlcNAc leads to altered gene expression and protein function, ultimately causing vascular dysfunction, inflammation and oxidative stress[90]. Hyperglycaemia also leads to the excess metabolism of diacylglycerol, which activates the protein kinase C (PKC) pathway. In turn, excessive PKC activation impairs Na^+/K^+ ATPase activity and neurovascular blood flow through increased vasoconstriction[91].

Under hyperglycaemic conditions, proteins, lipids and nucleic acids can undergo irreversible non-enzymatic reactions, forming advanced glycation end-products (AGEs). In DSPN, AGEs are formed throughout the peripheral nervous system, including nerve axons, neural microvasculature, Schwann cells and extracellular matrix, inducing permanent structural and functional changes[92]. The interaction of AGEs with their receptors (RAGE) also triggers the activation of intracellular signalling pathways, leading to downstream inflammation, oxidative stress and nuclear DNA degradation, ultimately resulting in vascular dysfunction and nerve conduction deficits[92,93].

Oxidative stress

Oxidative or nitrosative stress occurs when there is an imbalance in the production of reactive oxygen or nitrogen species, respectively, and antioxidant defence. In DSPN, reactive oxygen species production overwhelms endogenous antioxidant defences[94], impairing neural blood flow, nerve conduction, neurotrophic support and neuronal mitochondrial function[95]. Indeed, mitochondrial superoxide production induced by hyperglycaemia has even been postulated as a unifying hypothesis of diabetic microvascular complications[90]. The overproduction of superoxide through the electron-transport chain inhibits GAPDH enzyme activity, which results in the diversion of upstream glycolytic metabolites into molecular pathways of glucose overutilization (that is, the polyol, hexosamine, PKC and AGE pathways)[90].

Serum markers of oxidative stress have also been linked to human DSPN[14] in prospective studies[96,97]. However, caution needs to be exercised in interpreting these studies as the changes might not have been driven by DSPN alone[96,97].

Poly(ADP-ribose) polymerases (PARP) are a family of enzymes involved in DNA repair, cellular proliferation and programmed cell death[98]. Oxidative and/or nitrosative stress induced by hyperglycaemia leads to DNA damage and subsequent hyperactivation of PARP[99]. The over-activation of PARP consumes NAD^+, slowing glycolysis and impairing ATP function, with concurrent GAPDH inhibition. PARP activation feeds forward to further superoxide and peroxynitrite formation[99] and induces intra-epidermal nerve fibre density loss, endothelial dysfunction, nerve conduction slowing, reduced nerve blood flow and neuronal energy deficits[99,100].

Mitochondrial dysfunction

Mitochondrial structural abnormalities have been observed in experimental rodent models of DSPN[101,102]. In DSPN, an imbalance seems to exist between mitochondrial biogenesis and fission, which leads to the development of small, dysfunctional mitochondria[102–104].

Although several studies have reported that glucose overload leads to excessive endothelial cell mitochondrial respiration[90], studies from the past few years show impaired neuronal respiratory function with a reduction in mitochondrial reactive oxygen species production[104,105]. The explanation for this finding might be that acute hyperglycaemia increases mitochondrial gene and protein expression, whereas mitochondrial gene and protein expression are downregulated in chronic diabetes mellitus, with reduced mitochondrial oxidative phosphorylation and a shift to less energetically efficient anaerobic metabolism[103–105]. Hence, with chronic hyperglycaemia, peripheral nerves might be susceptible to energy failure, particularly the distal terminals.

Dyslipidaemia

Rodent models of diet-induced obesity and diabetes mellitus fed on a high-fat diet develop a peripheral, predominantly small-fibre, neuropathy[106,107]. Patients with progressive DSPN had been reported to have elevated serum levels of triglycerides, which was related to a decline in myelinated fibre density[108]. Additionally, excess levels of fatty acids impair neuronal mitochondrial trafficking and bioenergetic function[109]. Furthermore, Schwann cells cultured in high concentrations of long-chain fatty acids develop mitochondrial

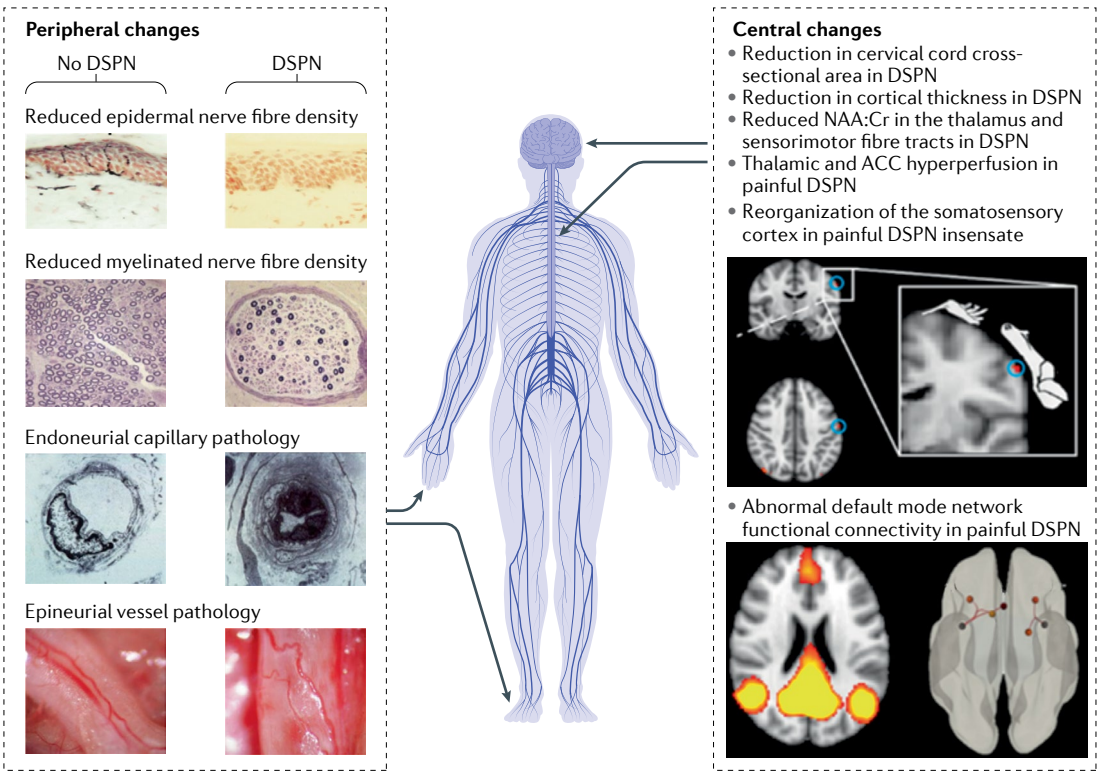

Fig. 2 | **Peripheral and central nervous system structural and functional abnormalities in DSPN.** Peripheral alterations include a reduction in the density of intra-epidermal nerve fibres and sural nerve myelinated fibres, sural nerve endoneurial microangiopathy with increased basement membrane cell thickening, endoneurial cell proliferation and vessel occlusion, and sural nerve epineurial arterial attenuation, venous distention and tortuosity, and arteriovenous shunting. Central alterations include structural changes (such as to the spinal cord and somatosensory cortex), neurochemical changes (for example, a reduction in the *N*-acetylaspartate to creatine (NAA:Cr) ratio in the thalamus and white matter tracts of the parietal lobe), vascular alterations (in the anterior cingulate cortex (ACC) as well as thalamic hypervascularity) and functional alterations (such as abnormal resting and task-based functional connectivity)[13,131,142,144–147,191,290,291]. DSPN, diabetic sensorimotor peripheral neuropathy. Reduced epidermal nerve fibre density image adapted from REF.[291], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Endoneurial capillary pathology image reprinted from REF.[290], Springer Nature Limited. Epineurial vessel pathology image adapted from REF.[132], Springer Nature Limited. Reorganization of the somatosensory cortex in painful DSPN insensate image adapted with permission from REF.[149], ADA.

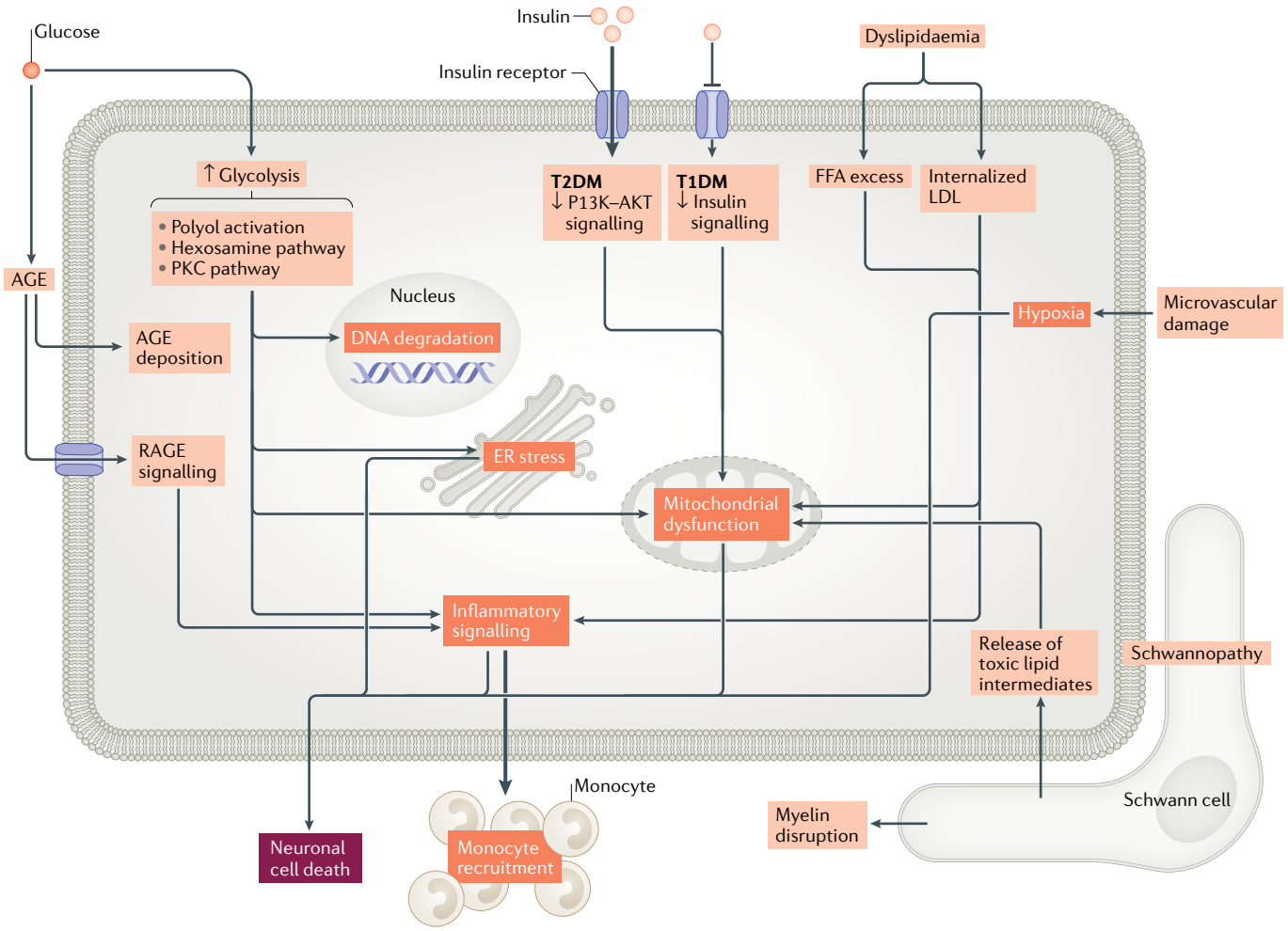

Fig. 3 | **Mechanisms of neuronal cell death in DSPN.** Increased glucose metabolism in diabetes mellitus leads to excessive activation of the polyol, hexosamine and protein kinase C (PKC) pathways and advanced glycation end-product (AGE) formation and/or receptor (RAGE) activation. Insulin deficiency in type 1 diabetes mellitus (T1DM) leads to reduced insulin signalling, whilst insulin resistance in type 2 diabetes mellitus (T2DM) results in reduced PI3K–AKT signalling. Dyslipidaemia and hyperglycaemia further induce the release of pro-inflammatory cytokines and chemokines, which results in inflammatory-mediated and immune-mediated neurotoxicity. Microvascular dysfunction and downstream DNA degradation, endoplasmic reticulum (ER) stress and mitochondrial dysfunction ultimately cause neuronal cell death. Downstream common pathways of neuronal cell death are represented by dark orange boxes. DSPN, diabetic sensorimotor peripheral neuropathy; FFA, free fatty acid.

dysfunction as well as endoplasmic reticulum and oxidative stress, ultimately leading to cell death[110].

Under hyperglycaemic conditions, oxidized lipoproteins are injurious to dorsal root ganglion[111] and vascular endothelial cells[112], which is also consistent with findings from in vivo studies[113]. Gene profiling of sural nerve samples in patients with confirmed mild-to-moderate DSPN has demonstrated the altered expression of genes with protein products involved in lipid metabolism[114]. Finally, the differential expression of the genes involved in lipoprotein and adipocytokine signalling have also been reported in rodent models of DSPN[115,116].

Inflammation

Cross-sectional and longitudinal studies have reported an association between serum biomarkers of inflammation and DSPN[14,85,117,118]. Increased immune cell infiltration has also been found in sural nerve biopsy samples from patients with DSPN[119]. Gene expression analysis of the sural nerve in rodent models and patients with DSPN has demonstrated the dysregulation of inflammatory and immune pathways[84,114].

Inflammation has been linked to hyperglycaemia[120], insulin resistance, impaired insulin signalling[121] and dyslipidaemia[122] as well as to known downstream pathways of neuronal injury, including oxidative and/or nitrosative stress[123] (FIG. 3). Although not fully understood, this link might be mediated through direct glucose or lipid toxicity as well as by the activation of kinases such as PKC, mitogen-activated protein kinase and Jun N-terminal kinases and the transcription factor NF-κB. The end result is the triggering of cytokine recruitment, chemokine production and enhancement of existing inflammation and immune responses, further exacerbating downstream oxidative stress, endothelial dysfunction and neurotoxicity[123].

Impaired neurotrophic support

In experimental animal models of DSPN, growth factors, such as nerve growth factor, have an altered expression and receptor function[124,125]. The dysfunctional retrograde transport of neurotrophins from distal axons to neuronal cell bodies and nuclei has also been observed[124,125]. Impaired signalling of other growth factors (for example, C-peptide, insulin and insulin-like growth factors) has been reported in DSPN, which might partly explain the inefficiency of neuronal regeneration in DSPN[126].

Schwann cell injury

Schwann cells are essential for the survival of peripheral nerves as they provide energy and protection for neurons. Many of the pathways involved in DSPN (for example, polyol pathway activation, oxidative stress, mitochondrial dysfunction and inflammation) are also injurious to Schwann cells, ultimately resulting in myelin disruption, demyelination, axonal conductance abnormalities and impaired neuronal regeneration[127]. Additionally, Schwann cells have been proposed to be key sensors of axonal activity, providing energetic metabolites to axons, and this process is disrupted in DSPN[10]. Indeed, in a mouse model, mitochondrial dysfunction in Schwann cells has been shown to trigger altered lipid metabolism, which leads to dysfunctional myelination and the release of toxic lipid intermediates, inducing axonal degeneration[128].

Microvascular disease

Endoneurial microangiopathy in DSPN occurs early and relates to clinical, neurophysiological and morphological abnormalities[129,130]. Profound sural nerve epineurial vessel anatomical and blood-flow abnormalities, including arteriovenous shunting, have been demonstrated in DSPN[131] (FIG. 2).

In patients with DSPN, the sural nerve conduction velocity has been shown to increase with direct warming but not following strenuous exercise, whereas patients with diabetes mellitus without neuropathy and healthy control individuals demonstrate an increase in conduction velocity after exercise[132]. This observation shows that the neuropathic nerve is unable to increase its blood flow in response to the demands of exercise because of poor microcirculation, providing indirect evidence for the importance of vascular factors in DSPN. Endothelial dysfunction, characterized by a loss of endothelium-derived nitric oxide and a pro-inflammatory state, is well recognized in DSPN[133]. Furthermore, systemic markers of both endothelial dysfunction and vascular inflammation have also been associated with DSPN[14,117]. In addition, microvascular disease and endothelial dysfunction result in impaired nerve blood flow[134] and endoneurial hypoxia[135]. Capillary dysfunction with reduced glucose and oxygen extraction has also been hypothesized to contribute to endoneurial hypoxia[136].

Central nervous system involvement

Evidence supports the view that diabetes mellitus involves not only the peripheral nervous system but also the central nervous system (CNS)[137] (FIG. 2). This was first recognized in the 1960s when human autopsy studies of patients with advanced diabetes mellitus demonstrated spinal cord pathology (for example, spinal cord atrophy, degeneration of ganglion cells, demyelination and axonal loss). These findings were largely dismissed as being secondary to poor diabetes mellitus control and infection rather than DSPN[138]. Cerebral and spinal sensory-evoked potential deficits have also been observed in humans with DSPN and rodent models[139–141]. However, clear evidence for the involvement of the spinal cord in DSPN was obtained from MRI studies demonstrating spinal cord atrophy[142,143]. Imaging studies have also found a reduction in the primary somatosensory cortex (SSC) grey matter volume in both painful DSPN and painless DSPN[144].

In addition to spinal cord and cerebral structural changes, important functional abnormalities relating to DSPN have been identified in the brain[137]. Proton MR spectroscopy studies have demonstrated evidence of neuronal dysfunction with a reduced *N*-acetylaspartate to creatine ratio in the thalamus[145] and parietal white matter tracts[146] in patients with painless DSPN. In addition, increased thalamic vascularity[147], altered thalamocortical connectivity[148] and functional reorganization of the SSC[149] have been associated with painful DSPN. Thus, the involvement of the CNS in DSPN, hitherto considered a purely peripheral neuropathy, has opened a whole new area for further research and has great potential for the development of new therapeutic targets[137] (FIG. 2).

Mechanisms of painful DSPN

Neuropathic pain occurs as a result of persistent maladaptive structural and functional changes within the somatosensory system after peripheral nerve injury[11]. The mechanisms of neuropathic pain have largely been investigated in experimental models of mechanical nerve damage. These studies have demonstrated a gain of excitation and the facilitation of pain signals as well as a loss of inhibition in the peripheral nervous system and CNS[11,150]. However, the reasons why some individuals with DSPN develop neuropathic pain whereas others with similar levels of neuropathy are entirely asymptomatic are not completely understood[151]. Moreover, although the risk factors for DSPN are well described, there is a paucity of data regarding the risk factors for painful DSPN. Several studies[61,71,72], although not all[62], have found that an increasing severity of DSPN is associated with painful DSPN[152]. However, neurophysiological measures, molecular pathways and pathological findings do not provide a full explanation for the presence of neuropathic pain in diabetes mellitus[11,21,151]. Thus, current opinion suggests that a complex interaction of risk factors (environmental and genetic), vascular and metabolic abnormalities (glycaemic flux, the metabolic syndrome, vascular injury and/or dysfunction), and psychosocial factors lead to downstream peripheral and CNS maladaptations[20,151,152] (FIG. 4).

Peripheral mechanisms of painful DSPN

Small-fibre injury. The small fibres (thinly myelinated Aδ-fibres and unmyelinated C-fibres) that are responsible for temperature and pain perception are hypothesized to be preferentially impaired in painful DSPN. However, measurements of intra-epidermal nerve fibre

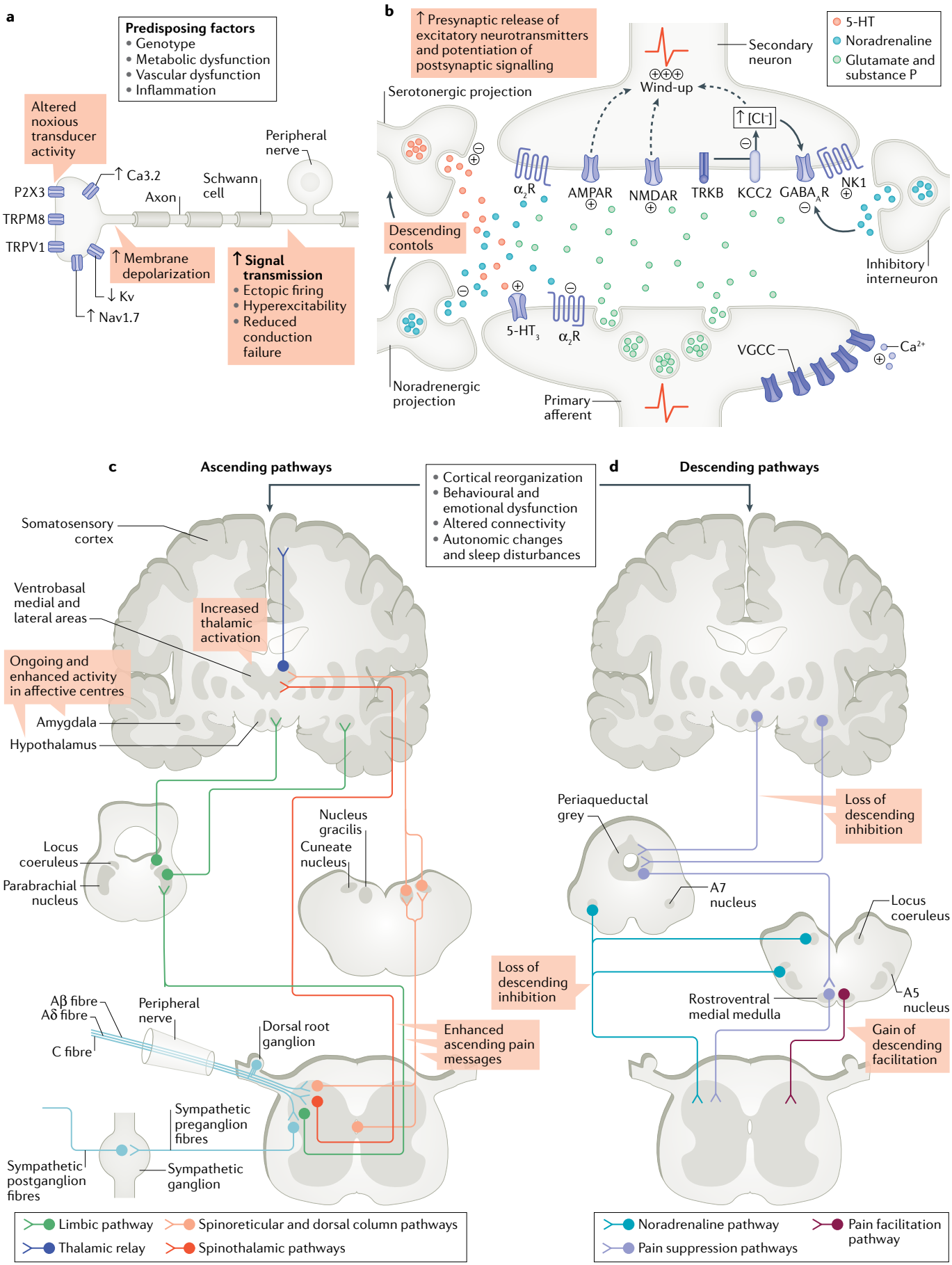
a
Predisposing factors
• Genotype
• Metabolic dysfunction
• Vascular dysfunction
• Inflammation
Altered noxious transducer activity
↑ Ca3.2
P2X3
TRPM8
TRPV1
Axon
Schwann cell
Peripheral nerve
↑ Membrane depolarization
↓ Kv
↑ Nav1.7
↑ Signal transmission
• Ectopic firing
• Hyperexcitability
• Reduced conduction failure
b
↑ Presynaptic release of excitatory neurotransmitters and potentiation of postsynaptic signalling
5-HT
Noradrenaline
Glutamate and substance P
Secondary neuron
Wind-up
Serotonergic projection
↑ [Cl-]
α2R
AMPAR
NMDAR
TRKB
KCC2
GABAAR
NK1
Descending contols
Inhibitory interneuron
5-HT3
α2R
VGCC
Ca2+
Noradrenergic projection
Primary afferent
c
Ascending pathways
• Cortical reorganization
• Behavioural and emotional dysfunction
• Altered connectivity
• Autonomic changes and sleep disturbances
Somatosensory cortex
Ventrobasal medial and lateral areas
Increased thalamic activation
Ongoing and enhanced activity in affective centres
Amygdala
Hypothalamus
Locus coeruleus
Parabrachial nucleus
Nucleus gracilis
Cuneate nucleus
Aβ fibre
Aδ fibre
C fibre
Peripheral nerve
Dorsal root ganglion
Enhanced ascending pain messages
Sympathetic preganglion fibres
Sympathetic postganglion fibres
Sympathetic ganglion
d
Descending pathways
Periaqueductal grey
Loss of descending inhibition
A7 nucleus
Locus coeruleus
Loss of descending inhibition
Rostroventral medial medulla
A5 nucleus
Gain of descending facilitation
Limbic pathway
Thalamic relay
Spinoreticular and dorsal column pathways
Spinothalamic pathways
Noradrenaline pathway
Pain suppression pathways
Pain facilitation pathway

Fig. 4 | **Mechanisms of painful DSPN.** Numerous alterations occur in the peripheral and central nervous system in painful diabetic sensorimotor peripheral neuropathy (DSPN), leading to an overall gain of facilitatory and loss of inhibitory signalling. Predisposing factors for painful DSPN might include genotype, metabolic and vascular abnormalities, and inflammation. Peripheral nerve alterations: nerve injury induces nociceptor hypersensitivity through inflammation, altered distal transducer activity (for example, TRPV1, TRPM8 and P2X3) and altered expression of ion channels (for example, sodium, potassium and calcium channels) (part **a**). Alterations in synaptic transmission: persistent nociceptive input increases pre-synaptic neurotransmitter release (for example, glutamate and substance P) and the potentiation of post-synaptic signalling to the spinal cord via enhanced AMPA and NMDA receptor activation. Substance P acts on neurokinin 1 (NK1) to add to this excitation (part **b**). Reduced spinal inhibition through GABA and the transporter potassium-chloride transporter member 5 (KCC2) aids enhanced pain messages. Reduced noradrenaline descending inhibition via α_2 adrenoceptors (α_2Rs) and increased 5-hydroxytryptamine (5-HT) descending excitation via 5-HT_3 receptors add to the dominance of excitatory transmission. Central sensitization develops through an imbalance in the facilitation and inhibitory modulation of pain signals in the spinal cord (parts **c** and **d**) and brain. Autonomic alterations and sleep disturbance as well as psychological, behavioural and emotional factors further enhance pain perception. AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Ca3.2, T-type calcium channel 3.2; GABA, γ-aminobutyric acid; Kv, potassium channel; Nav1.7, sodium ion channel 1.7; NMDAR, *N*-methyl-D-aspartate receptor; P2X3, P2X purinoceptor 3; TRPM8, transient receptor potential cation channel subfamily M member 8; TRPV1, transient receptor potential cation subfamily V member 1; VGCC, voltage-gated calcium channel. Adapted with permission from REF.[20], Elsevier, with permission from REF.[21], ADA, and from REF.[81], Springer Nature Limited.

density and basic QST have not provided conclusive evidence for their preferential involvement in painful DSPN[151]. Two large cross-sectional studies using detailed QST profiling (according to the German Research Network on Neuropathic Pain[153]) showed greater thermal insensitivity, suggestive of more advanced small-fibre dysfunction in painful compared with painless DSPN[71,72]. Small-nerve fibres might become sensitized following increased distal terminal injury and regeneration in the presence of neurotrophins[154]. An alternative explanation could be that hyperexcitable small-fibre neurons in painful DSPN might be more susceptible to bioenergetic failure, resulting in increased distal nerve fibre degeneration[10,155]. More severe corneal small-fibre damage[156–158] and increased levels of markers of degeneration (axonal swelling) and regeneration (GAP43)[159,160] have also been reported in painful DSPN compared with painless DSPN; however, these are not consistent findings[161–163]. Selection bias and the small scale of the studies might have contributed to the inconsistency.

Autonomic dysfunction and vascular alterations. Studies have demonstrated greater cardiac autonomic dysfunction in painful DSPN than in painless DSPN[164–166]; however, other studies have found no such association[167,168]. Profound abnormalities in the arteriovenous anatomy have been described on the epineurial surface in patients with acute painful neuropathy of glycaemic control (insulin neuritis)[169]. Moreover, patients with painful DSPN have increased epineurial blood flow and intravascular oxygen saturation, perhaps secondary to arteriovenous shunting due to sympathetic denervation[170]. Small studies have demonstrated that topical application of vasodilators provides pain relief in painful DSPN, which suggests a role for hypoxia and/or vascular dysfunction in the generation of neuropathic pain in DSPN[171,172].

Inflammation and the immune system. Neuronal injury promotes a neuroinflammatory response, which leads to the accumulation of immune cells and the release of inflammatory cytokines and contributes to neuronal hypersensitivity. These mechanisms might also occur in painful DSPN, facilitating ectopic neuronal activity and enhanced response to sensory stimuli in the peripheral and central nervous systems[173]. Cross-sectional studies have found inflammatory mediators, such as TNF, IL-6 and C-reactive protein in serum and macrophage expression of TNF, in association with painful DSPN[117,174,175]. Two separate studies have also demonstrated increased serum levels of soluble intracellular adhesion molecule 1, which is elevated in a number of conditions but might be indicative of increased vascular inflammation and/or endothelial dysfunction in painful DSPN[117,175].

Microglia are neuroimmune cells within the CNS. Microglia can become activated within the spinal cord following peripheral nerve injury, releasing pro-inflammatory mediators and thus enhancing central pain signals[176]. Additionally, microglia might contribute to neuropathic pain through impaired descending modulation, altering the balance between descending inhibition and excitation towards the latter[176]. Minocycline, a compound known to reduce microglial activation, has been reported to reduce neuropathic pain in Sprague–Dawley rat models of T1DM with DSPN[177].

Methylglyoxal. Methylglyoxal, a reactive dicarbonyl by-product of glycolysis, induces post-translational modifications of the VGSC Nav1.8, increasing the excitability of nociceptive neurons[178]. Despite showing promise as a biomarker of neuropathic pain, a cross-sectional study found no association between methylglyoxal and painful DSPN[168].

Ion channel dysfunction. Peripheral nociceptor terminals respond to noxious stimuli via an array of receptors (such as transient receptor potential (TRP) channel family members) and ion channels to initiate an action potential. The altered expression and function of these transducers contribute to peripheral sensitization and might play an important role in pain phenotyping. For example, individuals with abnormal TRPV1 expression in nociceptors might have preferential heat hyperalgesia and burning pain and those with TRPM8 or TRPA1 dysfunction might have cold pain or cold hypersensitivity[179].

Painful neuropathies cause alterations in ion channels[150]. The gain of function of sodium channels leads to increased neuronal excitability, signal transduction and neurotransmitter release[180]. Gene variants affecting key sodium channels (such as Nav1.7, Nav1.8 and Nav1.9) have been related to inherited and acquired painful peripheral neuropathies. Preclinical[178,181] and human genetic studies[76,77,180] in painful DSPN have shown evidence of an enhanced function of VGSC. Concurrently, there is a downregulation in the expression of components of voltage-gated potassium channels, which normally regulate neuronal excitability, repolarization and frequency of action potentials[182]. Voltage-gated calcium channels (VGCCs)

are functionally diverse and involved in both peripheral and central nociception[183]. VGCCs are present in the pre-synaptic terminal and are responsible for neurotransmitter release and the propagation of pain signals to second-order neurons[184]. Components of the sub-types of these channels are upregulated in rodent dorsal root ganglion cells displaying neuropathic pain and agents targeting these channels have been reported to provide analgesia[15,185].

Central mechanisms of painful DSPN

The barrage of neuropathic signals arriving at the dorsal horn of the spinal cord leads to central sensitization that is characterized by increased spontaneous activity, a reduction for threshold activation by peripheral stimuli, increased responses to sub-threshold stimuli and enlargement of their receptive fields[186]. *N*-methyl-D-aspartate receptors are activated, which amplifies and lengthens the responses of spinal dorsal horn neurons[21,179]. Alterations in the balance of descending modulatory mechanisms have been hypothesized to be involved in the maintenance of the chronic pain state, with a loss of inhibition and excess of facilitatory activity within the brain and spinal cord[21,150]. Dysfunction within the ventrolateral periaqueductal grey-mediated descending pain modulatory system has been reported in patients with painful DSPN[187]. A number of other centrally mediated factors can alter the pain experience, including cognitive (that is, attention, distraction, catastrophizing), contextual (that is, pain beliefs) and emotional (that is, depression and anxiety) factors[21,137,188].

The thalamus — the gateway for all sensory information reaching the brain — is responsible for the initial modulation and processing of somatosensory information prior to presentation to the cerebral cortex and might have a central role as a biomarker of neuropathic pain in diabetes mellitus[137]. In rat models of T1DM, hyperexcitable thalamic ventroposterolateral neurons have been identified in response to phasic brush, press and pinch stimuli[189]. The ventroposterolateral thalamic neurons also displayed enhanced spontaneous activity, independent of ascending afferent barrage, and enlarged receptive fields. These results suggest that thalamic neurons act as central generators or amplifiers of pain in DSPN[190]. Abnormal pain evoked by non-painful stimuli (allodynia) has been associated with an amplification of the thalamic response. An MR perfusion imaging study found increased thalamic vascularity in patients with painful DSPN in the resting state, probably reflecting increased neuronal activity[145,147]. In addition, decreased thalamocortical functional activity using resting-state functional MRI has been reported in people with painful DSPN[148].

Higher brain centres are involved in the localization of pain (such as the SSC). These areas (such as the anterior cingulate cortex and insular cortex) are also involved in the processing of behavioural, cognitive and emotional components of pain. The anterior cingulate cortex, an important brain area for emotional pain processing, has also been found to have increased blood flow in patients with painful DSPN[191]. A study has demonstrated normalization of this hyperperfusion following treatment with duloxetine[191]. Augmented BOLD (blood oxygen level-dependent signal) functional MRI responses in multiple limbic and striatal structures (anterior cingulate cortex, superior frontal gyrus, medial thalamus, anterior insular cortex, lentiform nucleus and premotor area) have also been reported in response to heat pain in patients with painful DSPN[192]. Moreover, we have reported both structural and functional alterations in the primary SSC that seem to be related to the pain phenotype in DSPN[149,193]. In addition, the analgesic response to the sodium channel inhibitor, intravenous lidocaine, in patients with painful DSPN was associated with an increased SSC volume and enhanced functional connectivity between insular and corticolimbic circuitry[193]. Further advanced imaging studies are required to elucidate the relationship between CNS alterations and the individualized pain phenotype.

Management of patients with DSPN

The holistic management of a patient with DSPN involves the treatment of symptoms (such as neuropathic pain, comorbid mood disorders, insomnia, autonomic symptoms, unsteadiness and falls), strategies aimed at the prevention of progression of DSPN (management of cardiometabolic risk factors) and addressing foot complications[194] (FIG. 5). The first point of consultation might be with an endocrinologist, a neurologist or a pain specialist. However, ideally, a multidisciplinary team approach, with the involvement of specialist nurses, podiatrists, psychologists, physical therapists, pain specialists, orthotists, orthopaedic surgeons, vascular surgeons and microbiologists (when there is bacterial infection of an ulcer), might be best placed to provide personalized and enhanced patient care.

Glycaemic control

For the treatment of DSPN, achieving glycaemic targets seems to be more efficacious in T1DM than in T2DM. For instance, the DCCT (Diabetes Control and Complications Trial) clearly demonstrated that an optimized glucose control reduces the incidence of DSPN in patients with T1DM[195]. A key strength of this study was the robust neuropathy assessment, with standardized protocols for nerve conduction studies[195]. However, the risk of DSPN was not entirely ameliorated with intensive glycaemic control in DCCT. By contrast, in a small longitudinal observational study of patients with T1DM over 24 years, achieving near-normal glycaemia prevented incident DSPN[196]. Moreover, the normalization of glycaemic control with pancreas transplantation in T1DM was reported to halt DSPN progression[197] and to reverse certain neuropathic deficits[198].

In contrast to T1DM, a Cochrane review published in 2012 found that enhanced glucose control did not reduce the incidence of DSPN in T2DM ($P=0.06$)[82]. Large trials, such as ACCORD[199], UKPDS[200] and VADT[201], did not report the slowing of DSPN progression with intensive glucose treatment. However, DSPN was not the primary outcome in these trials and inconsistent and insensitive measures of peripheral neuropathy were used. When nerve conduction studies are used, smaller trials have shown significant improvements in nerve function with

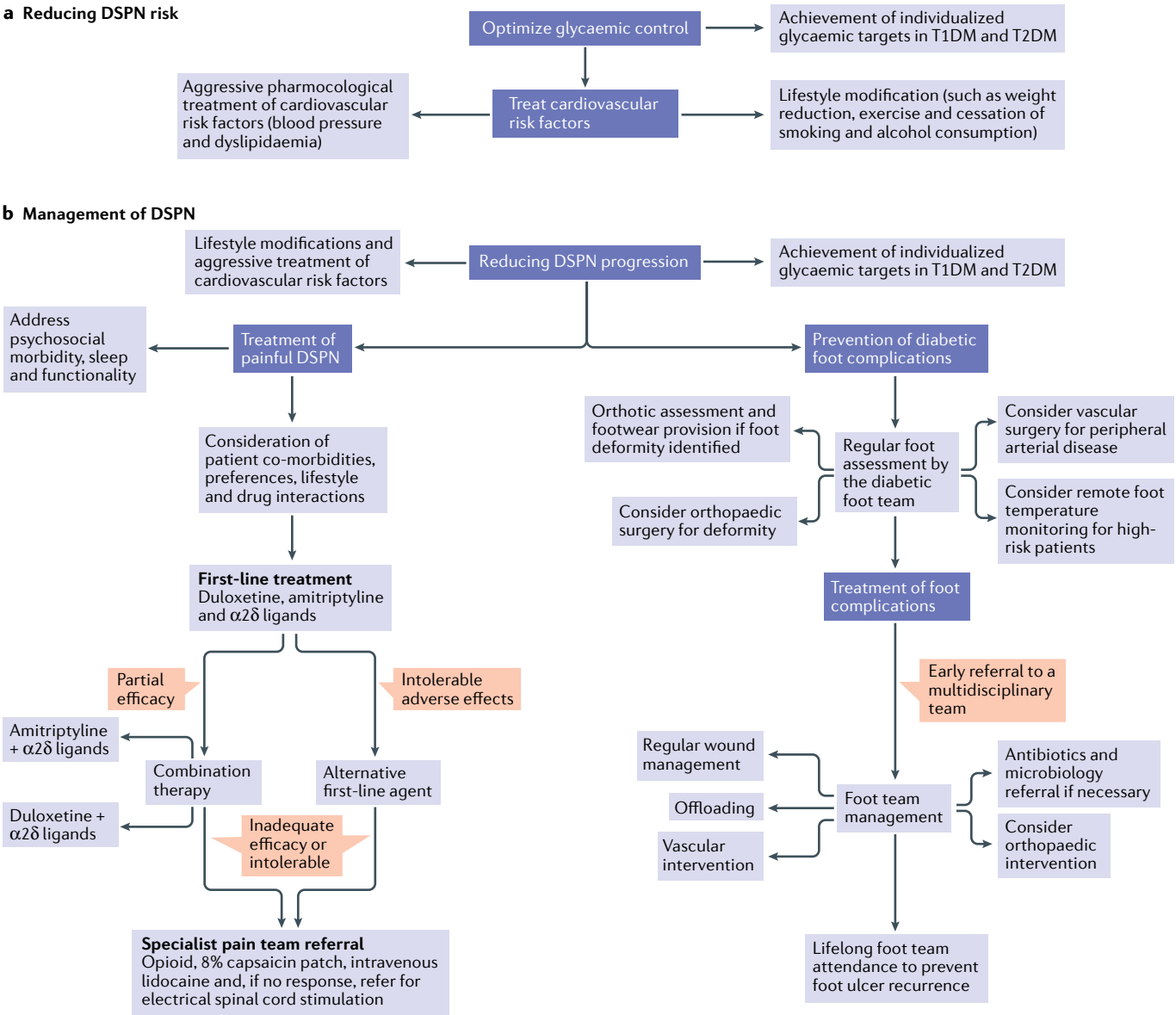

Fig. 5 | **Management of DSPN.** The prevention of diabetic sensorimotor peripheral neuropathy (DSPN) involves optimizing glycaemic control and achievement of cardiometabolic targets. A multidisciplinary approach aimed at the management of painful DSPN and the prevention (part **a**) and treatment (part **b**) of foot complications is vital. In the management of painful DSPN, combination treatment is recommended in instances of partial efficacy of first-line agents. If there is pain despite combination treatment, the use of opioids can be considered with caution. In refractory painful DSPN, consider a high-dose capsaicin (8%) patch, intravenous lidocaine infusion and electrical spinal cord stimulation. The management of diabetic foot ulcer disease includes the use of therapeutic footwear, early involvement of vascular surgeons when necessary, regular podiatry (such as callus debridement and wound dressing), treatment of infection in collaboration with microbiologists, the surgical management of foot deformities in collaboration with orthopaedic surgeons, and the use of appropriate offloading and immobilization strategies (for example, casting). The management of Charcot neuroarthropathy is based on strict immobilization in the acute presentation and surgical treatment where indicated in the chronic setting. T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

intensive glucose control[202–204]. For example, a study of patients with uncontrolled T2DM reported improvement in corneal confocal microscopy and neurophysiological parameters with intensive glucose control over 4 years[203]. In addition, the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) study demonstrated a reduced cumulative incidence of DSPN in patients who received insulin-sensitizing treatments (metformin and/or thiazolidinediones) compared with those having insulin-providing therapy (sulphonylureas, meglitinides, insulin)[205].

Interventions for multiple risk factors

The UKPDS[206], STENO-2 (REF.[207]) and ADDITION[208] studies, which involved interventions designed to lower multiple risk factors, were ineffective in reducing

the incidence of DSPN. However, the methods used to assess DSPN in these studies lacked sensitivity and reliability. Moreover, in the ADDITION study[208], only minor differences in cardiovascular risk factors were achieved between the standard and intensive treatment groups.

Cardiovascular risk factors

Lifestyle and weight management. The Look AHEAD study reported a significant improvement in questionnaire-based reports of DSPN in people with T2DM who also have obesity or overweight who were randomly assigned to receive a lifestyle intervention[209]. Other smaller studies using more sensitive measures have found lifestyle interventions to be efficacious for preventing the onset of DSPN and improving intra-epidermal nerve fibre branching (assessed with thigh skin biopsy)[210,211]. Patients who underwent supervised aerobic exercise had significant improvements in sural and peroneal motor nerve conduction as well as in incident DSPN over 4 years[210]. However, the Diabetes Prevention Program Outcomes Study found no such improvement based on a crude neuropathy assessment using the 10 g monofilament test (an assessment of light-touch perception and foot ulcer risk)[212]. Bariatric surgery might also be beneficial in reducing the risk of complications of T2DM, including DSPN; however, the evidence is currently limited[213].

Dyslipidaemia. Large population-based observational studies have shown that statin use is associated with a reduced incidence of DSPN[214,215]. In addition, a longitudinal observational follow-up study of patients with T2DM who underwent an annual Michigan Neuropathy Screening Instrument assessment found that statin or fibrate treatment reduced the risk of incident DSPN over 6 years[216]. However, only small, short randomized studies have performed nerve conduction studies, which have also shown improvements in some neurophysiological measures of DSPN with statin treatment[217,218]. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study randomly assigned patients to receive fenofibrate or matching placebo for 5 years ($n = 9{,}975$)[219]. Fenofibrate reduced the incidence of non-traumatic lower-limb amputations, particularly in patients without evidence of large-vessel disease at baseline. The reason for the benefit of fenofibrate in this study is unclear as an improvement in sensitive markers of nerve function were not reported.

Hypertension. Small preliminary studies have reported the benefit of ACE inhibitor treatment for DSPN[220,221]. The largest study compared treatment with the calcium channel blocker manidipine and the ACE inhibitor delapril, placebo, or delapril alone over 3 years. Combined calcium channel blocker and ACE inhibitor treatment or ACE inhibitor treatment alone reduced the risk of incident DSPN compared with placebo[222].

Disease-modifying treatments

Although numerous studies have shown positive results in rodent models of diabetes mellitus and phase II studies, potential disease-modifying treatments have been universally disappointing in phase III studies[14,223]. Indeed, no disease-modifying treatment is currently approved by the EMA or the FDA.

A powerful antioxidant, α-lipoic acid (also known as thioctic acid), has been investigated in several studies suggesting that the antioxidant improved neuropathic symptoms and deficits in patients with DSPN[14,224–226]. However, the evidence is largely confined to the treatment of neuropathic symptoms over 3 weeks with intravenous α-lipoic acid[227] and oral treatment over 5 weeks[225]. Longer trials have not demonstrated any improvements in neuropathic symptoms[226] or neurophysiological measures[228] in patients with DSPN.

Benfotiamine is a lipid-soluble thiamine derivative that inhibits the major metabolic pathways of hyperglycaemia-induced vascular damage (such as AGE formation, the PKC pathway, the hexosamine pathway and NF-κB activation)[229]. Despite the initial promise of an improvement in nerve conduction velocity in a small cohort of patients with DSPN[230], a larger study did not show an improvement in neuropathic symptoms in the intention-to-treat analysis[231]; however, a significant benefit in the per-protocol analysis was found[231]. A small study ($n = 67$) found that benfotiamine supplementation in patients with T1DM over 24 months had no significant effect on nerve conduction measures compared with placebo[232]. Nevertheless, the study had methodological limitations such as a short duration and inappropriate case definition; therefore, the study might be falsely negative.

C-peptide treatment has been reported to ameliorate functional and structural abnormalities of the peripheral nerves in rodent models of T1DM and DSPN[223]. Although a 6-month trial showed a promising improvement in sensory sural nerve conduction velocity in patients with DSPN treated with C-peptide[233], no such improvement was demonstrated in a 12-month trial[234].

Many studies involving aldose reductase inhibitors (ARIs) have failed to show clear efficacy and some have been complicated by notable adverse effects with ARI treatment[235]. However, the ARI epalrestat has regulatory approval for use in DSPN based on a large open-label, randomized controlled study[236]. This study showed that epalrestat prevented the deterioration of median motor nerve conduction velocity over 3 years and was associated with an improvement in neuropathic symptoms in patients with DSPN.

Other disease-modifying drugs that have had mixed or weak clinical trial data for the treatment of DSPN include recombinant human nerve growth factor[237], the PKC inhibitor ruboxistaurin[238], prostaglandin E_1 (REF.[239]) and acetyl-L-carnitine[240]. Currently, the only drugs licensed for the treatment of DSPN are α-lipoic acid, benfotiamine and actovegin (a deproteinized haemoderivative produced from calf blood[241]) as well as epalrestat in several European countries, Japan, India and China[223].

Treatment recommendations for DSPN

A clear rationale exists for intensively treating patients with T1DM to achieve near normoglycaemia to reduce the incidence and progression of DSPN[195]. This strategy

will probably also benefit patients with T2DM; however, the magnitude of DSPN improvement might be more modest than in patients with T1DM[82]. Moreover, there is the potential risk of increased mortality with intensive glucose-lowering therapy in T2DM[242]. Caution must therefore be exercised when intensifying glucose control, using individualizing targets and the newer antiglycaemic agents that are less likely to result in hypoglycaemia than older agents. Aggressive, target-driven and early treatment of cardiovascular risk factors (such as hypertension, dyslipidaemia, smoking and obesity) will be beneficial in reducing the incidence and/or severity of cardiovascular and peripheral vascular disease, for which patients with DSPN are at particularly high risk. This strategy might also be beneficial for slowing DSPN progression; however, further studies with sensitive endpoints are required for the confirmation of initial findings[204]. Lifestyle, exercise and weight management changes should be encouraged as part of a holistic approach to patients with diabetes mellitus and early evidence indicates that this approach might improve DSPN outcomes[13].

Why has the development of efficacious, pathogenetic treatments for DSPN approved by the FDA and EMA proved difficult? There is little doubt that the early trials were dogged by poor trial design, including the recruitment of patients with advanced disease and a short follow-up period[243]. Furthermore, significant improvements in signs, symptoms and quantitative vibration testing have been reported in the placebo arms because of improvements in the standards of cardiometabolic management[223,244]. Finally, great care needs to be taken to choose a sensitive and reproducible endpoint for a trial based on the pathophysiological target of the molecule being investigated. In addition, when an appropriate endpoint is identified, the assessment must be performed with rigour. For example, electrophysiology assessments of the nervous system should be performed by Board-certified neurophysiologists to account for all applicable variables[18].

Treatment of painful DSPN

Current treatments for painful DSPN are purely symptomatic and do not alter the disease process and provide a number needed to treat for 50% pain relief ranging from 4 to 10 (REF.[15]). Unfortunately, these benefits are offset by intolerable adverse effects. The most commonly recommended first-line agents for painful DSPN include α2δ ligands (gabapentin and pregabalin), serotonin–noradrenaline reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs) (FIG. 5).

Anticonvulsants. Although several anticonvulsant agents have been trialled for painful DSPN, the α2δ ligands have the most robust evidence. Both pregabalin and gabapentin are non-selective ligands for the α2δ-1 and α2δ-2 subunit of the VGCC proteins. Gabapentin at doses of ≥1,200 mg per day has demonstrated efficacy for the management of painful DSPN[15,245]. Gabapentin needs to be administered three times daily and requires gradual dose titration[17]. However, pregabalin has linear pharmacokinetics, is more potent and can be given in two daily doses. Pregabalin has been assigned a first-line status in all current guidelines[17,246]. Randomized, double-blind placebo-controlled trials have found that pregabalin is superior to placebo in the treatment of painful DSPN[247]. Pooled analyses found that pregabalin is superior to placebo at doses of 300 mg and 600 mg per day, with lower doses less likely to be efficacious[15,248]. Common adverse effects of α2δ ligands include dizziness, somnolence, euphoria, peripheral oedema and weight gain.

Tricyclic antidepressants. Although TCAs do not have a license for use in painful DSPN, they have been prescribed for several decades and indeed are included in major international guideline recommendations[15,17,249]. Amitriptyline is the most frequently prescribed agent in this drug class and is fairly inexpensive[246]. Small, randomized, double-blind, placebo-controlled studies have found that amitriptyline is superior to placebo[250,251] and comparator trials have demonstrated it is as efficacious as other agents used for painful DSPN[252,253]. However, these studies were underpowered and hence susceptible to bias[254]. The adverse effects with TCAs include postural hypotension, urinary retention, dry mouth and drowsiness. Furthermore, TCAs are contraindicated in patients with cardiac arrhythmias and should be used with caution in patients with cardiovascular disease.

Serotonin–noradrenaline reuptake inhibitors. Duloxetine is the most prescribed SNRI for painful DSPN and has regulatory approval for the treatment of neuropathic pain[15,17,249]. SNRIs relieve pain by increasing the synaptic availability of 5-hydroxytryptamine and noradrenaline in the descending pathways, which are inhibitory to pain. Duloxetine at doses of 60 mg and 120 mg per day significantly reduces the severity of neuropathic pain in patients with painful DSPN in randomized, double-blind, placebo-controlled trials[255]. The most common adverse effect is nausea, with dry mouth, dizziness, somnolence, fatigue and constipation occurring less frequently. Venlafaxine can be used as an alternative agent, although less evidence is available to support its use[256]. In addition, in a randomized controlled trial of 244 patients with painful DSPN, 7 patients on venlafaxine developed clinically significant electrocardiogram changes during treatment and venlafaxine is therefore not the preferred SNRI in patients with DSPN[257].

Combination therapy. In clinical practice, monotherapy often provides insufficient analgesia; therefore, combination therapy is frequently prescribed. However, there is little evidence to support this approach[15]. Studies have demonstrated the efficacy of combining opioids and TCAs with α2δ ligands[246,258]. The largest combination study, COMBO-DN, compared the combination of pregabalin and duloxetine at moderate doses against high-dose monotherapy and found neither approach to be statistically superior[259]. However, secondary endpoints consistently favoured standard-dose combination therapy that was well tolerated[259].

Opioids. Opioid treatments are associated with high rates of misuse, addiction potential[260] and increased mortality[261]. Increasing evidence also indicates that socioeconomic

harm occurs with the use of these agents[262]. Although there are moderate-quality randomized controlled trials confirming the efficacy of a number of weak (tramadol and tapentadol) and stronger (oxycodone) opioids in neuropathic pain[263–265], the evidence overall is limited in the context of non-cancer chronic pain[266]. Given the increasing tide of opioid misuse, particularly in North America, the initial use of non-opioid analgesics for chronic non-cancer-related pain conditions is now being closely examined[262]. When opioid agents have been prescribed, very close monitoring of the patient is advised[267].

Treatment of refractory painful DSPN

Several treatments for refractory painful DSPN might only be available at specialist centres. The high-dose capsaicin (8%) patch has been approved for use in painful DSPN by the EMA[268]. This treatment has been proposed to defunctionalize nociceptive fibres, causing the temporary reversible retraction of hypersensitive nerve fibres[154]. Its application requires the use of personal protective equipment. A single application, over 30 minutes, can provide up to 3 months of pain relief[154]. Intense pain could occur at the site of application, which might necessitate the use of a local anaesthetic cream. Another form of treatment, intravenous lidocaine (5 mg/kg infusion delivered over 1 hour), has also shown efficacy in some[269] but not all studies[270] for painful DSPN. Although a safe treatment that can provide pain relief for up to 4 weeks, its administration requires continuous cardiac monitoring[269].

Some patients with painful DSPN might not respond to any pharmaco-therapeutic agents or to combined therapies. Affected patients can be extremely disabled and, in this situation, implantable electrical spinal cord stimulation might be considered[271]. The modalities of treatment include conventional waveform, burst and high-frequency stimulation. The treatment requires an operation under local anaesthesia. Significant pain relief is found in around 60% of patients using conventional spinal cord stimulation therapy; however, this treatment should only be performed in specialist centres with appropriate expertise[272]. A prospective, multicentre, randomized controlled trial found that 79% of patients with refractory painful DSPN treated with high-frequency (10 kHz) spinal cord stimulation achieved ≥50% pain relief on a visual analogue scale, compared with 5% assigned to conventional medical management (REF.[273]).

Box 4 | **Recommendations for further research in DSPN**

- Large prospective studies need to be conducted to investigate the reliability and predictive validity of point-of-care devices (such as DPNCheck and corneal confocal microscopy) for use in the early diagnosis of diabetic sensorimotor peripheral neuropathy (DSPN) in clinical practice.
- Robust clinical trials utilizing sensitive endpoints need to be designed to investigate the benefit of cardiometabolic risk factor reductions on the progression of DSPN, particularly in patients with type 2 diabetes mellitus.
- Studies need to investigate the mechanisms that link DSPN to high cardiovascular mortality. For example, clinical trials might evaluate the effect of multifactorial interventions on cardiovascular outcomes in patients with DSPN who have previous or current foot ulceration.
- The factors that differentiate DSPN in patients with type 1 diabetes mellitus and type 2 diabetes mellitus need to be investigated.
- Appropriately designed genetic studies need to be conducted to increase our understanding of the disease mechanisms of DSPN and painful DSPN.
- The interaction between patient phenotype and peripheral and central mechanisms of DSPN should also be investigated.
- Whether combination therapy is beneficial and well tolerated in painful DSPN needs to be investigated.
- Patient stratification methods based on quantitative sensory testing, other DSPN diagnostic techniques and central nervous system imaging need to be refined to enhance the mechanism-based treatment response for painful DSPN.

Emerging treatments

Over the past decade, no new first-line agents for painful DSPN have been approved. Currently, we do not know which first-line agent nor which combination is the most clinically efficacious[246]. The OPTION-DM study (trial registration number: ISRCTN17545443) is investigating which monotherapy and combination therapy (treatment pathways) of amitriptyline, duloxetine and pregabalin are the most clinically efficacious and tolerable[274]; the results are expected in 2021.

Mirogabalin is an emerging α2δ ligand that has undergone phase II and III clinical trials and is currently approved for use in Japan[275,276]. VGSC agonists have also undergone clinical trials[277]; however, the results have been negative. Despite compelling genetic validation, drug developers are struggling to unlock the therapeutic promise of the Nav1.7 sodium channel as a pain target[278].

Low-dose combination therapy with gabapentin and trazodone showed a synergistic effect in animal models and is currently being trialled in patients with painful DSPN (CT03749642)[279]; the results are expected in 2021. PL37, a dual enkephalinase inhibitor that increases the concentration of enkephalins peripherally and hence enhances the endogenous opioidergic system[280], showed a significant analgesic effect in animal models[281]. However, similar results were not found in a phase II trial involving patients with painful DSPN; this trial was prematurely discontinued and the results have not been published (EudraCT Number: 2013-004876-37).

Antagonists of P2X receptor channels (P2X3, P2X4 and P2X7) are effective in relieving neuropathic pain in preclinical models[282]. Clinical trials are now required to determine whether this benefit translates to human DSPN. Finally, cibinetide (ARA 290), a non-erythropoietic peptide engineered from erythropoietin, improved neuropathic symptoms and corneal nerve fibre density in a phase II trial in patients with T2DM and painful DSPN[283].

Pain phenotyping and treatment response

Trials that have stratified patients according to pain characteristics have found an enhanced analgesic response depending on the pain phenotype[193,284–286]. Examples include oxcarbazepine[284] and intravenous lidocaine[193], which have shown better efficacy in patients with the irritable nociceptor phenotype[284]. Furthermore, the addition of duloxetine to pregabalin was more effective at reducing pressing and evoked pain than maximal dose duloxetine, which appeared to be more beneficial

in improving paraesthesia[285]. In addition, the presence of conditioned pain modulation predicted the efficacy of duloxetine[286]. These studies support the emerging concept of mechanism-based treatment for painful DSPN[287]. There is a case for future neuropathic pain trials to be designed using detailed patient stratification at baseline. Even if trials did not meet the primary endpoint, a subgroup analysis can be performed to see whether there is efficacy in a particular phenotype and, if that was the case, a further larger (adequately powered) trial could be performed comparing drug efficacy in that phenotype versus in other phenotypes.

Conclusions

The management of DSPN and its clinical sequelae presents a major clinical challenge. Lower-limb amputations secondary to diabetes mellitus are on the increase[5] partly as a result of the late detection of DSPN using clinical methods. The clinical management of painful DSPN is also inadequate. Although this Review has highlighted progress in our understanding of the mechanisms of DSPN both from the periphery and CNS, in order to accelerate game-changing advances in the field, a number of research questions arising from this Review will need to be addressed (BOX 4). The therapeutic landscape for diabetes mellitus has benefited from large, multicentre outcome trials driven by big pharma; however, most studies in DSPN remain single centre and small, with little impact. International collaborative studies need to be encouraged by funders and neuropathy institutions to increase critical mass in tackling key research questions.

Published online: 28 May 2021

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Acknowledgements
The authors thank M. Yorek (University of Iowa, USA) for his advice on the manuscript.

Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
S.T. has received honoraria (speaker fees) from Abbott, Astellas Pharma, AstraZeneca, Eva Pharma, Grunenthal, Hikma, Impeto Medical, Merk, Novo Nordisk and Pfizer. S.T. is on, or has been on, the Advisory Board of Angelini, Bayer, Mitsubushi Tanabe Pharma, Nervo, Trigocare International and Worwag Pharma. G.S. and D.S. declare no competing interests.

Peer review information
Nature Reviews Endocrinology thanks D. Armstrong, who co-reviewed with L. Shin; R. Malik; A. Veves; and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.