

## Review Article

# Diabetic neuropathy: a comprehensive review of prevalence, screening and diagnostic approaches, clinical symptoms, complications and evidence-based management strategies

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## ABSTRACT

Diabetic neuropathy (DN) is a frequent and significant complication of diabetes that has a major impact on patients' quality of life and contributes to higher rates of illness and mortality. DN impacts approximately 50% of people who have diabetes. It is characterized by distal symmetric polyneuropathy, leading to sensory loss, pain, and challenges with movement. This condition often results in diabetic foot ulcers and the amputation of lower limbs. The onset of diabetic neuropathy is influenced by multiple factors, such as elevated blood sugar levels, dyslipidemia, oxidative stress, mitochondrial issues, and inflammation, all of which can damage peripheral nerves. Despite extensive research, no effective treatments that modify the disease have been identified, and existing methods primarily focus on symptom management. This review explores the complex mechanisms of diabetic neuropathy and highlights recent advancements in its diagnosis and treatment. Recent diagnostic techniques, such as corneal confocal microscopy and biomarker-based tests, have improved the early detection of conditions and the provision of prompt treatment. Modifications in lifestyle and methods that include various healthcare professionals can enhance patient outcomes. Despite significant progress, further research is necessary to develop treatments that can effectively halt or reverse the progression of the disease, which would improve the quality of life for individuals with DN. This review offers a complete summary of the current knowledge and future trends in diabetic neuropathy research and management.

**Keywords:** Diabetic neuropathy, Type 1 diabetes, Type 1 diabetes, Diagnostic approach

## INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease that is a long-acting problem where there is chronic hyperglycemia due to insulin secretion and insulin action disorders. It is divided into: type 1 and type 2 diabetes. Type 1 diabetes, is an autoimmune disease that destroys the pancreatic beta cells causing complete insulin deficiency.

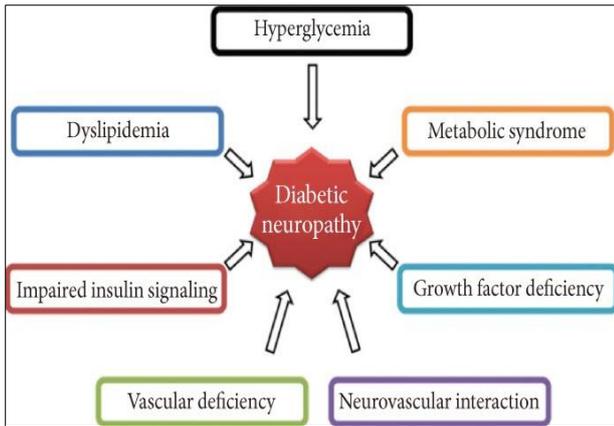
Type 2 diabetes represents the majority of the cases worldwide. The worldwide burden of diabetics is rising, and the World Health Organization (WHO) reveals that there are more than 400 million diabetics worldwide. It is expected that in 2045, may reach 700 million, around the

world.<sup>1</sup> Obesity, sedentary lifestyle, and aging are the most significant risk factors of type 2 diabetes.<sup>2</sup>

### *Definition and significance of diabetic neuropathy*

#### *Diabetic neuropathy*

Is one of the most prevalent DM complications, caused by durative hyperglycemia, leading to nerve desolation, diverse of sensory, motor, and autonomous symptoms. It can be divided according to the affected nerve fiber: like the sensory, motor, and autonomic, causing the heart, gastrointestinal tract, and urinary system to lose functionality (Figure 1).<sup>3</sup>



**Figure 1: Pathogenesis of diabetic neuropathy (DN).**

The most common type is peripheral diabetic neuropathy (PDN), described as distal symmetric polyneuropathy. Its symptoms include tingling, burning and numbness in the feet and hands. In severe cases, it may lead to motor dysfunction, muscle atrophy, and amputations.<sup>4</sup>

**Global burden and public health impact**

Diabetic neuropathy plays a significant role in the overall burden of disease globally. It is common in diabetic patients with a range between around 28-50% at some point in their lives.<sup>3</sup> WHO reported that an impressive amount of the global healthcare spending can be attributed to diabetes complications.<sup>1</sup> Research indicates that the lengthier a person has diabetes the more the chances of neuropathy occurrence.<sup>4</sup> Depending on the type, DN may have physical, psychological and social impact on public health.<sup>4</sup>

**Rationale for the review and objectives**

There is necessity of a summarized knowledge on the aspects of the disease, including the causes and management methods. It is intended to offer an in-depth discussion of the prevalence rates of diabetic neuropathy, clinical presentation the condition has, and the most recent evidence-based approaches to the diagnosis and management. This review aims to offer an in-depth grasp of the epidemiology of diabetic neuropathy, including global and regional prevalence rates. And also address the most recent developments in the screening, diagnostic and management of diabetic neuropathy.

**PREVALENCE OF DIABETIC NEUROPATHY**

**Global and regional prevalence rates**

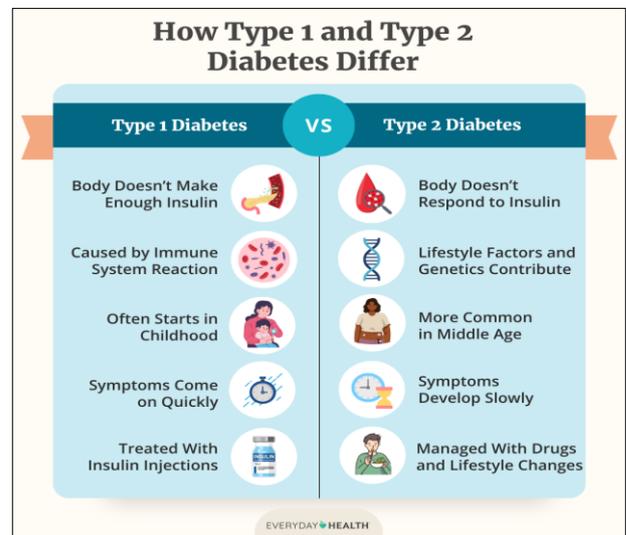
Diabetic neuropathy (DN) is believed to affect about 28-50 per cent of the total population with diabetes worldwide.<sup>6</sup> The prevalence rates of diabetic neuropathy are lower in high-income countries where diabetic care and management of the disease are more effective, unlike low-

and middle-income countries where the overall quality of diabetic care and management are poor.<sup>7</sup>

Surveys conducted recently demonstrate that diabetic neuropathy is a problem primarily demanded in distinct parts of the globe where diabetes burden is high including Asia, Middle East, and Sub-Saharan Africa. There have been reports that over 70 percent of people with diabetes can have some form of neuropathy, particularly when diabetes has not been controlled properly over a long time.<sup>8</sup>

**Prevalence by type of diabetes (type 1 versus type 2)**

The prevalence of diabetic neuropathy depends on the type of diabetes. Research proposes that about 50% of persons having diabetes type 2 will create neuropathy to a degree in the time journey of 10-20 years since being diagnosed (Figure 2).<sup>9</sup>



**Figure 2: Type 1 versus type 2 diabetes.**

In type 1 diabetes, the complication may occur, especially in patients with long histories of diabetes and frequent poor glycemic control.<sup>6</sup>

**Trends over time**

The incidence of diabetes has doubled as compared to incidences of 30 years ago and this has also contributed to an increase in the incidence of diabetic neuropathy.<sup>10</sup>

Aging, increasing prevalence of type 2 diabetes, and younger age of persons with diabetes due to lifestyle change are among other causes that have contributed to increasing the prevalence of diabetic neuropathy.<sup>11</sup>

The higher prevalence of diabetic neuropathy is not limited to developing countries only, but also in more developed states as USA and Europe. In the United States, nearly one-third of diabetics feel some form of neuropathy.<sup>12</sup>

Similarly, in Europe, diabetic neuropathy is estimated to occur in approximately 25-30% of individuals with Type 2 diabetes.<sup>13</sup>

### **Prevalence risk factor**

Studies have confirmed that the longer the person lives with diabetes, the more the risk of neuropathy, particularly those who do not respond best at maintaining glycemic status.<sup>10</sup> Boulton et al in 2018 has established that, over a 10-year span, approximately 20 and 50% of individuals with type 1 and type 2 diabetes will develop diabetic neuropathy, respectively.

Poorly controlled blood sugar is associated with increased risks of nerve damage because hyperglycemia catalyzes increased production of advanced glycation end products (AGEs) that promote inflammation and oxidative stress in nerve cells.<sup>6,14</sup> Evidence shows that tight glycemic control could reduce the incidence and progression of diabetic neuropathy.<sup>13</sup>

Other lifestyle complexities such as obesity, inactive lifestyles, and smoking are also very prevailing aspects that induce the onset of diabetic neuropathy. Obesity is a well-known health risk to the development of type 2 diabetes, by increasing the metabolic burden on the body.<sup>11</sup> Dyslipidemia and hypertension play a role in enhancing the risk of diabetes.<sup>3</sup>

## **SCREENING AND DIAGNOSTIC APPROACHES**

### **Screening recommendations**

#### *Guidelines by ADA, IDF, and WHO*

The American Diabetes Association (ADA) recommends all patients with type 1 diabetes should be screened against diabetic neuropathy five years after being diagnosed with diabetes.<sup>15</sup> Type 2 diabetes screening can be carried during diagnosis and with periodical repetitions.<sup>16</sup>

The international diabetes federation (IDF) also suggests that all diabetic patient should be subjected to clinical examination in order to identify the diabetic neuropathy.<sup>17</sup> Similarly, the WHO has urged extreme screening within regions with a prevalent population of diabetes.<sup>18</sup>

#### *Timing and frequency of screening*

The period and time of screening against diabetic neuropathy is based on quite a number of factors which include the type of diabetes, the age at which the diabetes was detected and the general health status of the patient.

The initial screening of diabetic neuropathy should be carried out within 5 years of diabetes development by type 1 diabetics. Screening can be done at the time of diabetes detection in people with type 2 diabetes and then annually, to monitor the presence of signs of neuropathy.<sup>19</sup>

### **Diagnostic modalities**

#### *Clinical assessment and history-taking*

Detailed clinical examination is the first step in diagnosing diabetic neuropathy. The initial process of healthcare providers is history of a patient. The characteristic symptoms of diabetic neuropathy include pain, paresthesia, numbness, and weakness, and the history must contain the assessment of patient lifestyle, comorbidities, and medications that can affect nerve functions.<sup>13</sup>

Risk factors including hypertension, dyslipidemia, and smoking, should be evaluated.<sup>20</sup>

#### *Physical examination*

Physical examination is an essential part in the diagnosis of diabetic neuropathy. The main objectives are to evaluate the sensory, motor and autonomic functions.

#### *Monofilament testing*

One of the most common and readily available diagnostic tools is monofilament. The test focuses on the sensitivity of the patient to the light tactile touch, and the presence of the patient witnessing the monofilament is a signal of sensory loss.<sup>21</sup> ADA encourages monofilament testing since it is easy and useful to detect patients with a risk of foot ulcers and other complications.<sup>15</sup>

#### *Vibration perception (tuning fork)*

Another test to determine sensory ability in diabetic neuropathy is through vibration perception. Using tuning fork test, a vibration is applied over bony prominences of the patient (ankle or knee) and his accuracy of perceiving the vibration will be examined. Dullness or loss of sensation of vibration is a common symptom of peripheral neuropathy.<sup>13</sup>

#### *Temperature and pinprick sensation*

Temperature sensation and pinprick sensation can also be used to determine sensory functioning. It is possible to test change in temperature by using cotton wool or alcohol pad all over the body to check how the patient responds to temperature changes or checking the response to sharp stimulus by using a pinprick test.

With diabetic neuropathy, the patients can display impaired or lack of feeling of temperature and pain.<sup>21</sup>

#### *Quantitative sensory testing*

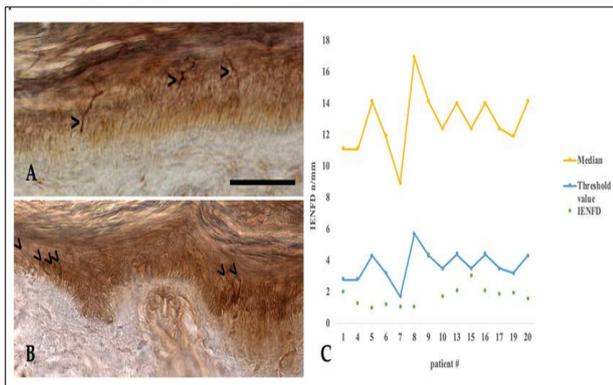
Quantitative sensory testing (QST) is a higher level of diagnostic modality which measures the level of sensory threshold to some stimuli some of which are temperature, pressure, and vibration.<sup>22</sup>

*Nerve conduction studies*

The gold standard diagnostic test of diabetic neuropathy, by nerve conduction studies (NCS). NCS measure the electrical impulses speed and level of amplitudes traveling down a nerve and is used to provide details on the integrity of motor and sensory nerve.<sup>16</sup>

*Skin biopsy and intraepidermal nerve fiber density (IENFD)*

One emerging technique is the use of skin biopsy and measuring the intraepidermal nerve fiber density (IENFD) which gives a clue about the small nerve fibers that are mostly affected by the diabetic neuropathy (Figure 3).<sup>23</sup>



**Figure 3: Intraepidermal nerve fiber density (IENFD), and immunohistochemical.**

*Emerging diagnostic tools*

*Corneal confocal microscopy (CCM)*

CCM is a new non-invasive diagnostic tool and features high-resolution imaging technology to assess the corneal nerve fibers. The site of exposure to the cornea is specifically well adapted to nerve damage in patients with diabetic neuropathy because of the exceptional permeability and the numerous nerve fibers.<sup>24</sup>

*Novel biomarkers*

Research is in progress to identify new biomarkers that might be useful in the diagnosis of diabetic neuropathy. Some of the biomarkers studied to identify neuropathy early and forecast the disease progression include nerve growth factor (NGF), advanced glycation end products (AGEs), and various inflammatory cytokines.<sup>25</sup>

*Limitations and challenges in diagnosis*

Despite the presence of a large number of diagnostic tools, there are various problems in the diagnosis of diabetic neuropathy. The first constriction is the lack of a single, distinctive test capable of detecting any form of neuropathy. Nerve conduction tests combined with skin

biopsy are still highly sensitive; however, these tests are not always available and the required equipment may need specialized equipment and expertise.<sup>26</sup>

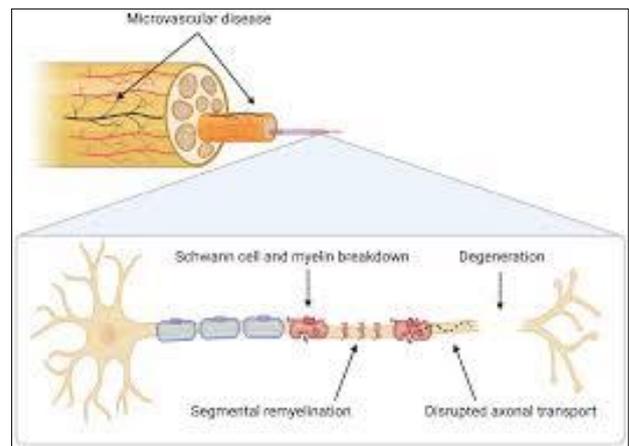
A further complication is the asymptomatic characteristics of diabetic neuropathy in its early stages. The condition cannot be detected easily because of the lack of perceived symptoms in many early neuropathy patients.<sup>16</sup>

**CLINICAL SYMPTOMS AND PHENOTYPES**

*Common presentations*

*Peripheral sensory neuropathy (distal symmetric polyneuropathy)*

The most prevalent form of diabetic neuropathy is peripheral sensory neuropathy or distal symmetric polyneuropathy (DSP). The condition mainly targets the sensory nerves in hands and feet which causes symptoms like tingling, burning and numbness and it also makes feel pain changes and temperature change less (Figure 4).<sup>27</sup>



**Figure 4: Pathogenesis of distal symmetrical polyneuropathy in diabetes.**

Loss of protective sensation, a typical feature of distal symmetric polyneuropathy, makes it more susceptible to injuries and infections that the patient might be unaware.<sup>28</sup> Sensory losses to light touch, vibration and temperature is also considered to be a key diagnostic characteristic of DSP, commonly in the toes and soles of the feet and often diagnosed through monofilament testing and tuning fork tests.<sup>16</sup>

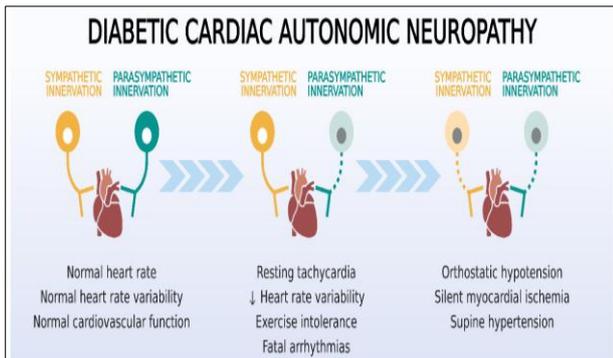
*Motor symptoms*

The motor symptoms in diabetic neuropathy involve muscle weakness, atrophy, and decreased coordination, which are the outcomes of degeneration of the motor nerves that drive muscle activity.<sup>29</sup> Foot drag on walking is a typical form of motor neuropathy of the brain afflicting diabetic patients because foot dragging could result when patients are unable to lift the foot.<sup>16</sup> There can also be

muscle wasting, particularly in the muscles of the thigh; the resulting condition is called diabetic amyotrophy, and is typified by intense pain and a gradual weakening of the targeted muscles.<sup>20</sup>

*Autonomic neuropathy*

Autonomic neuropathy (AN) affects the autonomic nervous system, which regulates such unconscious body functions as the heart rate, blood pressure, digestion process, and temperature control (Figure 5).<sup>30</sup>



**Figure 5: Diabetes-induced cardiac autonomic neuropathy.**

Gastrointestinal complications can be also a result of autonomic neuropathy: gastroparesis when the stomach empties too slowly which can lead to nausea, bloating, and inability to digest food, bladder dysfunction, urinary retention or incontinence or sexual dysfunction such as erectile dysfunction in men and vaginal dryness in women.<sup>16</sup>

*Less common presentations*

*Focal and multifocal neuropathies*

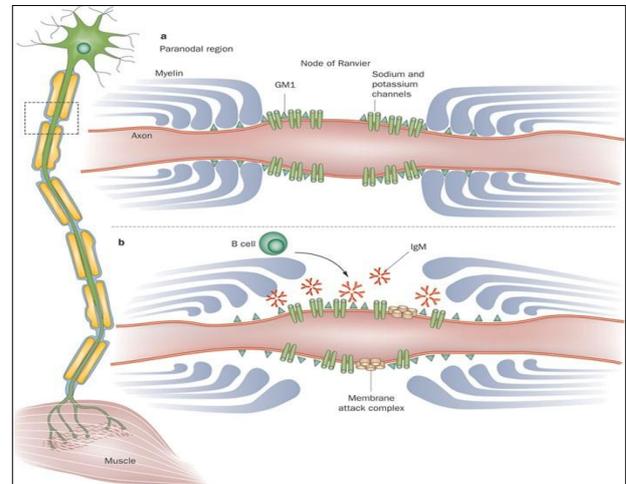
Focal neuropathy describes an acute outbreak of neuropathy in one nerve or a collection of nerves that commonly affects cranial, cervical, or lumbosacral nerves. In contrast to more prevalent distal symmetric polyneuropathy, focal neuropathies frequently involve discrete areas of the body and may result in localized pain, weakness, or disability (Figure 6).<sup>20</sup>

Multifocal neuropathies involve more than one nerve or nerve root damage, frequently in dissimilar body locations. These are not prevalent but can be highly disabling, as they involve impairment of several parts of the body. Multifocal neuropathies, which often involve the lower limbs and may cause muscle weakness, pain and even foot deformities including the Charcot foot.<sup>29</sup>

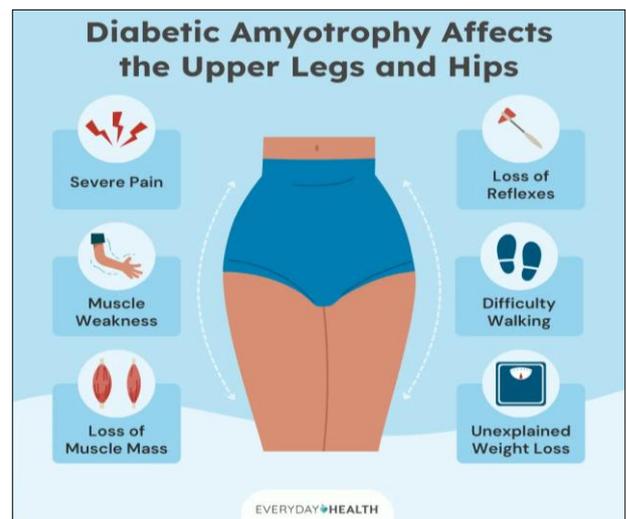
*Diabetic amyotrophy*

Diabetic amyotrophy is a lesser prevalent and intense motor neuropathy manifested by diabetic patients who

have type 2 diabetes. Despite a frequent acute and accelerated onset, diabetic amyotrophy introduces patients to severe pain that can easily be confused with arthritis or hip fractures (Figure 7).<sup>20</sup>



**Figure 6: Multifocal motor neuropathy.**



**Figure 7: Diabetic amyotrophy.**

*Cranial neuropathies*

Cranial neuropathies, though not a common result of diabetic neuropathy, may include the destruction of the cranial nerves, leading to facial pain, eyesight impairment, or swallowing difficulties.<sup>16</sup>

Despite being generally self-limiting, cranial neuropathies may be a sequela of diabetes and cause meaningful discomfort and suffering to the affected patient.<sup>31</sup>

*Natural history and development*

Diabetic neuropathy usually has mild symptoms, numbness, tingling or pain which at the initial phases are either ignored or attributed to other factors.<sup>29</sup>

Neuropathy can stabilize or even improve by optimal glycemic control and lifestyle changes in some instances. Nevertheless, nerve damage that has already taken place does not lend itself to recovery, and the focus of treatment becomes symptom management and avoidance of further complications.<sup>32</sup>

## COMPLICATIONS OF DIABETIC NEUROPATHY

DN may result in various types of complications, which affect the quality of life, resulting in significant morbidity and mortality. Such complications occur as a result of the gradual destruction of the peripheral nervous system along with the autonomous one, following the long-term hyperglycemia and the resultant metabolic imbalances.

### *Foot ulcers and infections*

Examples of the most frequent and incapacitating diabetic neuropathy complications include foot ulcers and infections. These usually occur as a result of no protective feeling in the feet, and develops when the sensory nerves have been damaged.<sup>33</sup> These ulcers, just as they advance, become harder to treat and are at risk of infection; infection, in turn, can be aggravated by poor circulation, a characteristic symptom of diabetes.<sup>34</sup>

Foot ulcers tend to be on weight-bearing locations of the feet (the heel or the balls of feet) and may cause serious complications, including cellulitis, osteomyelitis, and sepsis.<sup>35</sup> Further complicating the healing process is peripheral arterial disease (PAD) which slows down the movement of crucial nutrients and oxygen to the area.<sup>36</sup>

### *Amputations*

Amputations are a serious outcome of diabetic neuropathy and usually is the outcome of developing non-healing foot ulcers or infections. Diabetic neuropathy promotes the risk of amputation in a number of ways. First, individuals cannot detect the injuries or infection in the feet, since they will be without sensation. Second, it is less obvious since the co-occurrence of neuropathy and PAD significantly contributes to the development of severe infection since insufficient blood flow makes it more difficult to cope with bacterial infection and enhances the development of tissue necrosis.<sup>35,37</sup>

Amputations occur much more frequently in diabetic patients than the average population, and it is estimated that patients with diabetes face a 15-20-fold higher risk of amputation.<sup>3</sup> As a matter of fact, diabetic neuropathy is the most frequent cause of non-traumatic amputations of lower-limbs internationally.<sup>38</sup>

### *Balance problems and falls*

Motor and sensory neuropathies lead to poor proprioception and coordination, which is essential during balance. The ability to feel the impact of the ground under

the foot is also impacted by sensory neuropathy, and is therefore critical in terms of picking up small changes in the location and preventing falls.<sup>29</sup>

Balance issues among individuals with diabetic neuropathy are associated with injury, fractures of the bones, and admissions. The fear of falling also contributes to the risk since patients may become less mobile and engage in fewer physical activities.<sup>32</sup>

### *Cardiovascular autonomic neuropathy and mortality*

Cardiovascular autonomic neuropathy (CAN) is the most common and severe form of autonomic neuropathy that concerns the blood vessels and the heart. It is a result of the damage to the autonomic nerves.<sup>27</sup>

The autonomous control of the heart rate limit may entail disturbed responses to stress, exercise, and postural maneuvers such as lack of sensitivity to increase in heart rate or decrease in blood pressure during standing and exercise. It may cause dizziness, fainting, and the increased risk of falls.<sup>30</sup> In addition, the risks of heart and vascular pathology and other unfavorable results are significantly increased among individuals with diabetes with CAN.<sup>32</sup>

### *Gastrointestinal, genitourinary, and sudomotor dysfunction*

Autonomic neuropathy can cause multiple organ systems to be involved like the gastrointestinal (GI), genitourinary, and sudomotor. The gastroparesis phenomenon is the most common manifestation of gastrointestinal dysfunction in diabetic neuropathy.<sup>32</sup> Gastroparesis can severely impact the quality of life and nutrition, also the movement of the stomach can be delayed causing the regulation of the blood glucose to be unpredictable.<sup>16</sup>

Genitourinary dysfunction follows diabetic neuropathy, which presents itself in urinary retention, urinary incontinence and bladder activities.<sup>16</sup> A sudomotor dysfunction, can cause abnormal sweating patterns, that can lead to problems with temperature management.<sup>36</sup>

### *Impact on quality of life and mental health*

The consequences of diabetic neuropathy are both physically impairing and a pattern of overwhelming significance on an emotional wellbeing and overall attitude of existence.<sup>33</sup> The condition of fear of falling can lead to the reduction of physical activity, consequently, to the further strengthening of feelings of depression and helplessness.<sup>35</sup>

Moreover, economic strain of diabetic neuropathy, including healthcare financial costs, costs of the medication, and potential loss of earnings can also be further sources of mental and emotional distress to the individual, and their families.<sup>16</sup>

## EVIDENCE-BASED MANAGEMENT STRATEGIES

DN needs a holistic approach to minimize its symptoms, hamper its development, and enhance quality of life. Diabetic neuropathy can be treated, pharmacologically and non-pharmacologically. The following section discusses evidence-based techniques of managing diabetic neuropathy including glycemic control measures, drug therapies, non-drug measures, and how autonomic neuropathies are handled.

### **Glycaemic control**

#### *Intensive versus standard glycaemic control*

The focus of diabetic neuropathy management is glycemic control. Its main aim is to decrease hyperglycemia as it is the factor that occurs and leads to an onset and further development of neuropathy.<sup>39</sup> Blood glucose intensive glycemic control intervention has been found to delay and arrest the development of diabetic neuropathy in both type 1 and type 2 type of diabetes.<sup>40</sup> In type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) and outcome proved that the risk of developing neuropathy is much reduced by tight glycemic control.<sup>16</sup>

Not every patient can receive intensive glycemic control, especially those who are older, have complications, or exhibit hypoglycemia unawareness.<sup>41</sup>

#### *Impact on neuropathy progression*

The correlation of glycemic control and neuropathy development is well-studied. Strict glycemic control has the benefit of slowing nerve parenchymal dysfunction.<sup>16</sup> Glycemic control alone cannot resolve nerve damage after it has occurred but plays a crucial role in preventing additional damage.<sup>41</sup>

### **Pharmacological management**

#### *Pain management*

Pain management is one of the most significant components of managing diabetic neuropathy because pain is one of the most incapacitating symptoms of the burden. Several classes of drugs are usually applied to treat neuropathic pain; these include the anticonvulsants, antidepressants, and topical agents.<sup>42</sup>

#### *Anticonvulsants (Pregabalin, Gabapentin)*

The use of anticonvulsant medications, particularly pregabalin and gabapentin, is widely used in the management of diabetic neuropathy because of neuropathic pain. Such drugs exert a moderating effect on the release of excitable neurotransmitters to transmit pain and stabilize nerve action.<sup>26</sup>

#### *Antidepressants (duloxetine, amitriptyline)*

Antidepressants at a specific stage serotonin-norepinephrine reuptake inhibitors (SNRI) like Duloxetine and tricyclic antidepressants (TCA) like Amitriptyline are also used to treat the neuropathic pain of pain.<sup>43</sup> Its application is occasionally combined with such side effects as sedation and anticholinergic effects and may thus be restricted with elderly patients.<sup>41</sup>

#### *Topical agents*

Local pain relief Capsaicin cream and lidocaine patches are often applied topically to relieve neuropathic pain.<sup>40</sup> The use of lidocaine patches in pain management provides local analgesia by inhibiting the passage of pain impulses through sodium channels.<sup>26</sup>

#### *Opioids (last-resort considerations)*

Opioids are seen as an end-of-line treatment in the management of pain associated with diabetic neuropathy due to the risks of addiction, tolerance, and a plethora of side effects. Although opioids may be useful in treating intense neuropathic pain, they should never be taken except in cases when all other remedies have been tried and are ineffective.<sup>41</sup>

#### *Disease-modifying treatments under investigation*

Beyond symptom treatment, disease-modifying therapies that could pause or repair the underlying nerve damage caused by diabetic neuropathy are actively being studied. There is interest in agents that may prevent or reverse neuropathy by targeting the polyol pathway such as aldose reductase inhibitors.<sup>16</sup>

### **Non-pharmacological interventions**

#### *Lifestyle modifications*

Non-pharmacological interventions are vital in the management of diabetic neuropathy through lifestyle changes, such as exercise, diet, and smoking cessation.<sup>44</sup>

#### *Exercise*

One of the best ways of treating diabetic neuropathy is exercise. Exercises increase blood flow in the legs, and decrease the manifestations of neuropathy.<sup>29</sup> Aerobic exercise, strength, and balance training improve mobility, pain, and functional autonomy.<sup>16</sup> And have a beneficial effect on glycemic control, to the slowdown neuropathy progression.<sup>20</sup>

#### *Diet*

Dietary modifications are important in the management of diabetes and diabetic neuropathy. To address the metabolic health of individuals with diabetes, people are expected to

pursue large dietary trends that include a high fiber-low glycemic index, healthful fat, protein diet.<sup>43</sup>

Fruits and vegetables contain antioxidants and can reversal of the oxidative stress that contributes to nerve damage.<sup>32</sup>

#### *Smoking cessation*

The adverse vascular consequences of smoking place it as a primary risk factor to the occurrence and severity of diabetic neuropathy.<sup>26</sup>

#### *Psychological and supportive therapies*

Psychological management of the patients with diabetic neuropathy would be crucial since a patient may become depressed, anxious and will have social isolation (CBT).<sup>33</sup>

#### *Complementary and alternative therapies (with evidence base)*

Acupuncture, massage, and herbal treatments, among other complementary and alternative treatments have risen as new ways of handling diabetic neuropathy.<sup>32</sup> Moreover, some herbal supplements, including alpha-lipoic acid and evening primrose oil, are found to have antioxidant and anti-inflammatory properties.<sup>43</sup>

#### **Management of autonomic neuropathies**

##### *Cardiovascular*

Cardiovascular autonomic neuropathy (CAN) is a threat of diabetic neuropathy that affects the work of the heart rate, blood pressure, and blood vessels. Management of CAN involves blood pressure management and reduced risk of cardiovascular events.<sup>16</sup>

##### *Gastrointestinal*

Most gastrointestinal abnormalities of diabetic neuropathy occur via gastroparesis. To manage gastroparesis, dietary interventions include low-fat diets and small meals with increased frequency.<sup>45</sup> Gastrointestinal function can also be assisted through prokinetic drugs, e.g., metoclopramide.<sup>26</sup>

##### *Genitourinary*

UTI, incontinence, urinary retention, and erectile dysfunction are part of the genitourinary dysfunction associated with diabetic neuropathy, so management of these conditions may help improving the cases.<sup>16</sup>

##### *Sudomotor*

Sudomotor dysfunction is a failure to sweat, which can cause heat intolerance and dryness of the skin. Lifestyle

interventions to manage sudomotor dysfunction involve exposure to cool surroundings and light clothing.<sup>45</sup>

#### **EMERGING THERAPIES AND FUTURE DIRECTIONS**

Over the past years, major breakthroughs have been achieved in terms of exploring new pharmacological agents, regenerative therapies, neuroprotective strategies and wearable technology. These treatments are potential sources of a better prognosis in diabetic neuropathy.<sup>46</sup>

##### *Novel pharmacological agents*

One type of medication that could prove effective is aldose reductase inhibitors (ARIs) which target the polyol pathway.<sup>47</sup>

Another emerging group of drugs is the use of neurotrophic factors. These proteins, which include nerve growth factor (NGF) and the glial cell-derived neurotrophic factor (GDNF), promote the development, growth and differentiation of neurons.<sup>41</sup>

##### *Regenerative therapies (stem cells, gene therapy)*

Regenerative therapies represent a move away from simple symptom management towards nerve tissue recovery and nerve regeneration. Stem cell therapy has also proved to be a potential treatment option in diabetic neuropathy, in its nerve regeneration methods.<sup>48,49</sup>

Gene therapy is another area of research investigation with high potential in the treatment of diabetic neuropathy.<sup>6</sup>

##### *Neuroprotective strategies*

Neuroprotectant approaches attempt to prevent or retard nerve injury through diabetic neuropathy by addressing the causative factors of neurodegeneration, including inflammation, oxidative stress, and dysfunction of mitochondria.<sup>12</sup>

Dysfunction of mitochondrial is another important issue in pathogenesis of diabetic neuropathy. Recent studies have concentrated on trying to come up with treatment methods which approach the functioning of the mitochondria and improve the mitochondrial biogenesis so that there is a nerve safety.<sup>16</sup>

In diabetic neuropathy, there are cytokines like the tumor necrosis factor-alpha (TNF-alpha) and interleukin-1B (IL-1B) causing breakdown of nerve fibers. Blocking of these inflammatory pathways would retard the progression of nerve damage and reduce pain.<sup>47</sup>

##### *Advances in wearable technology and digital monitoring*

Wearable technology and digital monitoring are revolutionizing the potential ways diabetes neuropathy can

be treated. The availability of wearable technologies, such as continuous glucose monitors (CGMs) and activity trackers can enable the assessment of glucose levels and activity levels continuously.<sup>50</sup> Moreover, things like movements and strides and other subjective issues can be monitored using activity trackers that could help such patients with diabetic neuropathy maintain their activity levels.<sup>51</sup>

## CONCLUSION

To summarize, DN is a debilitating and multifactorial diabetes complication that profoundly impacts the quality of life of the patients, and leads to the risk of serious complications including foot ulcers, amputations, and cardiovascular problems. The primary study findings are the significance of early interventions based on frequent screening and strict glycemic control to retard the course of the disease. Nevertheless, the existing knowledge still has gaps, especially in the processes behind neuropathy and the inefficiency of existing treatments. Clinical practice ought to focus on personalized care including a combination of pharmacological and non-pharmacological measures, besides also managing comorbidities such as hypertension and obesity. Additional research on new drugs, regenerative medicine, neuroprotective mechanisms to change the disease process, new wearable technologies, and real-time monitoring to manage and monitor the condition are also needed.

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