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Diabetic neuropathy: Clinical manifestations and current treatments

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Abstract

Diabetic peripheral neuropathy is a prevalent, disabling condition. The most common manifestation is a distal symmetric polyneuropathy (DSP), but many patterns of nerve injury can occur. Currently, the only effective treatments are glucose control and pain management. While glucose control dramatically decreases the development of neuropathy in those with type 1 diabetes, the effect is likely much smaller in those with type 2 diabetes. High levels of evidence support the use of certain anticonvulsants and antidepressants for pain management in diabetic peripheral neuropathy. However, the lack of disease modifying therapies for diabetic DSP makes the identification of new modifiable risk factors essential. Intriguingly, growing evidence supports an association between metabolic syndrome components, including pre-diabetes, and neuropathy. Future studies are needed to further explore this relationship with implications for new treatments for this common disease.

Introduction

Neuropathy, or damage to the nerves of the peripheral nervous system, is a debilitating yet surprisingly common and complex condition. Its prevalence is greater than 2% in the general population[1, 2] and approximately 15% in those over the age of 40[3]. By far, the most common cause of neuropathy is diabetes[4]. In fact, the prevalence of neuropathy in patients with diabetes is approximately 30%, and up to 50% will eventually develop neuropathy during the course of their disease[5]. Diabetes can damage the peripheral nervous system in a variety of ways, but the most common presentation is a distal symmetric polyneuropathy (DSP). Other patterns of injury include small fiber predominant neuropathy, radiculoplexopathy, and autonomic neuropathy, amongst others. Since DSP is the most common neuropathy subtype and is the best studied, this will be the main focus of this

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review. Currently, the only treatments available to patients with diabetic DSP are improved glucose control and pain management. Both of these topics will be covered in depth.

Given the limitations in current clinical care, it is essential to identify new modifiable risk factors for the development of neuropathy. Top candidates include metabolic syndrome components such as hypertriglyceridemia, obesity, hyperglycemia, hypertension, and dyslipidemia. Establishing whether there is a causal relationship between these components, including pre-diabetes, has the potential to lead to new disease modifying therapies.

Diabetic neuropathy: clinical manifestations

Diabetes can impact the peripheral nervous system in a multitude of ways. DSP accounts for such a large proportion of all peripheral nerve manifestations attributed to diabetes that some use the terms diabetic DSP and diabetic neuropathy interchangeably. Patients with DSP typically have numbness, tingling, pain, and/or weakness that begin in the feet and spread proximally in a length-dependent fashion (stocking and glove distribution). The symptoms are symmetric with sensory symptoms more prominent than motor involvement. Many patients with neuropathy experience a sensation of their socks being bunched up or their shoes not fitting correctly. They even have the apparent paradox of numbness and exquisite sensitivity at the same time. Interestingly, which symptom predominates varies dramatically from patient to patient.

The constellation of symptoms from DSP creates many down-stream effects that can affect patients' quality of life, both physical and mental[6]. DSP associated numbness often causes balance problems which can lead to falls. DSP is one of three main risk factors for falls in patients with diabetes, along with retinopathy and vestibular dysfunction[7]. In fact, patients with diabetic DSP are 2–3 times more likely to fall than those with diabetes and no neuropathy[7]. Additionally, patients with severe DSP are at risk for ulcerations and lower extremity amputations, with 15% developing an ulcer during the course of their disease[8]. Diabetes is the leading cause of lower extremity amputations, with a 15-fold increase in the likelihood of this life-changing complication[9]. Moreover, 80,000 lower extremity amputations are performed each year in patients with diabetes[9]. Overall, diabetic DSP can severely affect quality of life, particularly in those with pain[6].

This common, disabling disease also profoundly impacts the health care system. Costs associated with diabetic neuropathy are estimated to be between 4.6 and 13.7 billion dollars, with most of the cost attributed to those with type 2 diabetes[8]. Therefore, neuropathy is associated with one fourth of the total costs of diabetes care in the United States.

Neuropathic pain is one of the major disabling symptoms of patients with DSP. It is a difficult condition to treat and therefore causes significant patient suffering and societal burden[10]. It is estimated that diabetic neuropathic pain (DNP) develops in 10% to 20% of the diabetic population overall, and can be found in 40% to 60% with documented neuropathy[11–13]. However, these numbers are likely to be underestimates, as one study showed that approximately 12% of patients with DNP had never mentioned this condition to their doctors[11]. Like other types of neuropathic pain, DNP is characterized by burning, electric, and stabbing sensations with or without numbness. Frequently, patients develop

allodynia (painful sensations to innocuous stimuli) and hyperalgesia (increased sensitivity to painful stimuli). However, less than half are treated for pain, despite many available effective therapies[11]. Fortunately, there are multiple neuropathic pain screening instruments available to aid the clinician in identifying those who would benefit from treatment[14].

Other types of peripheral nerve injury that can occur in patients with diabetes includes small fiber predominant neuropathy, autonomic neuropathy, radiculoplexopathy (diabetic amyotrophy), radiculopathy, mononeuritis multiplex, mononeuropathy, and treatment-induced neuropathy (Figure 1). Small fiber-predominant neuropathy is an increasingly recognized pattern of involvement and typically is an early manifestation (Figure 2). In fact, patients often progress from a small fiber-predominant neuropathy to a DSP. Small fiber-predominant neuropathy can be difficult to diagnose because the examination (decreased reflexes, impaired vibration, weakness) and electrodiagnostic testing can be normal. Autonomic neuropathy (a type of small fiber neuropathy) is also common in patients with diabetes. Symptoms include gastroparesis, constipation, urinary retention, erectile dysfunction, and cardiac arrhythmias. Importantly, patients with autonomic neuropathy are at a greater than 2-fold increased risk of death[15]. Diabetic radiculoplexopathy can involve either the lumbosacral (more common) or the cervical plexus. Patients present with pain and weight loss followed by weakness in the distribution of the involved plexus. Pathology reveals evidence of ischemic injury and a microvasculitis, but whether immunosuppressive medications are effective is unclear[16, 17]. To date, only one randomized controlled trial has been completed for diabetic lumbar radiculoplexopathy and no significant effect was found on the primary outcome, although secondary outcome measures did show improvement with intravenous methylprednisolone[17]. Diabetes is also one of the few causes of non-compressive radiculopathy. Patients with diabetes can also present with mononeuritis multiplex without an underlying rheumatologic cause. Furthermore, patients are at increased risk of mononeuropathy which can be secondary to compressive or ischemic mechanisms. The most commonly involved nerves are the oculomotor and median nerves. Whether the mechanism of these four peripheral nerve manifestations (radiculoplexopathy, radiculopathy, mononeuritis multiplex, mononeuropathy) is the same is unclear. Though poor glucose control is associated with increased risk for neuropathy, the treatment of diabetes can also cause neuropathy. Treatment-induced neuropathy presents as acute pain and/or autonomic involvement, usually after the institution of insulin but can happen after any quick establishment of glucose control[18]. The pain and autonomic features can improve significantly with time, and this pattern of nerve injury underscores the fact that even quick improvements in glucose control can lead to neuropathy. Of note, there are also a substantial number of patients with diabetes that have asymptomatic neuropathy[19]. Thus, while DSP accounts for the vast majority of neuropathic manifestations in patients with diabetes, there are other important conditions for physicians to consider.

Glucose control in type 1 and type 2 diabetes

A body of research conducted over the past 20 years has added to our knowledge of glucose control as a modifiable risk factor for the development of neuropathy in patients with diabetes (Table 1). Seventeen randomized, controlled clinical trials have studied the effects of enhanced glucose control over at least a 12 month period on neuropathy[20–37]. Seven of

these studies focused on patients with type 1 diabetes, but only two of these reported on outcomes related to clinical impairment[20, 23, 26, 29, 31, 32, 34]. In 1993, the DCCT study group followed over 1400 subjects for five years and found a 60% reduction in the development of neuropathy in those receiving more frequent insulin dosing[20]. Similarly, Linn et al in 1996 followed 49 subjects for 5 years and reported an approximately 70% reduction in the development of neuropathy in those with enhanced glucose control[32]. Both of these groups revealed a large, statistically significant reduction in the development of neuropathy with tighter glucose control. Furthermore, only one of the seven studies did not show a statistically significant benefit of tighter glucose control.

In contrast to the robust results seen in subjects with type 1 diabetes, the 8 randomized, controlled trials in type 2 diabetes have produced less definitive results[21, 22, 24, 25, 28, 30, 33, 36, 37]. Only four of these studies investigated the effects of glucose control on clinical impairment secondary to neuropathy. In 2010, the ACCORD study group compared the effectiveness of a lower hemoglobin A1C goal (less than 6 compared to 7–7.9) on the Michigan Neuropathy Screening instrument[28]. In the more than 5500 subjects followed for a median of 3.7 years, they discovered a 7% reduction in the development of neuropathy, which was not statistically significant. In 2009, Duckworth et al followed 1791 military veterans for a median of 5.6 years and found a non-significant 5% reduction in the development of neuropathy[24]. Studies by Azad et al and Tovi et al followed much smaller numbers of patients and their results produced relative risks (RR) with large confidence intervals (no statistically significant differences)[22, 37]. However, three of the four studies that investigated nerve conduction studies and/or quantitative sensory testing revealed statistically significant results in favor of glucose control. One such study, performed by the UKPDS study group in 1998, is the second largest and longest randomized, controlled trial in patients with type 2 diabetes[21]. The main neuropathy outcome measure in this study was vibration threshold using a biothesiometer. This group followed 3867 subjects for 15 years and reported a RR of 0.95 (95%CI 0.76–1.18) at 3 years, 0.88 (95%CI 0.72–1.08) at 6 years, 0.84 (95%CI 0.68–1.04) at 9 years, 0.92 (95%CI 0.70–1.20) at 12 years, and 0.60 (95%CI 0.39–0.94) at 15 years (the only statistically significant result) in those receiving enhanced glucose control. Overall, these eight studies support only a modest reduction in the development of neuropathy in patients with type 2 diabetes receiving enhanced glucose control, which is in stark contrast to the substantial effect in those with type 1 diabetes. Possible explanations for this difference include the different outcome measures used, the different treatment regimens, the higher incidence of neuropathy in control subjects with type 2 diabetes, and the difference in baseline glucose control in these clinical trials. However, despite the similarities between type 1 and type 2 diabetes, these trials highlight the significant differences which exist in the disease mechanisms and complications of the two.

Pathophysiology of type 1 and type 2 diabetic neuropathy

Hyperglycemia is a major factor underlying diabetic neuropathy, but other changes also contribute. In type 2 diabetes, dyslipidemia is thought to play a major role[38]. Changes in insulin signaling are also key; in type 1 diabetes levels of both insulin and C-peptide are reduced, whereas in type 2 diabetes there is thought to be reduced neuronal insulin

sensitivity[39, 40]. Several recent reviews discuss the mechanisms of diabetic neuropathy in depth[38, 41–43]. Therefore, we will briefly outline the major mechanisms (Figure 3) and consider how the disease states in type 1 and type 2 diabetes are different, and why this may impact treatment efficacy.

Hyperglycemia

Excess intracellular glucose is processed by increased flux through one or more glucose metabolism pathways, and prolonged hyperglycemia can lead to cellular damage in several ways. First, excess glycolysis may lead to overload of the mitochondrial electron transport chain and generation of reactive oxygen species (ROS)[43]. Second, increased flux through the polyol pathway can increase cellular osmolarity, reduce NADPH levels and lead to oxidative stress[44]. Finally, increased flux through the hexosamine pathway is associated with inflammatory injury[41].

Another consequence of hyperglycemia is the generation of advanced glycation end products (AGEs)[45], via attachment of reactive carbohydrate groups to proteins, lipids or nucleic acids. This tends to impair the biological function of protein AGEs, thus impacting cellular function[46]. Extracellular AGEs also bind to the receptor for AGE (RAGE), initiating inflammatory signaling cascades, activating NADPH oxidases and generating oxidative stress[47]. Long-term inflammatory responses are also triggered, including the upregulation of RAGE and activation of NFκB[48].

Dyslipidemia

There is a high incidence of dyslipidemia in type 2 diabetic patients[49]. Dyslipidemia is linked to diabetic neuropathy[50], and several underlying mechanisms have been identified. Free fatty acids (FFAs) have been shown to directly cause injury to Schwann cells in vitro[51], but also have systemic effects such as promoting inflammatory cytokine release from adipocytes and macrophages[52]. Plasma lipoproteins, particularly low-density lipoproteins (LDLs), can be modified by oxidation (oxLDL) and/or glycation, and these modified LDLs can bind to extracellular receptors (including the oxLDL receptor LOX1[53], Toll-like receptor 4[54] and RAGE[47]), triggering signaling cascades that activate NADPH oxidase and subsequent oxidative stress[53]. Additionally, cholesterol may be oxidized to oxysterols, which have been shown to cause apoptosis in neurons[41, 55].

Impaired insulin signaling

While insulin is not involved in glucose uptake into neurons, it has been shown to have neurotrophic effects, promoting neuronal growth and survival[56, 57]. Reduction of this neurotrophic signaling due to insulin deficiency (type 1 diabetes) or insulin resistance (IR; type 2 diabetes) is thought to contribute to the pathogenesis of diabetic neuropathy[39]. In neurons, IR occurs by inhibition of the PI3K/Akt signaling pathway, similarly to IR in muscle and adipose tissues[42]. Disruption of this pathway may also lead to mitochondrial dysfunction and oxidative stress, further promoting neuropathy[39].

In type 1 diabetes, reduction in C-peptide may lead to nerve dysfunction in a number of ways, including reduction in Na/K ATPase activity, endothelial nitric oxide synthase

(eNOS) activity, and endoneurial blood flow[40]. Treatment with C-peptide may slow progression of neuropathy in type 1 diabetic patients[58].

The mechanisms outlined above lead to multiple cellular disturbances, including mitochondrial dysfunction, endoplasmic reticulum (ER) stress, DNA damage and apoptosis. Another layer of complexity is added when you consider that these processes of cell stress and/or damage occur in several different cell types within the nerves, including neurons (in axons and at nerve terminals), glial cells, and endothelial cells of the microvasculature. Furthermore, many of these changes will trigger activation and recruitment of macrophages[59], feeding back into inflammatory mechanisms of cell stress and death. Ultimately, these different forms of cellular stress cause dysfunction and/or death of the nerve, which manifests as clinical neuropathy.

As discussed above, tight glucose control can reduce neuropathy in type 1 diabetic patients but is not as efficacious in type 2 patients[20, 21]. This is likely to be related to differences in the underlying mechanisms: hyperglycemia and reduction in insulin signaling in type 1 diabetes, compared with a combination of hyperglycemia, dyslipidemia and IR in type 2 diabetes. Differences in the duration of pro-neuropathic changes prior to the onset/diagnosis of diabetes may also contribute to the differences in neuropathy progression between the two diseases. A patient does not typically develop type 2 diabetes rapidly; it occurs after many years of obesity and other aspects of the metabolic syndrome (see below). Tight glucose control will not necessarily reduce the dyslipidemia, systemic inflammation and IR, and following years of these insults it is not entirely surprising that neuropathy is difficult to halt/reverse. Although hyperglycemia contributes to the vicious cycles of oxidative stress, inflammation and cellular damage in type 2 diabetes, reducing hyperglycemia alone may not be enough to stop the cycle from continuing.

Pre-diabetes and neuropathy

Whereas the link between diabetes and neuropathy is well-established, there remains scientific uncertainty regarding the effects of pre-diabetes (impaired fasting glucose and/or impaired glucose tolerance (IGT)) on neuropathy. Two separate groups have shown that there is an increased prevalence of IGT in subjects with idiopathic neuropathy compared to literature-based controls[60, 61]. A third group identified an increased prevalence of neuropathy in patients with IGT compared with controls[62]. In addition, Smith et al followed a cohort of subjects with IGT and neuropathy that underwent an extensive diet and exercise regimen. They found that these subjects had an increase in nerve fiber density (NFD) over time, which is in stark contrast to historical controls[63]. The implication of this study is that treatment of IGT may improve neuropathy outcomes, although this study lacked a control group for comparison. In contrast, Hughes et al did not find a statistically significant association of IGT with neuropathy in a small case-control study[64]. Similarly, Dyck et al found no difference in the prevalence of neuropathy in patients with IGT compared to matched controls in a population based study in Olmsted County (abstract only)[65].

Since there are conflicting data linking pre-diabetes with neuropathy, there is a need for a comprehensive study investigating pre-diabetes to understand if it is one of the metabolic

"drivers" underlying the onset and progression of neuropathy. The answer has direct implications for potential therapies for many patients with neuropathy. Currently, one third of adult Americans meet criteria for pre-diabetes[66]. Since less than 5% have received a formal diagnosis from their providers and only a small percentage are being treated for this condition, establishing a causal relationship between pre-diabetes and neuropathy would change the clinical management of a substantial number of patients[66].

Pain management in DNP

While glucose control is the only disease modifying therapy for diabetic neuropathy, pain management is the other mainstay of treatment that can dramatically improve the quality of life of these patients. Over the last two decades, tremendous effort has been made to improve the treatment of DNP using randomized placebo controlled clinical trials. Data from these trials have provided support for the use of certain pharmacological treatments for DNP, as outlined below. Taking into consideration the efficacy of these interventions, several guidelines have been generated. The 2006 and 2010 guidelines from the European Federation of Neurological Societies task Force (EFNS) [67,68] and the 2011 guidelines from the American Academy of Neurology (AAN), the American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation[69] are the most thorough and recent guidelines on this topic. According to these guidelines, several classes of drugs are considered to be effective for the treatment of DNP (Table 2). Here we discuss and compare the EFNS and AAN guidelines (Table 3). The consensus from these guidelines provides information for the best evidence-based practice for the treatment of DNP.

Anticonvulsants

Pregabalin is classified as effective with Level A evidence by both the EFNS and AAN guidelines. This recommendation is based on three to four class I studies that all revealed superiority of pregabalin compared with placebo. Interestingly, the effect size was small in the highest quality studies. The recommended dosage for pregabalin is 300–600 mg/d.

Gabapentin is also classified as effective with Level A evidence by the EFNS, though the AAN (Level B) did not consider it to be a Level A drug based on the fact that only one class I study showed benefit and that one negative class II study has been published[70]. In contrast, the EFNS guidelines are based on a meta-analysis of 7 trials with class I evidence for a systematic review. The recommended dose is 900–3600 mg/d.

Lamotrigine is classified as ineffective or with discrepant results with Level A/B evidence by the EFNS because of one negative class I study and one class II study that showed comparable efficacy to amitryptiline[71]. Lamotrigine is also not recommended by the AAN based on two class I studies that failed to show benefit compared with placebo[72]. Similarly, both guidelines state that oxcarbazepine and lacosamide are not effective with Level A/B (EFNS) or Level B (AAN) evidence.

Sodium valproate is classified as ineffective or with discrepant results with Level A/B evidence by EFNS. In contrast, this medication is classified as effective with Level B

evidence by the AAN for doses of 500–1200 mg/d. The EFNS justified its decision to classify it as ineffective or with discrepant results because both positive studies were published from the same group[73,74] and one negative study has been published[75]. The negative study was not discussed in the AAN guideline. Of note, the two positive studies did not report a significant placebo effect or significant side effects that are usually attributed to this medication. The two guidelines disagree on whether the current evidence supports or refutes the effectiveness of sodium valproate for the treatment of DNP.

Antidepressants

Tricyclic antidepressants (TCAs) are classified as effective with Level A evidence by the EFNS based on two class I meta-analyses[76, 77]; however the EFNS guidelines do not provide a recommendation of a specific drug within the TCA class. In contrast, the AAN states that amitriptyline (25–100 mg/d) is supported by Level B evidence based on one class I and two class II studies[78,79, 80]. The AAN guidelines state that there is insufficient evidence in regards to other TCAs because only class III evidence is available for these drugs (Level U evidence).

Serotonin norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine are supported by both the EFNS (Level A) and the AAN (Level B) guidelines. The reason for the discrepancy in the level of evidence is that the EFNS describes three class I studies for duloxetine whereas the AAN classifies only one of these studies as class I. Similarly, the AAN classifies only one of the two studies of venlafaxine as class I. The recommended dosages are 75–225 mg/d for venlafaxine and 60–120 mg/d for duloxetine.

Opioids

Controlled release oxycodone is recommended by EFNS as effective with Level A evidence based on two class I studies. In contrast, the AAN recommends both controlled release oxycodone (mean 37 mg/d and up to 120 mg/day) based on three class II trials and *morphine sulfate* (up to 120 mg/d) based on one class II trial [81] as effective with Level B evidence.

Tramadol 200–400 mg/d and 37.5 mg + acetaminophen were listed by the EFNS as Level A effective treatments based on two class I studies. In contrast, only tramadol 210 mg/d was recommended by the AAN as effective with Level B evidence for DNP (two class II studies).

Other medications

Dextromethorphan (400 mg/d) is classified as effective with Level B evidence in both EFNS and AAN guidelines based on one class I and one class II study.

Topical capsaicin treatment (0.075% QID) is supported with Level B evidence in the AAN guidelines based on one class I [82] and one class II study [83]. However, EFNS classified capsaicin as Level A/B for inefficacy or discrepant results based on a systematic review of 5 class I–II studies.

Isosorbide dinitrate spray is backed by Level B evidence in the AAN guideline based on one class I trial [84]. Similarly, the EFNS cited the same study but also reported a study that used

glyceryl trinitrate spray (class I) and determined treatment with nitrate derivatives is supported with Level A evidence based on these two studies[85].

Nicotine derivative *ABT-594* is listed by the EFNS as effective with Level A evidence based on one class I study[86]. This treatment is not discussed in the AAN guidelines.

Botulinum toxin and *levodopa* are classified as effective with Level B evidence by the EFNS based on one class II study for each medication; however, neither is discussed in the AAN guidelines.

The *lidocaine patch* is classified as effective with Level C evidence by the AAN based on two class III studies, but it was not discussed in the EFNS guidelines.

Overall, these two guidelines are in close agreement for the vast majority of medications evaluated. However, the data for sodium valproate and capsaicin cream is conflicting with one guideline providing evidence for and one revealing evidence against their use. The more subtle differences in Levels of evidence are likely due to the fact that the AAN guidelines required a completion rate of greater than 80%, which was not required by the EFNS. Therefore, many trials were downgraded from class I to class II because of this stringent criteria with a resulting effect that only pregabalin was shown to have Level A evidence in the AAN guidelines. Of note, with increasing knowledge of the proper conduct and reporting of clinical trials through the years, there is likely a bias in favor of newer medications. Furthermore, the levels of evidence do not take into account the number needed to treat or the number needed to harm. Rather, the levels of evidence are based on the number of high quality studies that show benefit. Unfortunately, few studies compare medications head to head or evaluate for effect on quality of life. Future studies are needed to further clarify the role of these medications in the treatment of DNP.

Treatment algorithm

Several review articles recommended treatment algorithms for DNP based on their efficacy and safety (Figure 4). We reviewed algorithms from Jensen et al.[87] and EFNS[68] for treating DNP and Dworkin et al for treating neuropathic pain[88, 89]. Importantly, there is no evidence to support one treatment algorithm versus another.

1st line treatment

All three algorithms recommend gabapentin, pregabalin, TCAs, venlafaxine, and duloxetine as first line medications. Which agent to choose is largely determined by co-morbidities of the patient and side effect profiles of the medications. This is especially important in treating DNP because none of the drugs were designed specifically for neuropathic pain and therefore they each have other indications such as the treatment of seizures and depression. Dworkin et al also recommends topical lidocaine for those with localized neuropathic pain and in those with concern for central nervous system side effects. All three sources recommend titrating a first line medication to a maximum tolerated dose before switching to a second first line medication or combination therapy. Only once all these options fail is a

second line agent recommended. All of these medications are supported by Level A evidence in the EFNS guidelines and by Level A or B evidence in the AAN guidelines.

2nd line

All three algorithms also support opioid analgesics and tramadol as second line medications. While these medications are also backed by Level A evidence in the EFNS and Level B evidence in the AAN guidelines, concern exists over their long term use given their addiction potential, side effect profile, and waning effectiveness over time.

None of the recommendations incorporate cost into the decision, but this is also an important consideration for not only the patients, but also the health system. TCAs are the most affordable of the first line agents. Gabapentin and venlafaxine are cheaper than pregabalin and duloxetine, respectively.

Metabolic syndrome: implications for future treatments

Currently, glucose control and pain management are the backbones of treatment for diabetic neuropathy. However, glucose control is not the sole answer as patients with adequate glucose control continue to develop neuropathy or their neuropathy worsens over time. Furthermore, pain management is not a disease modifying therapy. Therefore, discovery of modifiable risk factors for neuropathy is essential, with metabolic syndrome (MetS) components representing one possibility. Over the last 10 years, there has been an increased interest in the possible role of MetS in the development of neuropathy. In 2001, Isomaa et al compared 85 subjects with MetS and type 2 diabetes to subjects without MetS controlled for age, gender, glycemic control, and duration of diabetes[90]. They found that subjects with MetS had a higher prevalence of neuropathy, but that in multiple logistic regression models, MetS and its components were not associated with neuropathy. Later, Costa et al and the Metascreen investigators used cross-sectional designs to independently show that MetS was associated with neuropathy in subjects with diabetes[91, 92]. In 2007, Cull et al utilized the UKPDS cohort of 5102 subjects with type 2 diabetes followed for 10.3 years to assess for the association of MetS with neuropathy by using four different definitions of MetS[93]. They found that MetS was associated with a combined macrovascular endpoint, but not with a combined microvascular endpoint. Recently in 2008, Smith et al compared subjects with idiopathic neuropathy and normoglycemia to those with IGT and discovered that each group had the same prevalence of the separate components of the MetS[94]. This result suggests that the other components of the MetS besides IGT may have a role in the development of neuropathy. However, these studies have almost all been carried out on subjects with diabetes, have used cross-sectional designs, and have utilized inconsistent definitions of neuropathy.

Complementing the studies investigating the role of the MetS on neuropathy, many groups evaluated the effect of the individual MetS components on neuropathy. In 1994, Straub et al conducted a cross-sectional study of 91 subjects with type 2 diabetes, and stratified them based on Body Mass Index (BMI)[95]. Those subjects with a BMI > 26.5 had a worse clinical neuropathy score than those with a lower BMI. However, this study did not account for any confounding factors to this association. In 2005, Tesfaye et al followed 1172 patients with

type 1 diabetes for a median of 7.3 years and found that BMI and smoking were independent risk factors for the development of neuropathy[96]. They also found associations with hypertension and LDL in minimally adjusted models. In the same year, De Block and colleagues performed a cross-sectional study in 592 subjects with type 1 diabetes[97]. Their study revealed no association between BMI, lipid abnormalities, triglycerides, or hypertension and neuropathy. More recently in 2009, Van Acker et al investigated 1111 subjects with diabetes in a cross-sectional design[6]. They discovered that obesity, HDL, and triglyceride levels were all independently associated with neuropathy. Moreover, Wiggins et al revealed that diabetic subjects with progressive neuropathy had higher triglyceride levels compared to non-progressors.[50] While most studies have shown an association between some MetS components and neuropathy, all of these studies have been performed in subjects with frank diabetes, most have used a cross-sectional design, and the definition of neuropathy has differed between studies. Given the conflicting results reported to date, further studies are needed to adequately define the role of MetS in the development and progression of neuropathy. There is also a need to better understand the underlying mechanisms by which MetS components cause neuropathy.

Pathophysiology of the Metabolic Syndrome on neuropathy

Our knowledge of how MetS components damage nerves is rapidly evolving. We have already outlined the involvement of dyslipidemia and IR and their contribution to neuropathy in patients with type 2 diabetes (see “Pathophysiology of type 1 and type 2 diabetic neuropathy”). Another central MetS component, visceral adiposity, may be particularly detrimental as it causes increased plasma FFAs and also induces a pro-inflammatory state by secretion of adipokines (also contributing to development of IR)[98]. Hypertension, another aspect of the MetS, may also be connected to neuropathy, though the link is less well-established. The renin-angiotensin system (RAS), which controls blood pressure, is upregulated in obesity, and may also contribute to development of type 2 diabetes (in part through promotion of IR and pro-inflammatory cytokine secretion from adipose tissue)[99]. Angiotensin-converting enzyme (ACE) inhibitors have been shown to improve diabetic neuropathy in animal studies[100, 101], but the mechanism is unclear. Microvascular dysfunction in the nerve and decreased endoneurial perfusion are also thought to contribute to neuropathy[102]. While this may be regulated by metabolic factors, upregulation of RAS might also contribute[102].

These mechanisms are likely to be linked at multiple levels. Indeed, in terms of the mechanisms linking MetS and type 2 diabetes to neuropathy, it may be more accurate to describe these pathways as a network in which hyperglycemia, IR, dyslipidemia, systemic inflammation and RAS activation all feed into a self-perpetuating cycle of oxidative stress, inflammatory signals and disruption of normal cellular function. Thus, even in the absence of overt diabetes, other aspects of the MetS may be sufficient to cause neuropathy. One of the major challenges for research scientists is to determine which aspects of this network of mechanisms can be blocked at which times to effectively limit/prevent progression of the neuropathy.

Conclusions and future directions

Diabetes can injure peripheral nerves in a variety of distributions. The most common pattern is DSP, which is characterized by numbness, tingling, pain, and/or weakness that affect the nerves in a "stocking and glove" pattern beginning in the distal extremities. DSP leads to substantial pain, morbidity, and impaired quality of life. Societal, personal, and healthcare costs associated with diabetic neuropathy are high. Unfortunately, few interventions are currently available for the remediation of non-painful symptoms, and glucose control is the only proven disease-modifying intervention for these patients. While pain is a common feature, it is often under-reported and undertreated. However, many effective therapies exist for DNP including medicines designed to treat seizures and depression. Evidence-based consensus guidelines have been created to guide the use of these pain interventions.

There are many areas of research that are yet to be fully explored in regards to diabetic neuropathy, which could lead to improved prevention and treatment of the condition. The magnitude of the effect of glucose control on neuropathy is much smaller in patients with type 2 diabetes as compared to patients with type 1 diabetes. Given this small effect size and that many patients with type 2 diabetes continue to develop neuropathy despite adequate glucose control, discovery of modifiable risk factors for neuropathy is essential. MetS components, including pre-diabetes, are potential risk factors for neuropathy, and future studies are needed to define whether they are causally related to neuropathy with direct implications for new treatments.

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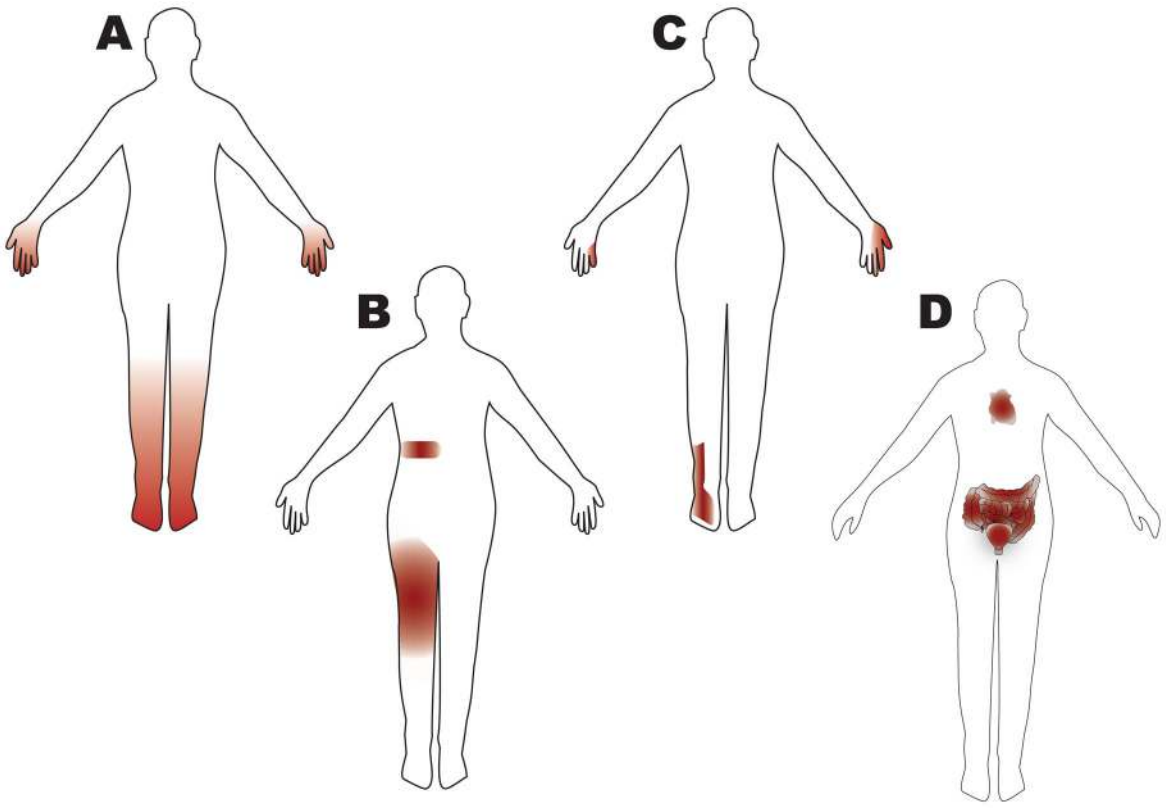
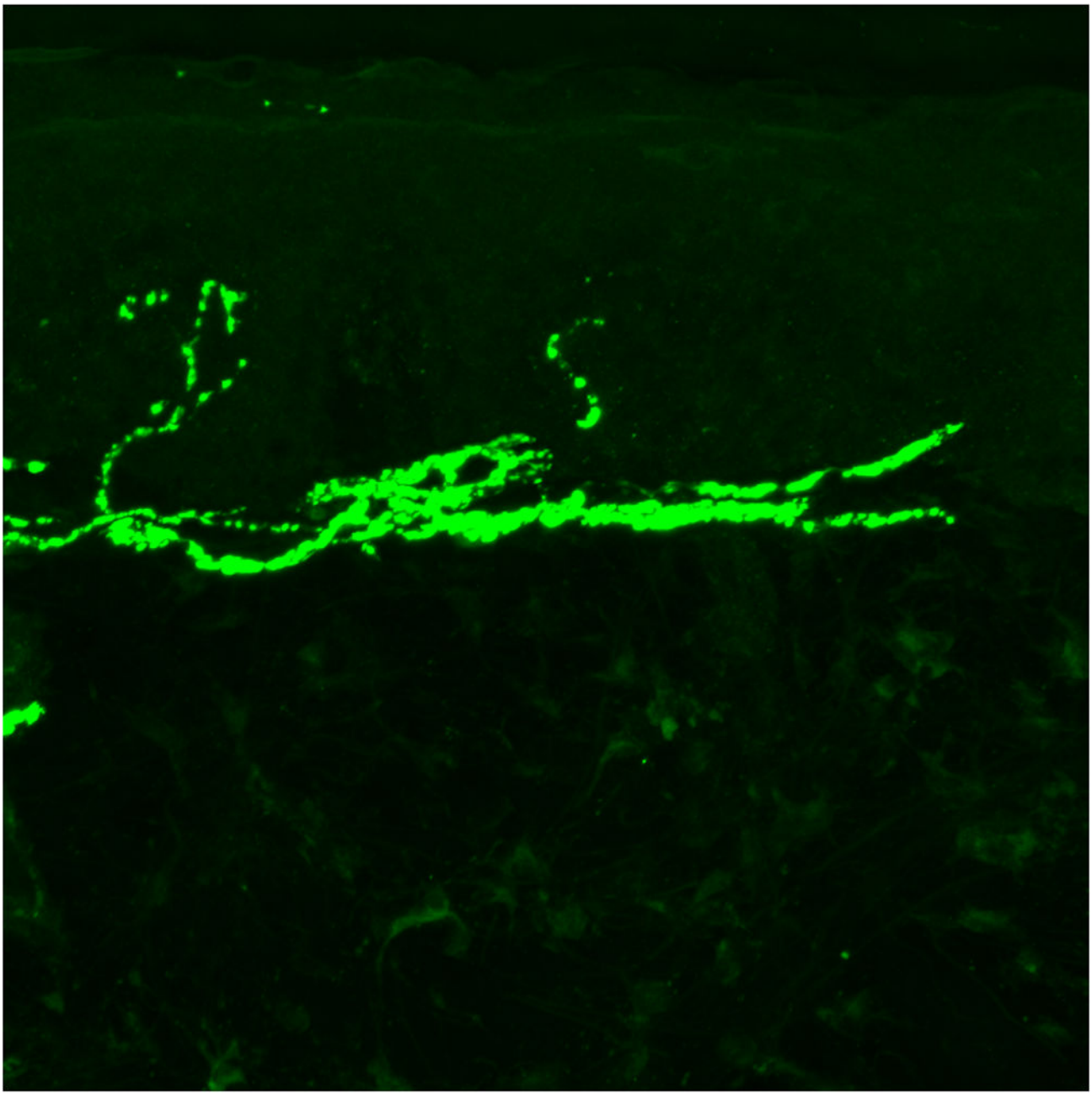
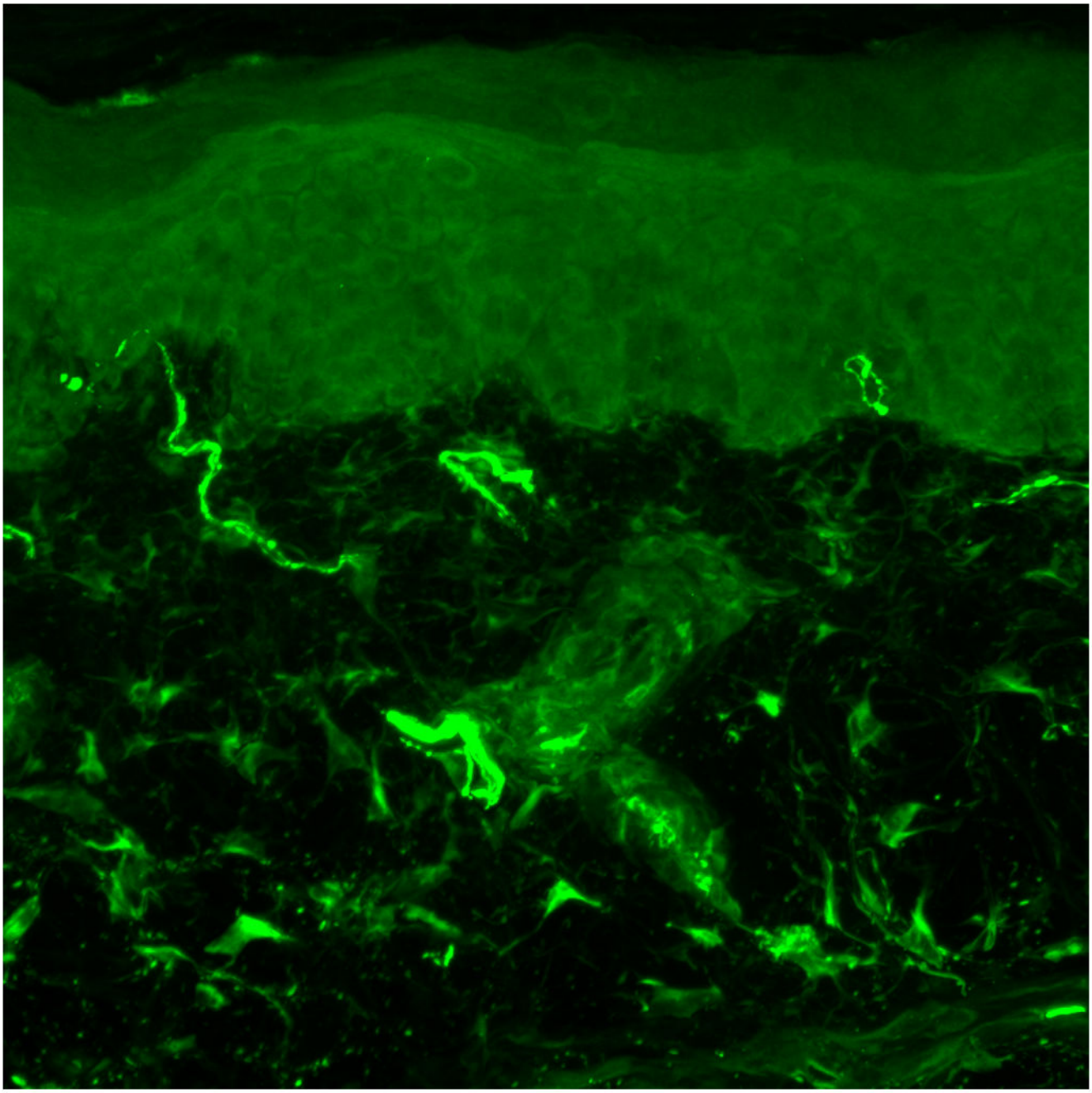


Figure 1. Patterns of nerve injury in diabetic neuropathy

Many patterns of nerve injury are observed in patients with diabetes. By far the most common neuropathy subtype is distal symmetric polyneuropathy (DSP), which is the focus of this review. However, clinicians should be aware of all potential patterns as they have implications for the evaluation and treatment of these patients. For example, patients with diabetes can develop a radiculopathy without a disc herniation or degenerative changes in the spine. This knowledge could prevent a patient from spine surgery in the case where imaging results are equivocal. Furthermore, patients with diabetes can have more than one pattern of nerve injury, and the clinician needs to ask patients about specific symptoms such as autonomic involvement, which is often overlooked. The following patterns are shown in the figure: (A) DSP, small fiber predominant neuropathy, treatment induced neuropathy (B) radiculoplexopathy, radiculopathy (C) mononeuropathy, mononeuritis multiplex (D) autonomic neuropathy, treatment induced neuropathy. Note that small fiber predominant neuropathy has the same pattern as DSP but that the neurologic examination and electrodiagnostic studies are quite different, which has the potential to lead the clinician astray. Diabetic radiculoplexopathy may be responsive to immunotherapy and in contrast to most nerve injury in patients with diabetes, usually improves with time[16, 17]. Treatment induced neuropathy is an under-recognized phenomenon[18]. Unlike the other peripheral manifestations of diabetes, this condition is caused by overaggressive control of glucose levels.





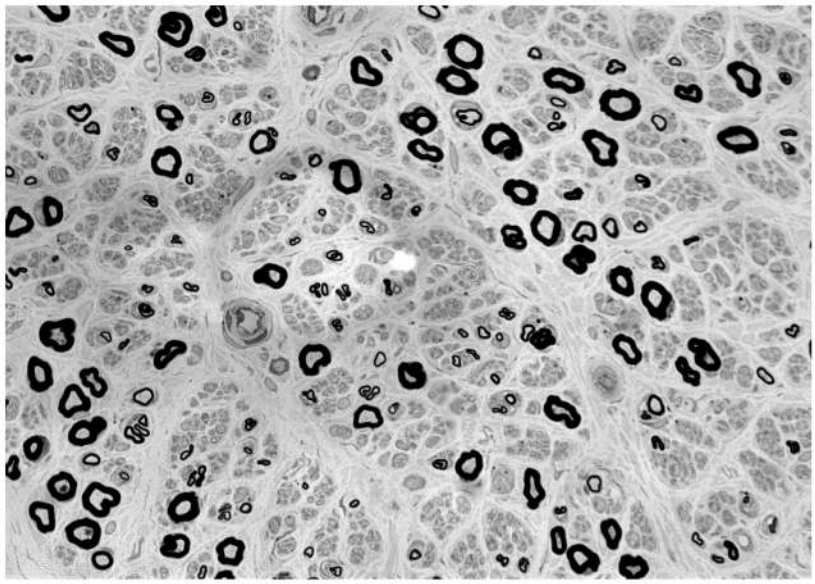


Figure 2. Small fiber predominant neuropathy on skin biopsy

(A) Skin biopsy evaluating intra-epidermal nerve fiber density (stained with protein gene product 9.5, 50 micrometer sections) from a 41 year old male without neuropathy. Two nerves are seen crossing the dermal-epidermal junction. (B) Skin biopsy evaluating intra-epidermal nerve fiber density from a 50 year old male with diabetic neuropathy. No nerves are seen crossing the dermal-epidermal junction. (C) Sural nerve biopsy from a 44 year old male with diabetic neuropathy (40X magnification). Biopsy reveals axonal loss of small and large diameter nerves.

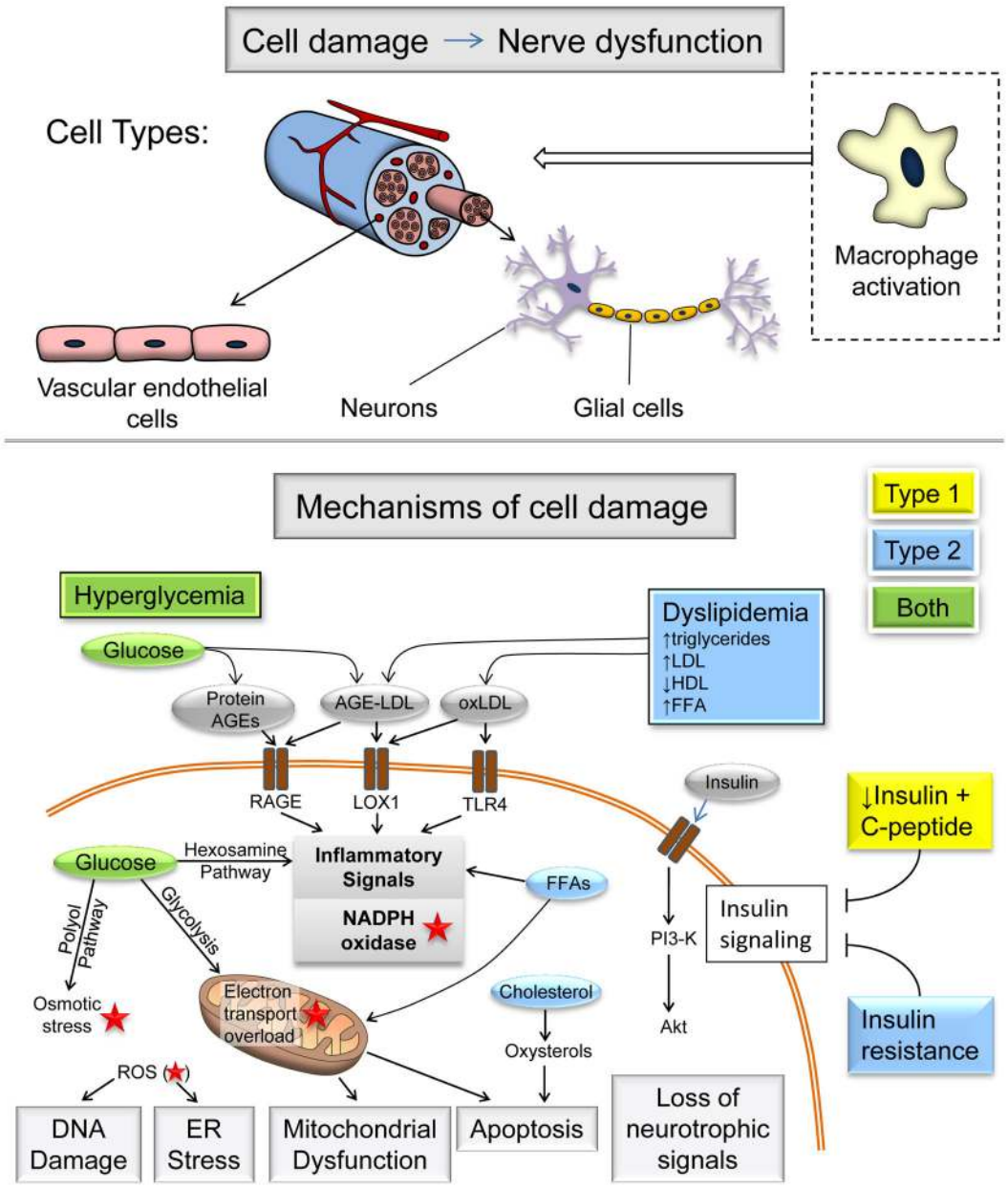


Figure 3. Mechanisms of diabetic neuropathy

Factors linked to type 1 diabetes (yellow), type 2 diabetes (blue) and both (green) cause DNA damage, ER stress, mitochondrial dysfunction, apoptosis and loss of neurotrophic signaling. This cell damage can occur in neurons, glial cells and vascular endothelial cells, as well as triggering macrophage activation, all of which can lead to nerve dysfunction and neuropathy. The relative importance of the pathways in this network will vary with cell type, disease profile and time. Abbreviations: AGE, advanced glycation end-products; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FFA, free fatty acids; ROS, reactive oxygen species (red star); ER, endoplasmic reticulum; PI3K, phosphatidylinositol 3-kinase.

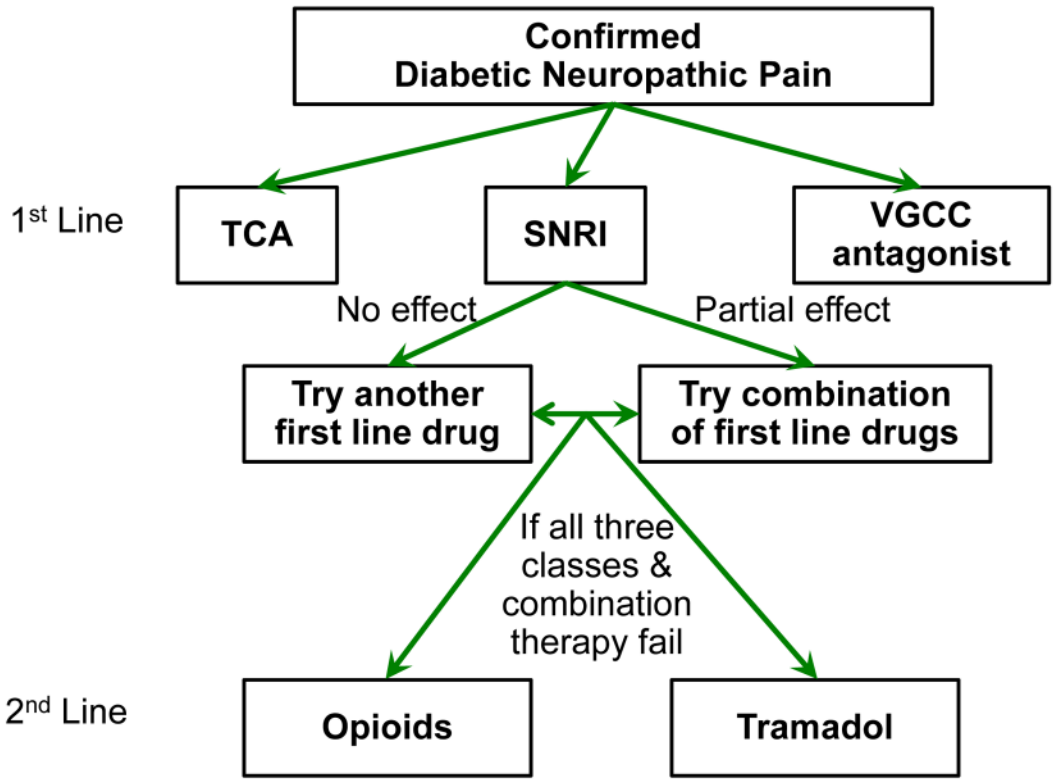


Figure 4. Algorithm for the treatment of diabetic painful neuropathy

First and seconds line treatments for diabetic painful neuropathy.

Table 1

Clinical trials investigating the role of enhanced glucose control on neuropathy

Investigator	Trial Size	Length of study	Clinical outcome	Other outcomes	Enhanced glycemic control superior?
Type 1 diabetes					
Holman 1983	74	2 years	No	QST	Yes
Lauritzen 1985	30	2 years	No	QST	No
Dahl-Jorgensen 1986	45	2 years	No	NCS	Yes
Jakobsen 1988	24	2 years	No	QST	Yes
DCCT 1993	1,441	5 years	Yes	NCS	Yes
Reichard 1993	102	7.5 years	No	NCS, QST	Yes
Linn 1996	49	5 years	Yes	None	Yes
Type 2 diabetes					
Kawamori 1991	50	4 years	No	NCS	Yes
UKPDS 1998	3,867	10 years	No	QST	Yes
Tovi 1998	38	1 year	Yes	None	No
Azad 1999	153	2 years	Yes	None	No
Shichiri 2000	110	8 years	No	NCS, QST	Yes
Gaede 2003	160	8 years	No	QST	No
Duckworth 2009	1,791	5.6 years	Yes	None	No
ACCORD 2010	10,251	3.7 years	Yes	None	No

Table 2

Published class I and class II evidence of pharmacological treatment for DNP

Drugs	Trial size	Dosage	Study design	Result	NNT	EFNS	AAN
Pregabalin	146	300 mg	Parallel, 8 weeks	Pregabalin > placebo[103]	3.9	I	I
	338	75, 300, 600 mg	Parallel, 5 weeks	Pregabalin (300, 600 mg) > placebo[104]	300 mg: 3.6 600 mg: 3.3	I	I
	246	150, 600 mg	Parallel, 6 weeks	Pregabalin (600 mg) > placebo[105]	600 mg: 4.2	I	I
	338	Fixed or Flexible: 150 – 600 mg	Parallel, 12 weeks	Fixed and flexible > placebo[106]	3.6		II
	167	600 mg	Parallel, 13 weeks	Pregabalin (600 mg) > placebo[107]		I	I
	396	150, 300, 600 mg	Parallel, 12 weeks	Pregabalin (600 mg) > placebo[108]	600 mg: 6.3		
Gabapentin	165	< 3600 mg	Parallel, 8 weeks	Gabapentin > placebo[109]	4	I	I
	40	900 mg	Crossover, 2×6 weeks	Gabapentin = placebo[70]			II
Lamotrigine	59	< 400 mg	Parallel, 8 weeks	Lamotrigine > placebo[72]	4	I	II
	360	200, 300, 400 mg	Parallel, 19 weeks	Lamotrigine = placebo[71]		I	I
	53	200 mg vs amitriptyline 75 mg	Parallel, 6 weeks	Lamotrigine = amitriptyline[110]		II	
Valproate	52	600–>1200 mg	Parallel, 4 weeks	Valproate > placebo[73]		II	II
	39	500 mg	Parallel, 16 weeks	Valproate > placebo[74]		II	II
	31	1500 mg	Parallel, 4 weeks	Valproate = placebo[75]		I	
Amitriptyline	29	≤150mg	Crossover, 2×6 weeks	Amitriptyline > placebo[78]	2.1		II
	24	25–75 mg	Crossover, 2×6 weeks	Amitriptyline > placebo[111]			II
	19	75 mg	3-phase, crossover amitriptyline and maprotiline	Amitriptyline > Maprotiline > placebo[80]			I
Desipramine	20	Average 201 mg	Crossover, 2×6 weeks	Desipramine > placebo[112]	2.2		II
Venlafaxine ER	244	150–225 mg	Parallel, 6 weeks	Venlafaxine > placebo[113]	4.5	I	I
	60	75–150 mg	Parallel, 8 weeks	Venlafaxine > placebo[114]		II	
Venlafaxine + gabapentin	11 and 42		Parallel, 2×8 weeks	Venlafaxine+gabapentin > placebo in gabapentin unresponsive patients[115]			II and III
Duloxetine	457	20, 60, 120 mg	Parallel, 12 weeks	Duloxetine (60mg, 120 mg) > placebo[116]	60 mg: 4.3 120 mg: 3.8	I	II

Drugs	Trial size	Dosage	Study design	Result	NNT	EFNS	AAN
	348	60 mg, 120 mg	Parallel, 12 weeks	Duloxetine (60mg, 120 mg) > placebo[117]	60 mg: 11 120 mg: 5	I	I
	334	60 mg, 120 mg	Parallel, 12 weeks	Duloxetine (60mg, 120 mg) > placebo[118]	60 mg: 6.3 120 mg: 3.8	I	II
Oxycodone CR	159	10–100 mg	Parallel, 6 weeks	Oxycodone > placebo[119]	N/A	I	II
	338	10–80 mg with gabapentin (100–3600 mg)	Parallel, 12 weeks	Oxycodone + gabapentin > placebo + gabapentin[120]		I	I
Morphine sulfate	57	120 morphine, 60 mg morphine +2400 mg gabapentin, 3600 mg gabapentin	Crossover, 4×4 weeks	Morphine + gabapentin>morphine>gabapentin>placebo[81]		I	II
Tramadol	127	100–400 mg (mean 210 mg)	Parallel, 6 weeks	Tramadol > placebo[121]	3.1		II
	45	200–400 mg	Crossover, 2×6 weeks	Tramadol > placebo[122]	4.3		II
	311	37.5 mg + 325 mg acetaminophen	Parallel, 8 weeks	Tramadol/APAP > placebo[123]		I	
Dextromethorphan	19	400 mg	Crossover, 2×9 weeks	Dextromethorphan > placebo[124]	3.2	I	I
	14	Mean 381 mg	Crossover, 2×6 weeks	Dextromethorphan > placebo[125]	4	I	II
Capsaicin 0.075%	252	0.075% qid	Parallel, 8 weeks	Capsaicin > placebo[126]	NA		
	22	0.075% qid	Parallel, 8 weeks	Capsaicin > placebo[82]			I
Isosorbide dinitrate	22	30 mg	Crossover, 2×4 weeks	Isosorbide dinitrate > placebo[84]			I
Glyceryl trinitrate	48		Crossover, 2×4 weeks	Glyceryl trinitrate> placebo[85]		II	
ABT-594	266	150, 225, 300 mg bid	Parallel, 7 weeks	ABT-594>placebo[86]		I	
Botulinum toxin	18	Fifty units of subtype A in 1.2 mL 0.9% saline intradermally into each foot, each injection 4 U subtype A	Crossover, 12×12 weeks	Botulinum toxin > placebo[127]		II	
Levodopa	25	100 mg levodopa plus benserazide 25 mg tid	Parallel, 28 days	Levodopa + benserazide > placebo[128]		II	

DNP = Diabetic neuropathic pain

Table 3

Comparison of the EFNS and AAN guidelines

Drug	EFNS[67]	AAN [69]
Pregabalin (300–600 mg/d)	A	A
Gabapentin	A	B
Lamotrigine	A/B ineffective/discrepant	B against
Oxcarbazepine	A/B ineffective/discrepant	B against
Lacosamide	A/B ineffective/discrepant	B against
Sodium Valproate	A/B ineffective/discrepant	B
TCA	A	B (amitriptyline)
SNRI	A	B (venlafaxine, Duloxetine)
Opioids	A (oxycodone)	B (morphine sulfate, oxycodone)
Tramadol	A	B
Dextromethorphan	B	B
Topical capsaicin	A/B ineffective/discrepant	B
Isosorbide dinitrite spray	A	B
ABT-594	A	
Botulinum toxin	B	
Levodopa	B	
Lidocaine patch		C

EFNS = European Federation of Neurological Societies task Force, AAN = American Academy of Neurology

A=Established as effective, B=Probably effective, C=Possibly effective