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Pheripheral Neuropathy in Diabetis

Dr. Sushma Jadhav[1], Dr. Devyani Londhe[2]

[1,2]M. B. B. S, DNB (Medicine)

ABSTRCT

The global epidemic of prediabetes and diabetes has led to a corresponding epidemic of complications of these disorders. The most prevalent complication is neuropathy, of which distal symmetric polyneuropathy (for the purpose of this Primer, referred to as diabetic neuropathy) is very common. Diabetic neuropathy is a loss of sensory function beginning distally in the lower extremities that is also characterized by pain and substantial morbidity. Over time, at least 50% of individuals with diabetes develop diabetic neuropathy. Glucose control effectively halts the progression of diabetic neuropathy in patients with type 1 diabetes mellitus, but the effects are more modest in those with type 2 diabetes mellitus. These findings have led to new efforts to understand the aetiology of diabetic neuropathy, along with new 2017 recommendations on approaches to prevent and treat this disorder that are specific for each type of diabetes. In parallel, new guidelines for the treatment of painful diabetic neuropathy using distinct classes of drugs, with an emphasis on avoiding opioid use, have been issued. Although our understanding of the complexities of diabetic neuropathy has substantially evolved over the past decade, the distinct mechanisms underlying neuropathy in type 1 and type 2 diabetes remains unknown. Future discoveries on disease pathogenesis will be crucial to successfully address all aspects of diabetic neuropathy, from prevention to treatment.

Keywords- ***Diabetes, Complications, Peripheral Neuropathy management***

INTRODUCTION

The International Diabetes Federation estimates that 425 million people worldwide have diabetes[1], making it the largest global epidemic of the 21st century[2]. 115 million people in China, 73 million in India and 30 million in the United States have diabetes[3]. These numbers are dwarfed by the number of individuals with prediabetes, which is estimated to be 388 million in China[4], 133 million in India[5] and 85 million in the United States[6]. 12% of global health expenditure, or $727 billion, is directed towards diabetes and its complications, and similar to the number of individuals with diabetes, this number continues to increase at an unsustainable rate[1].Among the complications of diabetes, a group of clinical syndromes caused by damage to the peripheral and autonomic nervous systems are by far the most prevalent. Generally referred to as different forms of neuropathy, these syndromes are caused by diffuse and focal nervous system damage and occur in up to half of all individuals with diabetes[7]. The most common form of diabetic neuropathy — distal symmetric polyneuropathy — is the focus of this Primer, and as such will be referred to as diabetic neuropathy throughout. Distal symmetric polyneuropathy manifests with a ‘stocking and glove’ distribution, whereby the hands and lower limbs are commonly affected. Other diffuse neuropathies secondary to diabetes can occur (FIG. 1) and include the constellation of autonomic neuropathies, such as cardiac autonomic neuropathy, gastrointestinal dysmotility and diabetic cystopathy and impotence (BOX 1). Focal neuropathies, although less common, include dysfunction of individual peripheral nerves leading to isolated mononeuropathies, or less commonly to nerve roots leading to radiculopathy or polyradiculopathy (FIG. 1).

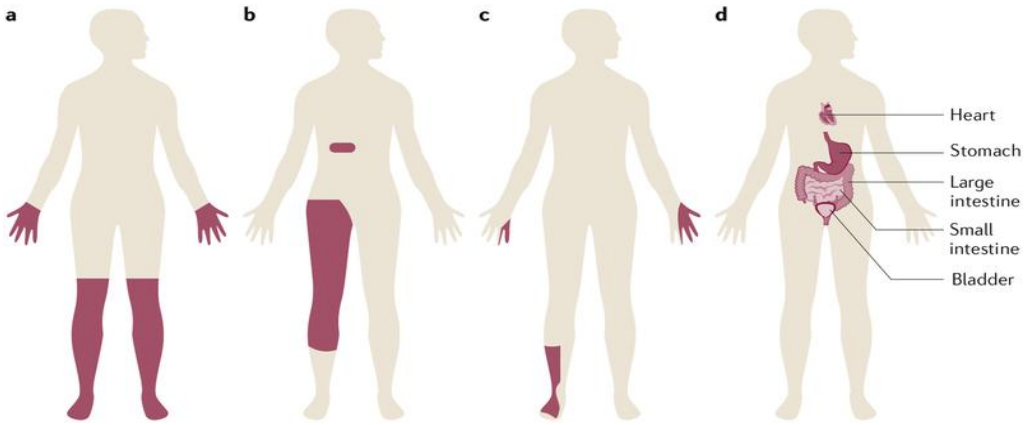


Fig. 1 |. Patterns of nerve injury in diabetic neuropathy.

Several different patterns of neuropathy can present in individuals with diabetes. Of these, the most common is distal symmetric polyneuropathy (DSP). Examples of patterns of neuropathy are DSP, small-fibre-predominant neuropathy or treatment-induced neuropathy (part **a**); radiculoplexopathy or radiculopathy (part **b**); mononeuropathy (part **c**); and autonomic neuropathy or treatment-induced neuropathy (part **d**). Small-fibre-predominant neuropathy has the same distribution as DSP, although the neurological examination and results from nerve conduction velocity studies are different. Diabetic radiculoplexopathy or radiculopathy can respond to immunotherapy and usually improves with time, unlike other types of nerve injury in individuals with diabetes. Treatment-induced neuropathy is under-recognized, is caused by overaggressive glycaemic control and can present in multiple forms (parts **a** and **d**). Adapted by permission from BMJ Publishing Group Limited. *BMJ* Peltier, A., Goutman, S. A. & Callaghan, B. C. **348**, (2014.

Diabetic Autonomic Neuropathy.
Diabetic autonomic neuropathy encompasses a group of disorders caused by impairment of the sympathetic and parasympathetic nervous system. Cardiac autonomic neuropathy (CAN) can present as generalized weakness, light-headedness or frank syncope accompanied by orthostatic tachycardia or bradycardia and exercise intolerance. Symptoms of gastrointestinal autonomic dysfunction (also known as gastroparesis) include nausea, bloating, early satiety with poor appetite, postprandial vomiting and brittle diabetes (that is, hard-to-control diabetes). Oesophageal dysfunction can also occur with dysphagia (difficulty swallowing) for solid foods and heartburn secondary to acid reflux. Urogenital autonomic neuropathy presents as bladder dysfunction (also known as diabetic cystopathy) that can range from urinary retention with hesitancy to urinary incontinence with urgency. Sexual dysfunction is another common manifestation of urogenital autonomic neuropathy. In men, sexual dysfunction manifests as impotence, decreased libido and abnormal ejaculation, whereas in women, sexual dysfunction presents as pain during intercourse, poor lubrication and reduced libido. Sudomotor autonomic dysfunction presents as dry skin (anhydrosis) with gustatory sweating.

Treatment of diabetic autonomic neuropathy depends on the specific subtype. Optimization of glucose control early in the course of type 1 diabetes mellitus (T1DM) is recommended to prevent or delay CAN, whereas targeting all metabolic risk factors is the recommendation for type 2 diabetes mellitus (T2DM). Volume repletion, physical activity, low-dose fludrocortisone or midodrine and compression stockings are among treatment options for CAN in patients with T1DM or T2DM. Excluding other causes of gastrointestinal autonomic dysfunction, particularly opioids or glucagon-like peptide 1 receptor agonists as well as gastric obstruction, is essential before instituting a short-term course of metoclopramide for gastroparesis. Urogenital autonomic neuropathy is a diagnosis of exclusion, with multiple medications, low hormone levels and infections being the main three differential diagnoses to consider before attributing dysfunction to diabetes. Pharmacological treatment of male erectile dysfunction includes phosphodiesterase type 5 inhibitors. The topical antimuscarinic drug glycopyrrolate can be used for the treatment of gustatory sweating, whereas daily moisturizing lotions provide relief for dry skin. A thorough review of diabetic autonomic neuropathy along with detailed treatment guidelines[9] can provide the reader with a more in-depth discussion of the topic.

This Primer reviews the current knowledge on the epidemiology and pathogenesis of diabetic neuropathy and the optimal approaches for diagnosis and screening. Treatment approaches are outlined and are personalized for patients with different types of diabetes and for those with and without associated pain. We close with a call to action. The global epidemic of diabetes and its most common complication, neuropathy, requires a public health mandate to address modifiable risk factors with growing urgency. Without successful intervention, it is estimated that of the expected 9.7 billion individuals living in 2050, one-third will have diabetes and half of those will have neuropathy[8]. The cost to the individual in terms of both physical and mental function, and to society in terms of productivity, is staggering.

MATERIALS AND METHODS

Epidemology-
Diabetic neuropathy is a highly prevalent condition that substantially affects patients by increasing falls, causing pain and reducing quality of life (QOL)[9]. The annual costs of diabetic neuropathy and its complications are more than $10 billion in the United States[10]. Several studies have assessed the prevalence and/or incidence of neuropathy, although the definition of neuropathy used is different in each study.

Two population-based studies using door-to-door screening reported prevalence estimates of 1%–4% for neuropathy, with 40–55% of these cases secondary to diabetes[11,12]. Similarly, in another study[13], the cause of neuropathy was attributed to diabetes in over half of cases after diagnostic work-up by a neurologist. In the Netherlands, the incidence of neuropathy increases dramatically with age[14], from <50 cases per 100,000 person-years in those <50 years of age to ~300 per 100,000 person-years in those >75 years of age, with diabetes accounting for 32% of all cases.

Risk factors

The duration of diabetes and haemoglobin A_{1c} (HbA_{1c}) levels (a measurement of glycated haemoglobin as a surrogate for average daily glucose levels) are major predictors of diabetic neuropathy[22]. These two predictors commonly associate with other metabolic factors that are correlated with diabetic neuropathy, particularly in T2DM, such as insulin resistance and hypertension. Obesity is common in patients with neuropathy in population-based studies in multiple countries, including the United States, Denmark, China and the Netherlands. Independent of HbA_{1c} levels, the number of metabolic syndrome components, such as hypertriglyceridaemia, hypertension, abdominal obesity and low high-density lipoprotein (HDL) levels, is consistently associated with diabetic neuropathy in patients with T2DM and in selected T1DM cohorts. Other independent risk factors for the development of diabetic neuropathy include smoking, alcohol abuse, increased height and older age.

Mechanisms/pathophysiology

Diabetic neuropathy is a unique neurodegenerative disorder of the peripheral nervous system that preferentially targets sensory axons, autonomic axons and later, to a lesser extent, motor axons. How diabetes mellitus targets sensory neurons remains debated. Progressive diabetic neuropathy involves retraction and 'dying back' of terminal sensory axons in the periphery, with relative preservation of the perikarya (cell bodies). Its 'stocking and glove' pattern of involvement reflects damage to the longest sensory axons first with, for example, loss of distal leg epidermal axons preceding loss in more proximal limbs; for this reason, diabetic neuropathy is considered a length-dependent neuropathy.

Substantial experimental evidence supports the notion that the entire neuron, from the perikaryon to the terminal, is targeted by diabetes. However, whether damage first targets peripheral axons and their associated Schwann cells or the neuron perikarya that reside in the dorsal root ganglia (DRG) and act to support the axons are debated (FIG. 2).

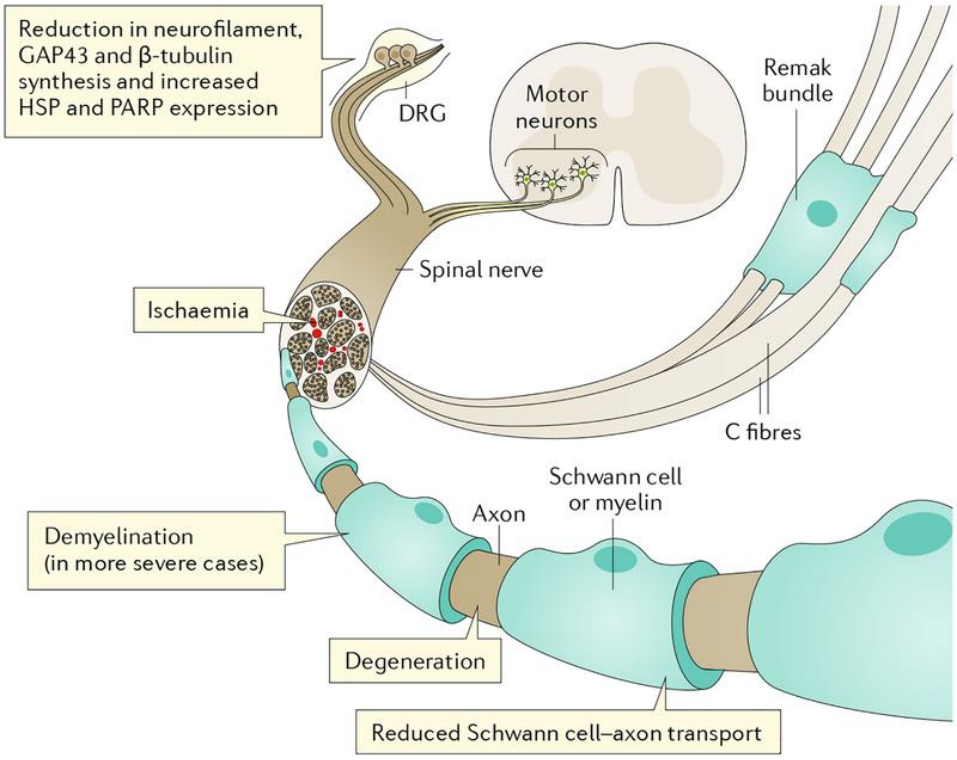


Fig. 2 |. The peripheral nervous system and alterations in diabetic neuropathy.

Hyperglycaemia and hyperlipidaemia

How the peripheral nervous system uses substrates for energy, especially in diabetes, is necessary to understand the pathogenesis of diabetic neuropathy. In Schwann cells, DRG neurons and axons, both glucose and fatty acids produce NADH and $FADH_2$ via glycolysis and the tricarboxylic acid cycle (glucose) and β-oxidation (fatty acids). When long-chain fatty acids are transported into Schwann cells to undergo β-oxidation, each β-oxidation cycle forms one molecule of acetyl-CoA, which is transported to the tricarboxylic acid cycle for NADH and $FADH_2$ formation. However, during substrate overload, such as in diabetes, the transport system becomes saturated, and acetyl-CoA molecules are converted to acylcarnitines. The accumulation of acylcarnitines is toxic to both Schwann cells and DRG neurons, adding to the ongoing nervous system injury in diabetic neuropathy. Accumulated acylcarnitines are released from

Schwann cells and can induce axonal degeneration, which has been proposed to involve mitochondrial dysfunction and a maladaptive integrated stress response in Schwann cells.

Increased glucose levels leads to glucose metabolism via the polyol and hexosamine pathways, resulting in increased ROS and inflammation, respectively, largely owing to mitochondrial injury, which contributes to ongoing nervous system dysfunction. Increased glucose levels lead to the glycation of numerous structural and functional proteins to produce advanced glycation end-products (AGEs). AGEs result in altered or loss of protein function and interact with AGE-specific receptor (RAGE) to modify gene expression and intracellular signalling and promote the release of pro-inflammatory molecules and free radicals. In parallel, the excessive free fatty acids catabolized by β-oxidation in response to hyperlipidaemia can injure the peripheral nervous system, particularly Schwann cells' through ROS generation and systemic and local inflammation via macrophage activation with subsequent cytokine and chemokine production (FIG. 3).

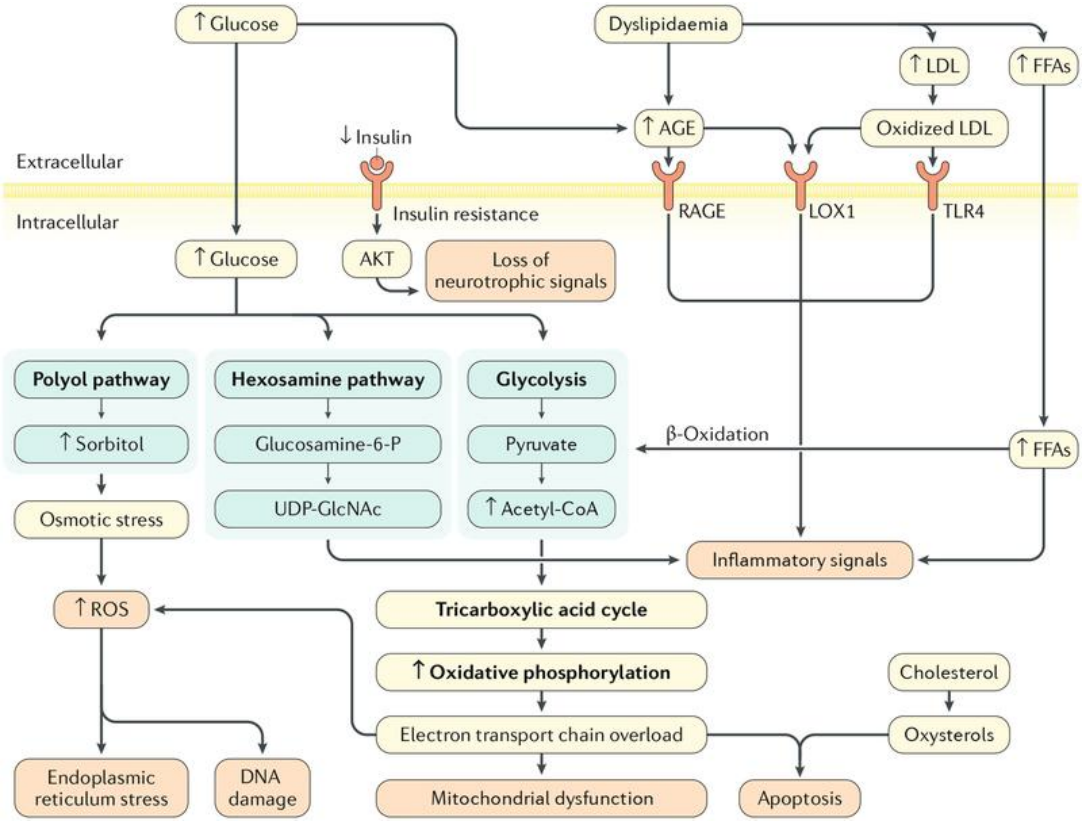


Fig. 3 |. Diabetic Neuropathy Pathogenesis.

Hyperglycaemia and dyslipidaemia, together with altered insulin signalling, lead to several pathological alterations in neurons, glia and vascular cells that can lead to nerve dysfunction and ultimately, neuropathy, including DNA damage, endoplasmic reticulum stress, mitochondrial dysfunction, neurodegeneration and loss of neurotrophic signalling, and can trigger macrophage activation. The importance of these pathways in the development of neuropathy varies with cell type, disease profile and time, as distinct cell types are more or less susceptible to injury depending on the metabolic impairments. AGE, advanced glycation end-product; FFAs, free fatty acids; Glucosamine-6-P, glucosamine 6-phosphate; LDL, low-density lipoprotein; LOX1, oxidized LDL receptor 1; RAGE, AGE-specific receptor; ROS, reactive oxygen species; TLR4, Toll-like receptor 4; UDP-GlcNAc, uridine diphosphate N-acetylglucosamine.

Microvascular contributions

Although many studies show no change in blood flow associated with the development of diabetic neuropathy, deficiencies in the blood supply to peripheral nerves is considered a possible additional pathological mechanism of diabetic neuropathy . Microcirculatory dysfunction is strongly associated with peripheral nerve dysfunction, and a cycle of poor microcirculation leading to additional nerve damage has been proposed. Increases in endoneuria capillary density are present in patients with diabetes compared with healthy individuals, suggesting that capillary density may respond to diabetes-induced nerve ischaemia[78]. Blood vessels develop thickening of their basement membrane that correlates with nerve damage in patients

Impaired insulin signalling
As structural similarities between NGF and insulin were first recognized, evidence of direct neuronal actions of insulin have emerged. Initial work demonstrated that insulin acts as a growth factor for cultured adult sensory neurons, leading to increasing neurite outgrowth. Subsequent studies demonstrated the expression of insulin receptors by sensory neurons in DRGs and axons, particularly at nodes of Ranvier , and the reversal of features of experimental diabetic neuropathy with intrathecally or intranasally delivered insulin independent of glucose levels.

Hyperexcitability of sensory neurons.
Injured sensory neurons, such as in diabetic neuropathy, develop hyperexcitability and can generate action potentials in the absence of a stimulus (spontaneous activity) and develop an altered stimulus–response function

Dysfunction within the CNS.
In diabetic neuropathy, enhanced input from spontaneously active nociceptors increases synaptic transmission within the spinal cord, further amplifying nociceptive signalling in a process termed central sensitization. This process occurs as a consequence of spatial and temporal summation of nociceptive inputs, such that neurons in the spinal cord dorsal horn have an enhanced response to the same nociceptive input. In animal models of diabetic neuropathy, spinal neurons have hyperexcitability to peripheral stimuli, which is associated with altered shape (increased length and spine head diameter), increased density and redistribution of dendritic spines. Changes in glial cells are also apparent in diabetic neuropathy. Microglia (the resident immune cells of the CNS) transform to a pro-inflammatory phenotype in diabetic neuropathy, although the mechanism by which this occurs is currently unknown. These cells can release factors, such as brain-derived neurotrophic factor (BDNF), that amplify nociceptive synaptic signalling within the spinal cord and contribute to mechanical pain-related hypersensitivity in animal models of painful diabetic neuropathy. The role of astrocytes is less clear, as some studies demonstrated activation of astrocytes in models of painful diabetic neuropathy whereas others have not[1]

Diagnosis
Diabetic neuropathy is the presence of symptoms and/or signs of peripheral nerve dysfunction in patients with diabetes after other aetiologies have been excluded[9]. Typically, the presence of more symptoms or signs of nerve dysfunction confers higher certainty about the diagnosis[9], although abnormalities in lower-limb NCV and sensory and motor nerve amplitudes assessed in nerve conduction studies (NCS) provide even further evidence. For the vast majority of patients, the diagnosis of diabetic neuropathy is based solely on the history and examination and no additional testing is needed[9,]. Objective confirmatory testing is most commonly used in the research setting or as part of the diagnostic work-up of patients with atypical clinical presentations.

The symptoms of diabetic neuropathy are numbness, tingling, pain and weakness and unsteadiness, starting distally (at the toes) and spreading proximally and then to the upper limb digits when the lower-limb symptoms reach the knees. Patients often have predominantly small-fibre neuropathy early in the course of diabetic neuropathy or when diagnosed with prediabetes, and have distal painful symptoms of burning, lancinating, freezing pain that are greater at rest. Large-fibre injury usually occurs later in the disease course, but this is not always the case.

Clinical findings of diabetic neuropathy are a loss of sensation to pinprick, temperature (mostly cold), vibration and proprioception in a ‘stocking and glove’ distribution. These sensory modalities are tested initially by the application of the sensory stimulus to a region where normal responses are expected, such as the forehead. Following this, the stimulus is applied to the great toe and then moved proximally up the limb to the level where the sensation is felt to be normal. Pinprick sensation is tested using a sharp object, such as a safety pin, that is discarded after each patient, whereas temperature is tested using a cool material, such as a metallic object. Vibration is tested by application of a vibrating tuning fork to the bony prominence at the dorsum of the great toe and then determining when the vibration stops, and proprioception is examined by small movements of the distal interphalangeal joint of the great toe. Pinprick and temperature sensations are mediated via small nerve fibres, whereas vibration sensation and proprioception are mediated by large nerve fibres.

Loss of ankle reflexes occurs early in diabetic neuropathy; thus, initial examination should include reflex testing. Later, weakness of small foot muscles and dorsiflexors is observed. Although many patients notice symptomatic weakness, major weakness on examination is only observed in later stages of advanced diabetic neuropathy. Early neurological dysfunction in the upper limbs should raise suspicion of a mononeuropathy or an alternative diagnosis.

The symptoms and clinical signs of diabetic neuropathy can be combined in scales, such as in the Toronto Clinical Neuropathy Score, the modified Toronto Clinical Neuropathy Score or the Michigan Diabetic Neuropathy Score, which have defined cut-off values for the presence of neuropathy. Other scales include signs only or a combination of signs and ancillary tests.

Screening

Screening for diabetic neuropathy using a recommended evidence-based screening algorithm is advised for all patients with diabetes[9]. Current position statements from the American Diabetes Association (ADA) and guidelines from the Canadian Diabetes Association recommend screening for diabetic neuropathy at diagnosis and annually for patients with T2DM and 5 years after diagnosis and then annually for patients with T1DM[9,].

Prevention

The consistent feature between T1DM and T2DM is hyperglycaemia; therefore, treatment of hyperglycaemia logically would be the best preventive treatment for diabetic neuropathy. However, although enhanced glycaemic control effectively reduced the incidence of diabetic neuropathy in patients with T1DM, the effect was much smaller, or in some studies absent, in patients with T2DM in one Cochrane systematic review. Indeed, the difference in patients with T2DM did not reach statistical significance in either the meta-analysis or in individual studies. The T1DM meta-analysis was dominated primarily by the Diabetes Control and Complications Trial (DCCT), which accounted for 1,186 of the 1,228 patients in the meta-analysis[16] and demonstrated an annualized risk difference of −1.84 (95% CI −2.56 to −1.11) in favour of enhanced glycaemic control. The T2DM meta-analysis was dominated primarily by the ACCORD and VADT studies, which accounted for 6,568 of the 6,669 patients in the meta-analysis and reported an annualized risk difference of −0.58 (95% CI −1.17 to 0.01) in favour of enhanced glucose control, although this value did not reach statistical significance. Since the publication of this systematic review, another study reported no difference in the prevalence of diabetic neuropathy in patients with screen-detected T2DM who received routine care compared with those who received intensive treatment (encompassing goal-directed glycaemia and cholesterol and blood-pressure management). Importantly, the two groups had little to no differences in glycaemic and other metabolic measurements. Taken together, current data indicate that enhanced glucose control has a large effect on the prevention of diabetic neuropathy in patients with T1DM, whereas the effect in T2DM is much less, although it is likely still important.

Management

The current approaches to management of diabetic neuropathy focus on improving glycaemic control (mainly in patients with T1DM), lifestyle modifications (mainly in patients with T2DM) and management of neuropathic pain. The optimal therapeutic approach for patients with T2DM includes lifestyle interventions, specifically diet and exercise, coupled with optimal lipid and blood pressure control. Glycaemic control with a HbA_{1c} goal of <6 increases mortality in patients with T2D and has little effect on diabetic neuropathy, therefore it is not recommended as standard of care. Rather, good glycaemic control as part of a more holistic, personalized approach to the treatment of T2DM is the optimal choice. Many therapeutic interventions have failed; however, several promising therapies are in ongoing clinical trials.

Improved Glycaemic Control

As previously mentioned, improved glycaemic control plays a role in preventing the onset and progression of diabetic neuropathy in patients with T1DM. The landmark trial with the most robust data supporting this is the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC); although diabetic neuropathy was uncommon at the start of DCCT/EDIC, intensive glucose control significantly delayed its development and progression over time[16], and similar improvements in neuropathy outcomes with intensive insulin treatment were reported by two other smaller European cohorts.

As previously discussed, large meta-analyses have demonstrated little to no effect of glucose control on diabetic neuropathy in patients with T2DM. However, some studies support the idea that glucose control remains important. For example, a relatively small trial of Japanese patients with early T2DM and diabetic neuropathy demonstrated improvement in several measures of diabetic neuropathy, including NCS, with intensive insulin treatment Most recently, data from two cohorts with uncontrolled T2DM and neuropathy at baseline demonstrated improvement in several measures of large-fibre and small-fibre neuropathy with improvement in HbA_{1c} to near-normal levels after 2 years. In addition, because factors other than hyperglycaemia, including metabolic factors such as dyslipidaemia or other components of the metabolic syndrome, insulin resistance and chronic inflammation, are involved in the pathophysiology of diabetic neuropathy, particularly in patients with T2DM, specific classes of glucose-lowering agents that target these factors are emerging as potentially effective in delaying progression of neuropathy[17].

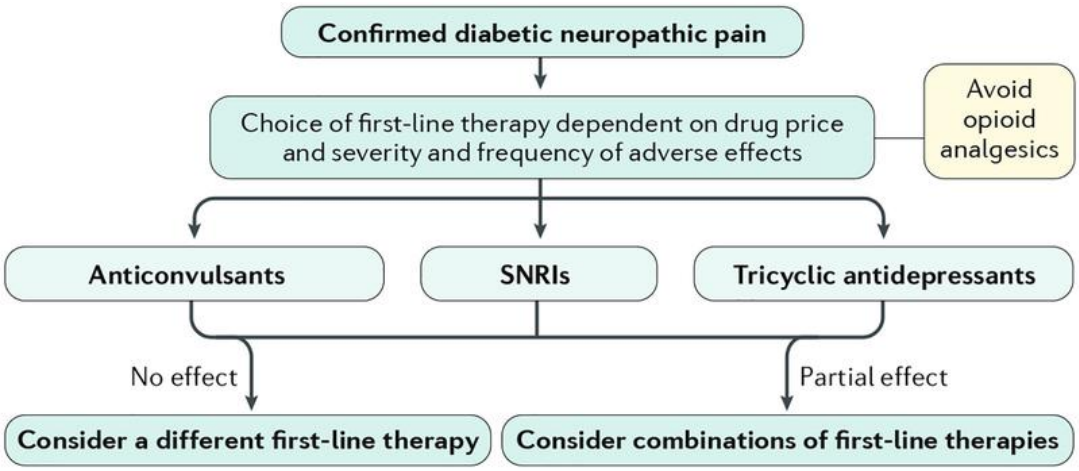
Diet and lifestyle interventions

Three uncontrolled studies and one small randomized study have shown the potential for exercise to improve neuropathy outcomes in patients with established neuropathy. One study evaluated the effect of a lifestyle intervention consisting of individualized diet and exercise for 12 months in 32 patients with neuropathy caused by impaired glucose tolerance. Although the BMI of participants decreased by only an average of 1.1 kg m^{-2}, IENFD levels in the proximal thigh significantly increased by 1.4 fibres mm^{-1} and significantly correlated with decreased neuropathic pain, indicating that the IENFD increase is likely clinically relevant to patients.A second study evaluated the benefit of 4 months of a lifestyle intervention of 30–90 min of supervised exercise twice weekly, with the addition of home exercise, in 36

patients with diabetes and/or metabolic syndrome. Dietary counselling was provided only twice during this study, and the BMI decreased by an average of only 0.11 kg m^{-2}. Following the exercise intervention, the cutaneous nerve regenerative capacity (measured by IENFD) increased from 0.051 to 0.072 fibres mm^{-1} per day (P = 0.002), and, notably, those with improvements in more components of the metabolic syndrome had a greater increase in cutaneous nerve regenerative capacity (P < 0.012)

The third study demonstrated improved intraepidermal nerve fibre branching at the proximal thigh after 10 weeks of aerobic and strengthening exercise (0.11 branch nodes per fibre; P = 0.008), despite no change in BMI, in 17 patients with diabetic neuropathy. Furthermore, neuropathic symptoms, including pain, were significantly reduced. IENFD at the proximal thigh also improved, although this result did not meet statistical significance (1.68 fibres mm^{-1}; P = 0.09). Finally, a small randomized trial that included a mixture of patients with T1DM and T2DM demonstrated improvements in both groups in some NCS parameters and vibration perception thresholds after 4 years of an aerobic exercise regimen BMI changed little over the study duration, and IENFD was not measured. Limitations of this study include the lack of designated primary and secondary outcomes, no blinded outcome assessments, inclusion of individuals with T1DM and T2DM, unequal randomization of the study population and no patient-oriented outcomes.These studies show the promise of exercise regimens to improve IENFD without significant weight loss, but importantly only one study included a control group. Overall, promising data for exercise to prevent and/or improve diabetic neuropathy exist, but well-designed future studies are needed to firmly establish this as an effective intervention.

Treatment of painful diabetic neuropathy



First-line and second-line treatments for painful diabetic neuropathy include several drug classes, such as anticonvulsants (gabapentin or pregabalin), serotonin and noradrenaline reuptake inhibitors (SNRIs; duloxetine or venlafaxine) and tricyclic antidepressants (amitriptyline, nortriptyline, desipramine or imipramine). Opioids should be avoided owing to their serious adverse effects and association with addiction.

Quality of life

As diabetes is a chronic condition that requires lifelong medications, monitoring and adherence to dietary advice, the majority of patients experience issues with their physical and mental well-being. ‘Diabetes distress’ is a term used to describe the hidden emotional burden of diabetes QOL further decreases if the patient with diabetes develops diabetic complications or comorbidities, such as retinopathy, nephropathy and neuropathy. The development of neuropathic foot ulcers can lead to substantial reductions in QOL owing to the prolonged immobilization required to heal the ulcers.

DISCUSSION

Our understanding of diabetic neuropathy continues to advance, although at a rate slower than needed to meet the impending health-care crisis. Preclinical and large, well-conducted clinical trials have changed our practice parameters and have led to a more personalized approach to the treatment of diabetic neuropathy.

Advances in our understanding of the clinical presentation and optimal therapeutic management of diabetic neuropathy form the foundation for the current paradigm shift in the preclinical research space. Previously, preclinical studies focused on cell culture and animal models of glucose metabolism alone, and between 1980 and the present, findings from these studies were translated into 70 clinical trials, with a focus on ten different aldose reductase inhibitors, all of which failed. Although the knowledge gap in the field remains large as the previous nerve-centric focus on glucose

alone did not move the field forward, the future is promising. Preclinical research is moving towards understanding global whole-nerve metabolism, nutrient overload and the sharing of energy between Schwann cells and axons in T1DM and T2DM. Progress is being made as fundamental questions are being asked by basic scientists, such as whether there is metabolic reprogramming of the peripheral nervous system during diabetes, the separate and combined roles of excessive glucose and lipids on nerve bioenergetics and the role of insulin and insulin resistance in the peripheral nervous system. Additional ongoing questions include whether axoglial sharing of energy and/or transfer of toxic byproducts occur during diabetes, how metabolic perturbations of diabetes regulate mitochondrial function in both the neurons and axons and, ultimately, how our understanding of basic peripheral nervous system metabolism and bioenergetics during diabetes will translate to the changes in neuronal and axonal structure and function that define diabetic neuropathy. Understanding these aspects of global metabolism and energy use by the peripheral nervous system is our only chance of developing meaningful therapies for diabetic neuropathy.

CONCLUSION

As the pandemic of diabetes and obesity continues to escalate, effective therapies to prevent and treat diabetic neuropathy are needed now. Unfortunately, large pharmaceutical companies have reduced research and clinical trials in diabetic neuropathy owing to our lack of basic understanding of this disease. This change has occurred despite the growing burden of this disease. The societal costs of diabetic neuropathy are outnumbered only by the individual costs to each patient, including pain, inability to work, poor QOL, multiple hospitalizations for ulcers and eventual amputations. Although diabetic neuropathy is the strongest predictor of mortality in T2DM, it remains the only microvascular complication of diabetes without a specific treatment.

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