82994_Auto_Edited.docx

WORD COUNT	7501	TIME SUBMITTED	06-APR-2023 09:57AM
		PAPER ID	98411975

Issues and challenges in diabetic neuropathy management: A narrative review

Ismail CAN. Challenges in diabetic neuropathy management

Che Aishah Nazariah Ismail

INTRODUCTION

Diabetes mellitus (DM), a global public health issue, affects up to half a million people worldwide. According to the World Health Organization (WHO), there was a marked increase in the number of individuals suffering from DM from 108 million in 1980 to as high as 422 million in 2014[1]. In the United States, the Center for Disease Control and Prevention reported that 37.3 million people, or 11.3% of the whole United States population are suffering from DM[2]. Diabetic neuropathy (DN) is a common complication of DM that encompasses various patterns of neuropathy as categorised by the location of nerve damage. A recent cross-sectional study among 473 type-2 DM patients from the United Kingdom between 2015 and 2020 demonstrated that the prevalence of diabetic peripheral neuropathy (DPN) was 26.6%, whereby more than half were male patients (52.3%). In terms of the DPN severity, 17.3%, 8.2%, and 1.1% of the patients suffered from mild, moderate, and severe DPN respectively[3]. These statistics showed a huge increase in DN among the DM patient population. Such a worrying trend warrants urgent attention to slowing the DN progression among affected individuals.

Generally, DN can be asymptomatic and only manifests when any disability arises. This disorder affects sensory nerves and it may progress from mild numbness to dysaesthesia, pain, and allodynia eventually. Furthermore, it commonly begins in the feet and lower limbs before spreading proximally[4]. Apart from that, DN may also interrupt motor functions, leading to weakness, atrophy, gait abnormality, and loss of

coordination. As a result of the difficulties in performing daily routines, many patients experience a poor quality of life (QOL). DN is also classified as a "length-dependent" neuropathy as it starts at the distal nerve endings of the longest nerve in the lower limbs and extends proximally[5]. In addition, DN can vary in its clinical manifestations. It is categorised either as "painful DN" that manifests as positive symptoms and gain of function (*e.g.*, pain, allodynia, and hyperalgesia) or "painless or insensate DN" that appears as negative symptoms and loss of functions (*e.g.*, numbness and dysaesthesia). Painless DN is a result of the predominant loss of small and large nerve fibres[6] starting at the distal nerve of the limbs before it progresses to the proximal ends in a "glove and stocking" distribution[7]. Despite massive research aimed at identifying the key culprits of DN, its underlying mechanisms remain complicated and unclear[8,9]. Several reviews of DN highlighted the shift in the management towards molecular-oriented approaches. However, the molecular mechanism leading to the progression of DN and its complications remains poorly understood. Consequently, the prevalence of DN continues to escalate and there is a very minimal enhancement in the management of DN. In this review, we aimed to highlight current issues and challenges in the management of DN, especially from the perspective of molecular mechanisms that lead to its progression with the hope of providing the future direction in the management of DN.

PATHOPHYSIOLOGY OF DIABETIC NEUROPATHY

The underlying metabolic abnormalities in DM patients can synergistically drive the development of DN. These abnormalities start with the development of obesity and insulin resistance in type 2 DM (T2DM) or insulin deficiency in T1DM, all of which can result in glucose dysregulation and subsequently, hyperglycaemia and dyslipidaemia[4,10]. In a healthy individual, insulin induces the release of neurotrophic and neuroprotective factors that ensure neuronal survival, as well as C-peptide that restores the structure and function of defective axons. In T1DM patients, as the insulin level falls, the sodium-potassium ATPase (Na^+/K^+-ATPase) and nitric oxide will be

disrupted, leading to neuronal dysfunction, oxidative stress, axonal swelling, and apoptosis[5]. Similarly, insulin resistance in T2DM patients may also reduce the anti-oxidant Akt, consequently producing mitochondrial dysfunction, oxidative stress overproduction, and neuronal apoptosis[11]. In addition, the concomitant dyslipidaemia in T2DM patients occurs when free fatty acids are excessively converted by β-oxidation. The acetyl-CoA transformation during the conversion leads to a great increase in acylcarnitines that are toxic to neurons and Schwann cells[12].

Meanwhile, hyperglycaemia can also activate some pathways that produce excessive polyol, glycation, protein kinase C (PKC), poly (ADP-ribose) polymerase (PARP), and hexosamine, all of which can simultaneously cause overproduction of oxidative stress in the nerves and micro vessels[4,5]. In the polyol pathway, the enzyme aldose reductase (AR) converts glucose to sorbitol. This conversion affects a number of downstream reactions that depletes N^+/K^+-ATPase activity, thus reducing nicotinamide adenine dinucleotide phosphate ($NADP^+$) and enhancing the production of reactive oxygen species (ROS), eventually impairing nerve functions[5,6,13,14] and lead to DN. Besides, excessive glucose molecules will enter the hexosamine pathway to produce inflammatory by-products and induce PKC activation secondary to the accumulation of diacylglycerol. Following this activation, insulin resistance is augmented in a way that interrupts the biology of growth factors biology and causes vasoconstriction of the nerves[10] on top of Na^+/K^+-ATPase dysfunction. As a result, the accumulation of Na^+ leads to axonal swelling and reduced nerve conductivity[5]. Furthermore, the elevated sorbitol and decreased NADH levels trigger ROS increment, glutathione reduction, and cellular osmolarity. Coupled with a decrease in ATP production, these effects can damage mitochondria and DNA as well as reduce the blood supply, eventually speeding up neuronal apoptosis[5]. Additionally, excessive glucose molecules also contribute to the formation of advanced glycation end products (AGEs). When they bind to the receptors (RAGEs), excessive ROS production leads to downstream inflammation that limits blood flow to the peripheral nerves[15]. Although the glycation pathway may take place in the cells of several organs, its effects in DN are more

prominent on both myelinated and unmyelinated axons, endothelial cells, pericytes, and Schwann cells[16]. Furthermore, the interference of AGEs on neurofilaments and microtubules of the nerves impedes the axonal transport whilst AGEs formation on the myelin sheath results in localised demyelination[5,16]. Besides, the attack of AGEs on the microvessels increases vascular permeability, hinders vasodilation, stimulates cytokine production, and amplifies oxidative stress levels, all of which lead to a blood flow restriction to the nerves[16]. As more blood capillaries are damaged, the closely connected microvasculature undergoes ischaemia because of the abnormal modification of basement membrane density, pericyte, endothelial cell functions, and arteriovenous shunt formation[5]. All these changes diminish the neuroprotective role of angiogenic factors such as vascular endothelial growth factor. Therefore, the severity of microangiopathy is shown to be associated with impaired nerve conductivity.

The overall pathomechanisms eventually affect the nerves, especially in the peripheral nervous system. Peripheral axons are more fragile compared to motor neurons since they are placed outside the blood-brain barrier. The location also predisposes peripheral axons to injury secondary to DM[10]. Among the different types of peripheral nerves, small unmyelinated C-fibres termed "small fibres" are the most common sensory axons. However, large fibres comprised of small and thinly myelinated Aδ-fibres as well as fully myelinated Aα- and Aβ-fibres are also prone to DN. Patients with DN may experience degeneration and loss of small fibres that result in new-onset pain, prickling or burning sensations (*i.e.*, dysesthesias) in the feet, followed by the initial demyelination or remyelination of the large fibres[12]. Most of the time, the axons that are farthest from the cell body (*i.e.*, located in the feet) are the most severely affected since the number of functional mitochondria produced in their neuronal cell bodies tracking down the axons would be depleted, causing energy deprivation. Amongst the nerve fibres, small fibres are the earliest to be affected due to their structures (*i.e.*, lack of myelination and encapsulation of Schwann cells). Schwann cell encapsulates large fibres to protect axons from external damage and toxic substances. This is an important step in slowing down diabetic-induced progressive

energy loss. Therefore, this explains why patients with painful DN often experience pain and dysesthesia as their first symptoms[10]. As diabetes progresses, the myelin sheaths of the nerve fibres undergo degeneration with the detachment of Schwann cells[9]. Subsequently, this leads to even fewer neurotrophic factors being released and eventually, neuronal apoptosis[9]. Consequently, the loss of large axonal fibres causes the patient to experience numbness and loss of proprioception distally in the feet that gradually progress proximally with time. The symptoms usually occur in a symmetrical, distal-to-proximal pattern in all populations of nerves, beginning at the tip of the toes and progressing proximally, giving rise to the "stocking-and-glove" clinical presentation[5,10,17]. Such symptom presentation is regarded as insensate or painless DN whereby the loss of sympathetic regulation of the arteriovenous shunt of the vessels and sweat glands in the foot predisposes the patients to bacterial infections that can later culminate in cellulitis and ulcers[18]. Simplified pathomechanisms to the development of DN are summarised in Figure 1.

Moreover, DN patients are at a high risk of developing diabetic polyradiculopathy; a syndrome that appears together with severe disabling pain in one or more than one distribution of nerve roots and is possibly linked with motor weakness[19]. Besides that, patients with uncontrolled DM and peripheral neuropathy are prone to Charcot neuroarthropathy (CN), also known as Charcot foot, a dreadful condition that can easily originate from microtrauma and neurovascular modifications (*i.e.*, arteriovenous shunting causing the escalation of blood flow and bone resorption)[17,20]. In due time, CN can result in deformities such as collapsed joints and pedal disfigurement[4,17].

In view of the wide range of disabling symptoms of DN, various management strategies have been recommended by healthcare professionals to alleviate the symptoms so that the QOL of the affected individuals can be improved.

CURRENT MANAGEMENT OF DIABETIC NEUROPATHY TO DELAY DISEASE PROGRESSION

To date, the management of DN emphasises delaying the progression of neuropathy, reducing the symptoms, and alleviating the complications arising from insensate in painless DN patients[18,19]. The success of DN management depends on the individual's pathogenic processes[18]. Currently, various clinical guidelines on strategies to prevent and manage DN are available worldwide based on the available published literature. The guidelines encompass a wide range of strategies to prevent the development of DN symptoms, hamper the DN progression, and cure the DN symptoms. Thus, the management of DN can be categorised as preventive or symptomatic approaches[19]. Nevertheless, there is very limited treatment available for DN that is aimed at underlying nerve impairment. To date, most of the management strategies emphasise the best way to slow down the progression of DN. Screening for any signs or symptoms of DN is crucial in clinical practice to detect the earliest signs of neuropathy so that prompt intervention can be started[6]. Table 1 outlines the current management to prevent DN progression as elaborated in the literature.

Recommended strategies to delay the progression of diabetic neuropathy

First and foremost, DN prevention strategies should begin with blood glucose monitoring and lifestyle modifications[4,6]. Reduction of sweet food can hinder the progression of distal symmetrical polyneuropathy and cardiovascular autonomic neuropathy in patients with T1DM and T2DM[6,21]. However, based on the Diabetes Control and Clinical Trials, this strategy appears to be more effective in T1DM patients whereby their clinical neuropathy is reduced by 60% within 6.5 years following the intensive therapy[22]. In 1998, The United Kingdom Prospective Diabetes Study reported that T2DM patients with neuropathy showed improvement in vibration perception after improvement in blood glucose levels with intensive treatment[23]. However, there was no significant impact of tight glycaemic control on neuropathy among T2DM patients from 1998 to 2015[24]. Although it is suggested that tight glycaemic control could prevent or delay the progression of DN among DM patients, Rodríguez-Gutiérrez *et al*[24] believed that this strategy alone is inadequate for T2DM patients since they are

more likely to suffer from other risk factors such as cardiometabolic factors that are unaddressed[25]. The finding that glycaemic monitoring alone is incapable to slow down the progression of DN in T2DM patients appears to be a new consensus. These patients often suffer from metabolic syndrome that includes obesity, hyperglycaemia, and dyslipidaemia, all of which are critical risk factors for neuropathy[10] as shown in several clinical trials conducted in various countries[24,26-31]. In the United States, The American Diabetes Association (ADA) has implemented different glycaemic target guidelines for children, teenagers, adults, pregnant ladies, and senior citizens in an effort to promote customised care based on individualised glycaemic targets[4,32-35].

Apart from glycaemic monitoring, lifestyle modification is also recommended to reduce cardiometabolic risk factors among T2DM patients to lower the risk of DN and delay its progression. Lifestyle modifications can be in the form of regular exercise and a balanced diet[10]. In animal studies, sustained exercise has been found to: (1) Decrease hyperglycaemia and overproduction of oxidative and nitrosative stress; (2) enhance mitochondrial bioenergetics in the nerve cell body and distal axon; (3) improve microvascular vasoreactivity and reduces nerve ischaemia; (4) elevate axonal transport; (5) counteract the inflammatory effects of dyslipidaemia, lipotoxicity, and obesity; and (6) improve nerve regeneration following metabolic injury[10,36-38]. However, clinical studies involving human subjects reported various outcomes. In 2006, a clinical trial investigating the effect of long-term exercise training on DPN patients reported a significant improvement in peroneal and sural motor nerve functions in the patients[39]. Over the four years of the study period, the development of motor and sensory neuropathy slowed down, thus suggesting that exercise may change the natural course of DN. However, recent studies reported contradicting findings on the effect of exercise on DN. In a randomised controlled trial (RCT) by Stubbs *et al*[40], a 12-wk physical exercise training regardless of type (*i.e.*, sedentary controls, aerobic, isokinetic strength, or a combination of aerobic-isokinetic strength training) did not improve or exacerbate the sensory or motor nerve electrodiagnostic findings (*i.e.*, sural, median, and ulnar sensory nerve responses) in older T2DM patients with length-dependent distal

symmetric polyneuropathy. However, a short-term structured program of aerobic exercise was found to selectively improve the sensory nerve functions in a subset of patients. This finding was supported by a recent meta-analysis that included 13 randomised controlled trials (RCTs) from 2014 to 2022 with 592 patients that underwent peripheral nerve conduction tests. Exercise, when combined with endurance and sensorimotor training programme was found to improve balance, glycaemic control, and peripheral nerve conduction, especially in DN patients[41]. Unfortunately, the implementation of such supervised exercise training among the general population in the healthcare system outside of the research setting can be challenging due to patient compliance, shortage of funding, infrastructure, and staff to supervise the patients[4].

In the literature, suggestions have been put forth to include diet observation as part of the prevention strategies in delaying the progression of DN. However, there is a lack of evidence on the effect of diet as the sole prevention strategy for DN since most of the studies incorporated diet as one of the multifactorial lifestyle strategies. For instance, the Diabetes Prevention Program demonstrated that the combination of exercise and diet counselling can reverse the symptoms of metabolic syndrome and lower the incidence of T2DM[42,43]. On a similar note, the ADA also recommends restriction of high-calorie and processed food intake to reduce the risk factors of DN. In turn, the patients should consume food rich in polyunsaturated fats and antioxidants to prevent the development of DN[10]. It is known that lipid metabolites and chronic cellular hyperglycaemia may induce pro-inflammatory cellular injury response reactions and generate oxidative stress that further diminishes the roles of mitochondria in distal axons[21]. Several dietary supplements are recommended to fight against oxidative damage, including the anti-oxidant a-lipoic acid. Besides, supplements containing nicotine riboside, a key generator of nicotinamide adenine dinucleotide (NAD^+) are also recommended as it can activate certain molecular pathways that shield against dyslipidaemia and obesity[44], resulting in the prevention of oxidative damage in the neurons and delay the onset of DN[45]. Therefore, dietary management can be effective in alleviating DN. However, it is best to be combined with exercise-based intervention

to ensure a long-term positive impact on glucose and lipid metabolism, as well as axonal regeneration in BM patients[21].

In addition, patients with DN are predisposed to a higher risk of lower extremity amputations. A recent systematic review that evaluated the 5-year mortality rate of patients with non-traumatic below-the-knee amputation and above-the-knee amputation was 40%-82% and 40%-90% respectively[46], emphasising the importance of annual foot examination and routine foot care in the prevention of lower limb amputations[17]. Education on proper diabetic foot care should be provided to DM patients, including the identification of the at-risk foot, daily examination and inspection, the use of suitable footgear, as well as accurate and early treatment of pre-ulcerative lesions[47]. The education should also be extended to family members and healthcare providers. Despite the available guidelines on foot care, there is a lack of comprehensive evidence on the best ways to hamper diabetic foot complications. A systematic review of 19 studies demonstrated a reduction in amputation severity, duration of hospital stay, and death rates with proper diabetic foot care. However, the studies were of low quality[48]. In addition, another systematic review of 12 RCTs revealed inadequate high-quality evidence on whether the application of educational strategies alone may minimise the incidence of diabetic foot ulcerations (DFUs) and amputations. The authors agreed that educational interventions should be combined with other interventions in the prevention of DFUs[49].

Current treatments for diabetic neuropathy

Although some non-pharmacological approaches have been introduced to manage the signs and symptoms of DN, anti-diabetic drugs remain the mainstay of DN treatment. Furthermore, there is a paucity of management strategies for individuals with painless or insensate DN as the current therapy focuses on the painful type of DN. Several antidepressants [tricyclic anti-depressants (TCAs), *i.e.*, duloxetine, venlafaxine, amitriptyline], analgesics (morphine, oxycodone, and tramadol), and anti-convulsant (gabapentin, pregabalin, topiramate, and valproic acid) are prescribed for patients with

painful DN. Table 2 summarises the available treatments for DN. Since there is a huge variability in pain between the patients, various types of medications are given to lower painful DN.

Generally, DN will first afflict small nerve fibres such as unmyelinated C-fibres before large fibres (myelinated A fibres), thus explaining the complaints of burning and discomfort among patients with painful DN[18,19]. Pregabalin and gabapentin are the gold standard drugs for pain management[50,51] and are therefore the first- and second-line medications to treat painful DN[4,51]. The exact mechanism of how these anticonvulsants alleviate DN symptoms is unclear. It is postulated that they bind to the α2δ subunit of calcium channels on presynaptic nerve terminals[52] to induce analgesia. However, these drugs are associated with adverse effects such as tachyphylaxis, somnolence, drowsiness, headache, dizziness, nausea, and diarrhoea[4,51,53]. Furthermore, pregabalin has been linked to misuse and a higher prevalence of deaths, thus there have been calls for its reclassification as a Class C controlled substance in the United Kingdom[54,55].

Apart from that, antagonists of serotonin and norepinephrine reuptake (SNRIs) are also used to reduce DN pain. Similar to pregabalin and gabapentin, duloxetine is recommended as the mainstay of treatment for painful DN. It attenuates the descending pain mechanisms and moderately hinders dopamine reuptake. Apart from producing similar side effects as anticonvulsants, this drug also unfavourably affects sexual functions and sleep[6]. Another selective serotonin reuptake inhibitor, venlafaxine, is also recommended by the European Federation of Neurological Societies Task Force and the American Academy of Neurology as a therapy for painful DN[56,57]. However, based on a previous Cochrane systematic review of six RCTs and 460 participants comparing the placebo effect with a venlafaxine dosage of 150-225 mg, the level of evidence for its effectiveness is low[58].

Apart from that, tricyclic antidepressants such as amitriptyline are also recommended for painful DN[4], especially acute pain[59]. Several RCTs have reported its effectiveness in alleviating painful DN[60]. In a RCT, Kaur *et al*[61] compared the efficiency of

duloxetine and amitriptyline. They found a similar efficacy of these drugs in treating patients with painful DN. The mechanism of TCAs in targeting painful DN is not understood, but amitriptyline is found to attenuate the reuptake of serotonin and noradrenaline at the nerve terminals and ion channels (sodium and potassium ion channels), as well as N-methyl-D-aspartate receptors (NMDARs) in central nervous systems[62]. However, amitriptyline is associated with side effects such as constipation, dry mouth, sleep disturbance, sexual dysfunction, somnolence, headaches, arrhythmias, sleep disturbances, and postural hypotension[63]. Apart from amitriptyline, other TCAs such as desipramine and nortriptyline have also been investigated as potential treatment for painful DN. Several RCTs reported a reduction in painful DN symptoms following desipramine[64-66], making it likely to be as effective as amitriptyline[64] with lesser side effects[65].

On top of that, some clinical guidelines recommended opioids be included as one of the treatments with or without other drugs for DN patients with severe pain intensity[67]. However, opioid is frequently associated with therapeutic abuse and misuse. Tramadol, one of the opioids, is fairly acceptable in the treatment of moderate to severe pain as it has a lower risk of abuse or misuse. It reduces pain by binding to opioid receptors (*i.e.*, κ-, δ-, and μ-receptors) centrally besides mitigating the serotonin and norepinephrine reuptake, thus augmenting the inhibitory effects of pain transmission in the spinal cord dorsal horn[68]. Apart from that, tapentadol is also suggested for the treatment of painful DN in the US. It shares a similar mechanism of action with tramadol, except for a higher affinity for μ-receptors. However, the level of evidence to show the efficacy of these opioids was low based on the above-mentioned Cochrane systematic review that included six RCTs and 438 participants[69].

Pertaining to the potential to target the C-fibres in peripheral sympathetic nerves, the use of sympathetic blocking medications (α-adrenergic antagonists) such as clonidine, regitine, or phenoxybenzamine is recommended in some studies to improve the pain secondary to the spontaneous firing of the affected nerve fibres[18,19]. An RCT conducted by Campbell *et al*[70] demonstrated that the level of foot pain subsided after the topical

application of clonidine gel among patients with painful DN. However, the effectiveness of this medication relies on the relative functionality level of nociceptors (*i.e.*, functional and possibly sensitised nociceptors in the affected skin). This trial failed to achieve significant results despite showing some evidence of the drug's efficacy. Another earlier RCT on transdermal clonidine application in diabetic polyneuropathy patients also failed to achieve promising results as drug withdrawal effects and pain recurrence were reported among the trial participants[71]. Even though this sympathetic blocking agent can be used to treat other complex regional pain syndromes, there is still very scarce analysis with regard to painful RN in the Cochrane database. This was concurred by Mackey *et al*[72] who reported that not only this class of medication did not show any efficacy in treating neuropathic pain, its use was challenging due to the side effects profile.

In some cases of patients with persistent severe painful DN despite multiple pharmacological approaches, shifting the pain relief mechanism to the sympathetic nervous system can possibly assist the management of the severe pain. In a clinical trial, permanent lumbar epidural blockade was found to produce satisfactory outcomes when several other pharmacotherapeutics failed to treat patients with painful DN[73]. In another case reported by Cheng *et al*[74], a painful DN patient who was unresponsive to several medications showed significant pain relief following the blockade of nine lumbar sympathetic nerves over a 26-month duration. His QOL was further improved over the two years. Further advancement of this approach, i.e. lumbar sympathetic pulsed radiofrequency combined with continuous epidural infusion, appeared to successfully manage painful symptoms of DN in the patients[75]. Meanwhile, the combined treatment of continuous lumbar sympathetic block and neurolysis with alcohol also produced a greater improvement of DN symptoms and rapid recovery in the patients, not to mention its satisfactory safety profile[76]. However, there are certain limitations to this approach, such as the requirement for additional tools to assess and diagnose the severity and duration of DN. Furthermore, the small size population, short period of follow-up, and duration of the combined treatment strategies in the previous

studies[75,76] restricts the generalisability of the results, thus further research is warranted.

Additionally, unmyelinated C-fibres release neurotransmitter substance P during the transmission of pain signals from the periphery to higher centres. This pathway could be blocked by the topical application of capsaicin[77], especially for patients with localised pain who are unable to tolerate oral medications[4]. Previous reports have demonstrated its effectiveness in improving nerve functions and lowering pain sensations in painful DN patients at a dosage of 0.075% four times a day[78,79]. Meanwhile, DN can also affect myelinated A-fibres that produce deep-seated, dull, and distressing pain that is usually unresponsive to sympathetic blocking agents and capsaicin[18,19]. This natural product blocks pain transmission by modifying the membrane potential of vanilloid receptor subtype 1 and certain ion channels, as well as the neurotrophic signalling at the nerve fibres[19,80]. Besides, it can also initiate acute production of vasoactive peptides from perivascular sensory terminals following topical application[81]. The use of topical capsaicin to treat painful DN is approved by Food and Drug Administration and the level of evidence for its efficacy ranges from moderate to low[82,83]. On the downside, several reports have emerged regarding the potential side effects of topical capsaicin in damaging small nerve fibre and interrupting nociceptive signalling[84].

Besides the above-mentioned pharmacological strategies, there are other alternative approaches to alleviate the symptoms of painful DN. Neuromodulation strategies using specific devices such as frequency-modulated electromagnetic neural stimulation (FREMS), spinal cord stimulation (SCS), neuromuscular electrical stimulation (NMES), and transcutaneous electrical nerve stimulation (TENS) represent new hopes for DN patients[4]. However, these strategies are still under investigation and not included in any clinical guidelines to treat DN as the level of evidence is very low[4,85,86]. Similarly, alternative complementary approaches such as acupuncture and static magnetic field therapy have also been used to manage painful DN[19]. Nevertheless, data on these management strategies are also limited.

Furthermore, a series of clinical trials have demonstrated the efficacy of the antioxidant nutritional supplement, *i.e.*, α-lipoic acid (ALA), acetyl-L-carnitine, and vitamin B_{12} in alleviating the pain linked to DN[57,87,88]. An oral supplement of ALA at 600 mg per day may reduce DN pain within two weeks, besides improving numbness and paraesthesia symptoms with minimal adverse effects[89]. Similarly, ALA lowers pain intensity by decreasing oxidative stress that afflicts nerves and micro vessels after metabolic modifications[4]. Meanwhile, the regular supplementation of vitamin B_{12} is recommended especially for T2DM patients who are on metformin to offset the side effect of vitamin B_{12} deficiency[90]. Despite promising outcomes, worldwide availability, affordable cost, and is regarded as a "safer option", there are concerns regarding these nutraceuticals in terms of lack of regulations including standardisation in manufacturing and quality control[91,92]. Furthermore, the safety profile of these nutraceuticals remains unclear due to the lack of high-qualities clinical trials[87,93].

ISSUES AND CHALLENGES IN DIABETIC NEUROPATHY MANAGEMENT

Since the prevalence of DN is rapidly rising, multiple strategies in terms of treatments, new therapeutic approaches, patient access to healthcare facilities, and provision of knowledge regarding DN have been introduced to slow down the disease progression. Unfortunately, several ongoing issues must be resolved in the management of DN. This section elaborates on the issues and challenges in improving the management of DN from the aspect of treatment, patient adherence, access to facilities, and knowledge.

Issues in diabetic neuropathy treatments

In the literature, a number of observational and interventional studies revealed that half of the patients with DM develop the signs and symptoms of DN during their lifetime[6,87,94-96]. The prevalence of DN is high (approximately 20%-30% in newly diagnosed and early-stage T2DM)[30]. Additionally, it is challenging to treat DN patients with symptomatic (painful) variants since the pain can be debilitating and excruciating. They often complain about pain sensation over the lower extremities that is apparent at

rest and intensifies during night time[19]. Unfortunately, the exact pathogenesis of this illness is unknown. Many clinical trials failed despite promising outcomes in pre-clinical studies. Therefore, novel disease-modifying medications are scarcely developed because of the doubts surrounding pharmacological targets.

On a further note, since the role of aldose reductase in the pathogenesis of DN was discovered by Dvornik *et al*[97] it has been extensively investigated due to its promising effects in reversing DN. Combating DN by antagonising this enzyme seems to be a promising step[14]. The application of aldose reductase inhibitors (ARIs) has been shown to hamper the overactivity of the polyol pathway. However, a previously published systematic review did not pinpoint a single RCT showing any superiority in ARIs compared to placebo in DN patients[98]. Although it has been three decades since the first discovery of ARIs, these drugs are still not established as the mainstay of DN treatment due to a high occurrence of side effect profiles[99]. Similar issues were also raised for other potential therapeutics involving the antagonism of PKC activation resulting from excessive diacylglycerol accumulation. A systematic review of RCTs on the application of PKC inhibitor ruboxistaurin (RBX) has reported its therapeutic effects on DN. However, the evidence from those studies was insufficient to establish its efficiency in treating DN[100]. Moreover, RBX has been shown to be more effective in relieving symptoms among patients with less severe DN[100,101].

Last but not least, other potential new drugs targeting RAGEs activation have also been extensively explored in animal models[102,103], some of which have produced encouraging therapeutic effects in patients[104]. However, the high toxic contents of these drugs become a major problem in human trials[10,15]. Due to these uncertainties and suboptimal therapeutic efficiency in improving nerve functions in T2DM-induced DN[15], the industry refuses to invest further in such drugs[5]. Thus, it limits the available medication option for patients. They have to rely on the combination of anti-diabetic medications with other management strategies to delay the progression of DN.

Challenges in patients' adherence to diabetic neuropathy medications

Although diabetic management guidelines have been established worldwide, not all patients can adhere to the recommended strategies due to many factors. Patients' non-adherence to T2DM treatment regimens continues to be a major issue in most countries[105,106]. It is closely related to poor knowledge regarding diabetes aetiology and disease progression, unstable socioeconomic status, poor family support, patient-staff engagement barriers, complex therapeutic regimens, and lack of medical insurance coverage[105-108]. Some patients even voluntarily stopped the treatment plan and shifted to traditional herbs following their concerns about the side effects of the medications.

Moreover, unsatisfactory healthcare also contributes to the non-adherence to self-care diabetic management[106]. Even with free medications provided by the government, patient adherence can be compromised if there is ineffective communication between the patients and healthcare providers[106]. It is undeniable that myths and cultural beliefs would influence the faith of patients in doctors' prescriptions and recommendations, especially if the patients lack an understanding of disease progression[105,109]. Therefore, it is vital to provide appropriate health education and counselling to increase the patient's adherence rate. As proven by Awodele and Osuolale[110], patients' clinical outcomes improved significantly (*i.e.*, 86.8% adherence rate) following health education and counselling.

Besides that, a complex treatment regimen can also contribute to non-adherence. Patients with multiple comorbidities generally have more medications from different pharmacological classes, giving rise to polypharmacy. A cross-sectional study among diabetic patients with no comorbidities demonstrated a higher adherence to diabetic medications[111] as compared to patients with comorbidities who required multiple medications[112,113]. This is further complicated by the poor awareness of the importance of diabetic medications, especially in rural areas of low-income countries[105,114,115]. However, this issue can be addressed by involving the community and healthcare providers to improve the awareness of the patients. Evidently, encouragement from family and friends has been linked with an improvement in patients' knowledge and adherence to dietary recommendations[106]. Moreover, elderly patients with multiple

comorbidities displayed better medication adherence when provided with more information on the benefits[116,117].

Poverty leads to poor management in DN

Although comprehensive diabetic management has been established and practised globally, not all are fully attainable, especially in low-income or developing countries with high rates of poverty. Financial restraint often leads to the non-adherence of patients. In Nigeria, 51% of diabetic patients, most of who were women and unemployed, could not afford DM medications. Another 69% had to purchase their medications in smaller dosages due to high costs[110]. To minimise these obstacles, support from high-income countries is crucial. National programmes in medical schools, health centres, and hospitals can be put in place under international collaborative partnerships[118]. Evidently, a 12-mo Kerala Diabetes Prevention Programme made up of a peer support education group led to significantly improved lifestyle changes and lower cardiovascular factors among the participants. However, there was an insignificant outcome for diabetic symptom improvement[119].

Restricted access to facilities and patient education due to the coronavirus disease 2019 pandemic

It is undeniable that the coronavirus disease 2019 (COVID-19) pandemic has cast a huge impact on the healthcare and management of many diseases, including DM. During the pandemic, a prolonged lockdown was implemented. In many low-income countries, there was a lack of proper guidelines for DM patients to attend follow-ups in hospitals. Furthermore, with the low coverage of sick pay or social security, people from low-income countries were less likely to practise preventive measures such as social distancing, the use of protective gear, and visiting emergency health services. Furthermore, since diabetic management requires a visit to healthcare centres for drug prescription, many patients faced restricted access to medications. Insulin was especially restricted during the COVID-19 outbreak. At some point, many outpatient

clinics and endocrinologists at private hospitals were temporarily shut down while the focus of emergency services shifted to the treatment of COVID-19 patients. These difficulties affected the care of diabetic patients, especially those who required hospital admission[120]. In short, the interruption of routine diabetic care created stress among patients not to mention worsening obesity due to physical inactivity, both of which worsened their hyperglycaemic conditions and diabetes-related complications[121].

As the crisis of COVID-19 unfolds over the past two years, new strategies were developed to enhance diabetes care, including the use of telehealth, remote patient monitoring, online glucose monitoring *via* wearable technologies supported by the internet and smartphones, free educational videos and e-books on self-management of diabetes *via* mobile applications[122-124]. However, these guidelines are established in developed countries, making them less suitable for patients in low-income countries with issues like poverty, poor education level, and suboptimal healthcare planning. Several suggestions were put forth to potentially improve the care of DM patients, such as replacing active follow-up with passive care, establishing community centres for patient visit and training purposes outside the hospitals (*e.g.*, in mosques, churches, and community centres), setting up more outpatient clinics and primary healthcare centres for the treatment of non-communicable diseases. At these centres, innovative steps were proposed and implemented, including self-monitoring of blood glucose levels without additional charges, guidelines for physicians on clinical management cases during disease outbreaks, needs assessment survey by trained investigators, contacting patients *via* landlines for consultation with physicians and endocrinologists, as well as spreading educational and intervention information *via* text messages for patients with smartphones[120].

FUTURE DIRECTION IN THE MANAGEMENT OF DIABETIC NEUROPATHY

It is crucial to implement strategies to prevent and slow the progression of DN, especially since severe DN can be challenging to treat. There are many suggestions to achieve this. In T1DM patients, not only are the insulin-producing pancreatic β-cells

destroyed, but the blood capillaries are also hugely affected. Blood capillaries are critical in insulin production; thus, it is vital to manage capillary destruction. A new drug from bone marrow stem cells has been developed to replenish the cells of blood capillaries and increase the production of β-cells. This intervention is based on the concept of introducing the formed β-cells in the form of "immunoprotective capsules" to avoid destruction by auto-immune cells[125]. This research is still ongoing. Issues related to the capability of multipotent stem cells in the formation of β-cells that can potentially proliferate into cancerous cells need to be fully addressed before the application of this drug[126]. Besides that, other proposed method includes dietary changes in DM patients such as the consumption of amino acid arginine to facilitate the metabolism of glucose as has been proven in animal studies[125]. Arginine stimulates the production of glucagon-like peptide-1 from endocrine cells in the gut following nutrient ingestion that can promote insulin secretion, reduce food intake, increase β-cell production, and minimise β-cell apoptosis[127].

Lastly, there is growing research in the area of metabolomics technology that may aid in the diagnosis and biomarkers discovery of DM. Since metabolites reflect the whole body's functions, it is hypothesised that they can provide a comprehensive picture of what happens in the body. The combination of metabolomics detection technology with computational biology and orthogonal experiments allows the screening of diabetic metabolites and evaluation of the related metabolic pathways[128]. Evidently, through metabolomics research, it is discovered that T1DM children who developed auto-antibodies before the age of 2 had twice the depletion rate of methionine level compared to the children who developed autoantibodies in later childhood or children who were auto-antibody-negative. The same research also speculated that the methionine pathway could be involved in the generation of antibodies during early infancy[129]. Following that, a metabolomics study using transgenic and knock-out mice models that resembled early stages of human T1DM also revealed metabolomics disturbances before the onset of T1DM. In their study, Overgaard *et al*[130] found a reduced level of lysophosphatidylcholine and methionine as compared to an elevated

level of ceramides before the onset of T1DM. Meanwhile, in a study on insulin autoantibody seroconversion among diabetic children, Li *et al*[131] discovered that the rapid growth of children's height is linked to the increased risk of islet autoimmunity and the progression of T1DM. These published studies represent the growing metabolomics research that has made great progress in the identification of the main factors and metabolites that helps to identify the pathophysiological process, aetiology, early prevention, and assessment of the treatment effects of diabetes.

DISCUSSION

Primary resources of diabetic care from published studies serve as the general guidelines for better diabetic prevention strategies and patient care worldwide. Along with lifestyle and dietary modifications, additional strategies need to be added to the guidelines for the betterment of diabetes care. For instance, glucose monitoring is one of the current strategies that has been proven effective in controlling the blood and dietary glucose in previous literature for T1DM patients. However, this strategy is more beneficial in reducing diabetic complications and progression for T1DM patients because the pathogenesis of DN differs between T1DM and T2DM. For example, hyperglycaemia is not the key factor to all the complications suffered by T2DM patients. In view of this, the general management of DN among T1DM and T2DM should be tailored accordingly. It is also important to note that over-aggressive glucose control can lead to hypoglycaemia-induced neuropathy in T2DM patients. It is especially devastating for neurons in the brain that use more glucose than other cells to fulfill their functions.

There are certain misconceptions regarding the dietary monitoring of glucose intake among DM patients. Most diabetic patients eliminated sugars in their beverages but fail to reduce the consumption of carbohydrate-rich meals and sugar-rich fruits, especially in countries where carbohydrate-rich food and exotic fruits are the staple diets. The consumption of these food may complicate the diabetic condition and accelerates the progression of DN. Therefore, it is critical to disseminate accurate knowledge about

dietary glucose through social media to avoid any misconceptions among diabetic patients.

Besides that, poor treatment adherence is also a major challenge in the prevention and management of DN as discussed in the previous section. In countries with traditional lifestyles such as Asian countries, many patients opted for herbal medicine rather than modern medications, possibly due to concern about side effects and a lack of trust towards modern medicine. Although some of the traditional herbs demonstrate a potent anti-diabetic effect, the herb preparation by local manufacturers may contain additional harmful substances such as steroids that can lead to other complications. Furthermore, the crude extracts of certain herbs can be unsafe as some of the unknown metabolites can worsen the diabetic condition. Therefore, governmental agencies should conduct strict screening of the content of traditional anti-diabetic herbs before it is commercialised to reduce the risk of complications. More importantly, patient education and continuous research on these new anti-diabetic agents should be emphasised by the government as a step to improve diabetic management.

CONCLUSION

The increasing prevalence of DN and its complications among DM patients is alarming and can be costly to individuals and countries alike. Recently, psychosocial impact and morbidity from DN also received widespread concern. Current clinical guidelines focus on preventing the progression of DN and managing the DN symptoms in patients. However, most of these guidelines failed to address the underlying factors contributing to DN, thus compromising the effectiveness of current management. Therefore, it is crucial to identify the mechanisms and risk factors of DN so that issues hindering the success of the current management of DN can be resolved. This review outlines various challenges in the management of DN on top of the pathomechanisms of DN. With a better understanding of DN pathogenesis, DN management can be enhanced. It is hoped that the additional recommendations pertaining to the raised issues can be addressed for the betterment of the quality of care and patients' health.

Figure 1 Possible pathomechanisms leading to the development of diabetic neuropathy. For further information, see text. PKC: Protein kinase C; T2DM: Type 2 DM diabetes mellitus; ROS: Reactive oxygen species; AGE: Advanced glycation end product; FFA: Food and Drug Administration; NADP: Nicotinamide adenine dinucleotide phosphate.

Table 1 Management strategies from the previous literature to prevent the progression of diabetic neuropathy in patients

Strategies	Description/indication	Intervention/strategies	Ref.
Glucose level monitoring	Prevention of distal symmetric polyneuropathy and cardiovascular autonomic neuropathy developments in patients with T1DM, delay the progression of distal symmetric polyneuropathy in T2DM patient	Treatments: Insulin; anti-diabetic medications; electrical stimulation, percutaneous nerve stimulation; Non-treatments: Lifestyle modifications (glucose-dietary control, exercises and physiotherapy); pancreas transplant; bariatric surgery	[6,4,132]
Lifestyle modifications	To reduce risk of DN and cardiometabolic causes	Glucose-dietary control; counselling; supervised training programs including physiotherapy/rehabilitation	[4]
Diabetic foot care	Delay or lower the risk of amputations	Five key elements for prevention of DFUs: (1) Recognition of the at-risk-foot; (2) consistent check and examination of the at-risk-foot; (3) education of patient, family and healthcare providers; (4) routine of wearing suitable footwear; and (5) management of pre-ulceration signs	[47]

Pharmacologic therapeutics	To manage diabetes, neuropathy and treatment for symptomatic pain	Three suggested phases can be useful: Step 1: Treatment with first-line therapy of TCAs (*e.g.*, amitriptyline), SNRIs (*e.g.*, duloxetine), pregabalin and gabapentin; step 2: Treatment with second-line therapy including tramadol (weak opioids and SNRIs); step 3: Treatment of last line therapy including strong opioids, cannabinoids and anticonvulsants Alternatives (anti-oxidant supplementations): α-lipoic acid; acetyl-L-carnitine vitamin B_{12}	[89,90,133]

T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; TCAs: Tricyclic antidepressants; SNRIs: Serotonin-norepinephrine reuptake inhibitors; DN: Diabetic neuropathy; DFUs: Diabetic foot ulcers.

Table 2 Available therapeutic medications for the management of diabetic neuropathy

Management strategy	Therapeutic approach	Description	Contraindications/issues
Pharmacological	Anti-convulsants: Gabapentin; pregabalin	First line medication for painful DN[4,51]; gold standard for pain management[50,51]	Reports on misuse and increased death rate in patients[54]
	SSRI and SNRIs: Duloxetine; venlafaxine	First- and second-line therapy for painful DN[56,57]	Low evidence on venlafaxine effectiveness for painful DN treatment[58]
	TCAs: Amitriptyline; desapramine	First and second-line therapy for painful DN	Associated with constipation, dry mouth, sleep disturbance, sexual dysfunction, somnolence, headaches, arrhythmias, constipation, sleep disturbances and postural hypotension[4,63]
	Opioids: Tramadol; trapentadol	Opted as acute salvage treatment or as a part of drugs combination for painful DN treatment	Strong opioids are frequently associated with therapeutic abuse and misuse[68]; use of tramadol is more preferred due to reduced risk of abuse or misuse[68]
	Sympathetic blocking agents (α-	One of the opted therapy	Limited evidences in RCT testing the drug's

	adrenergic antagonists): Clonidine; regitine; phenoxybenzamine	for complex regional pain syndrome treatment[72]	efficacy on painful DN patients; efficiency of clonidine depends on relative functionality of nociceptors in painful DN patients, however no statistical significance is achieved although the trends of efficacy is shown[70]
Non-pharmacological	Sympathetic nerves blockade: Lumbar sympathetic nerves blockade; combined strategies of lumbar sympathetic pulsed radiofrequency and continuous epidural infusion; combined treatment of continuous sympathetic block and neurolysis with alcohol	Recommended for severe painful DN patients who failed to any pharmacological treatments	Patients demonstrated improved life expectancy, greater DN symptoms improvemeny, satisfactory safety, rapid recovery and rapid relief of pain[73-76]; associated with several limitations of additional diagnostic tools, small size population, short period of follow-up and issue regarding combined treatment duration[75,76]
	Capsaicin	Recommended for patients with intolerable oral therapeutic consumption[4]	Low to moderate level of evidence for topical capsaicin efficacy[82,83]; associated with small nerve fibers injury and disturbed nociceptive signaling[84]
	Neuromodulation devices: FREMS;	Studies on their efficacy in	Not yet approved for clinical guidelines for

	SCS, NMES; TENS	painful DN is still on-going	painful DN treatment due to very low evidence of efficacy[4,85,86]
	Nutraceuticals: ALA; ALC; vitamin B_{12}	ALA improves numbness and paraesthesia with reduced side effects[89]; vitamin B_{12} is recommended to T2DM patients with metformin prescription[90]	There are lack of standardization in quality and manufacturing of nutraceuticals[91,92]; low safety level due to less evidence of high-quality studies[87,93]

TCAs: Tricyclic antidepressants; FREMS: Frequency-modulated electromagnetic neural stimulation; SCS: Spinal cord stimulation; NMES: Neuromuscular electrical stimulation; TENS: Transcutaneous electrical nerve stimulation; ALA: α-lipoic acid; ALC: Acetyl-L-carnitine; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

82994_Auto_Edited.docx

ORIGINALITY REPORT

9%
SIMILARITY INDEX

PRIMARY SOURCES

1	Sasha Smith, Pasha Normahani, Tristan Lane, David Hohenschurz-Schmidt, Nick Oliver, Alun Huw Davies. "Prevention and Management Strategies for Diabetic Neuropathy", Life, 2022 Crossref	230 words — 3%
2	www.researchgate.net Internet	76 words — 1%
3	www.mdpi.com Internet	52 words — 1%
4	"Textbook of Diabetes", Wiley, 2010 Crossref	42 words — 1%
5	www.ncbi.nlm.nih.gov Internet	35 words — < 1%
6	Lynn Ang, Kara Mizokami-Stout, Stephanie A. Eid, Melissa Elafros, Brian Callaghan, Eva L. Feldman, Rodica Pop-Busui. "The conundrum of diabetic neuropathies—Past, present, and future", Journal of Diabetes and its Complications, 2022 Crossref	27 words — < 1%
7	Sasha Smith, Pasha Normahani, Tristan Lane, David Hohenschurz-Schmidt, Nick Oliver, Alun	27 words — < 1%

Huw Davies. "Pathogenesis of Distal Symmetrical Polyneuropathy in Diabetes", Life, 2022
Crossref

8 Megha Gandhi, Emily Fargo, Lalita Prasad-Reddy, Katherine M Mahoney, Diana Isaacs. "Diabetes: how to manage diabetic peripheral neuropathy", Drugs in Context, 2022 — 18 words — < 1%
Crossref

9 www.science.gov — 17 words — < 1%
Internet

10 "Advances in Chronic and Neuropathic Pain", Springer Science and Business Media LLC, 2022 — 16 words — < 1%
Crossref

11 Patrick, Graham L.. "An Introduction to Medicinal Chemistry", An Introduction to Medicinal Chemistry, 2023 — 15 words — < 1%
Publications

12 Saeed Samarghandian, Mohsen Azimi-Nezhad, Tahereh Farkhondeh. "Crocin attenuate Tumor Necrosis Factor-alpha (TNF-α) and interleukin-6 (IL-6) in streptozotocin-induced diabetic rat aorta", Cytokine, 2016 — 12 words — < 1%
Crossref

13 www.researchsquare.com — 12 words — < 1%
Internet

14 iopscience.iop.org — 11 words — < 1%
Internet

15 cyberleninka.org — 10 words — < 1%
Internet

16 docksci.com

	Internet	10 words — < 1%
17	journals.humankinetics.com Internet	10 words — < 1%
18	www.intechopen.com Internet	10 words — < 1%
19	Joni J. Pagenkemper. "Chapter 6 Diabetes Mellitus", Springer Science and Business Media LLC, 2008 Crossref	9 words — < 1%
20	www.arcjournals.org Internet	9 words — < 1%
21	www.cdc.gov Internet	9 words — < 1%
22	Min Cheol Chang, Seoyon Yang. "Diabetic peripheral neuropathy essentials: a narrative review", Annals of Palliative Medicine, 2023 Crossref	8 words — < 1%
23	academic.oup.com Internet	8 words — < 1%
24	core.ac.uk Internet	8 words — < 1%
25	iytmed.com Internet	8 words — < 1%
26	N. C. Schaper, J. J. Van Netten, J. Apelqvist, B. A. Lipsky, K. Bakker. "Prevention and management of foot problems in diabetes: a Summary Guidance for Daily	6 words — < 1%

Practice 2015, based on the IWGDF Guidance Documents",
Diabetes/Metabolism Research and Reviews, 2016
Crossref

EXCLUDE QUOTES	OFF	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	OFF	EXCLUDE MATCHES	OFF