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CURRENT TRENDS AND FUTURE DIRECTIONS IN DIABETIC NEUROPATHY

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1. ABSTRACT

Diabetic Neuropathy is a type of nerve damage, which refers to the main cause with its discovery along with some brief history that includes long-short details about the origin and founder of the disease. Various types of Neuropathies are included which focuses on diabetic neuropathy in which further the symptoms and its signs are mentioned. The five stages of this disease gradually develop more symptoms and one can have one type or more than one type of neuropathy. Further the treatment with detail knowledge of prevention is added. A hint of new treatment and its approval along with it's working and conclusion is added for more and effective study of this topic. Changes in human behaviour and lifestyle over the last century have resulted in a dramatic increase in the incidence of diabetes worldwide. Neuropathy is a common and costly complication of both type 1 and type 2 diabetes. The prevalence of neuropathy is estimated to be about 8% in newly diagnosed patients and greater than 50% in patients with long-standing disease. There are two main types of diabetic neuropathies, named as sensorimotor and autonomic neuropathies. Sensorimotor neuropathy is marked by pain, paranesthesia and sensory loss, and autonomic neuropathy may contribute to myocardial infarction, malignant arrhythmia and sudden death.

2. INTRODUCTION

What is diabetic neuropathy?

Diabetic neuropathy is a type of nerve damage that can occur if you have diabetes. High blood sugar (glucose) can injure nerves throughout the body. Diabetic neuropathy most often damages nerves in the legs and feet.

Different types of nerve damage cause different symptoms. Symptoms can range from pain and numbness in your feet to problems with the functions of your internal organs, such as your heart and bladder.

Diabetic neuropathy is a serious diabetes complication that may affect as many as 50% of people with diabetes. But you can often prevent diabetic neuropathy or slow its progress with consistent blood sugar management and a healthy lifestyle.

Figure 1: woman checking blood glucose level.

Who is most likely to get diabetic neuropathy?

If you have diabetes, your chance of developing nerve damage caused by diabetes increases the older you get and the longer you have diabetes. Managing your diabetes is an important part of preventing health problems such as diabetic neuropathy.

Managing your diabetes is an important part of preventing health problems such as diabetic neuropathy.

You are also more likely to develop nerve damage if you have diabetes and

- Are overweight.
- Have high blood pressure.
- Have high cholesterol.
- Have advanced kidney disease.
- Drink too many alcoholic drinks.
- Smoke.

Research also suggests that certain genes may make people more likely to develop diabetic neuropathy.

 # What causes diabetic neuropathy?

Neuropathy is one of the long-term **complications** of diabetes.

Over time, high blood glucose (sugar) levels can damage the small blood vessels that supply the nerves in your body.

This stops essential nutrients reaching the nerves. As a result, the nerve fibers can become damaged, and they may disappear. This can cause problems in many different parts of your body, depending on the type of nerve affected.

 # How common is diabetic neuropathy?

Although different types of diabetic neuropathy can affect people who have diabetes, research suggests that up to one-half of people with diabetes have peripheral neuropathy.

More than 30 percent of people with diabetes have autonomic neuropathy.

The most common type of focal neuropathy is carpal tunnel syndrome *NIH external link*, in which a nerve in your wrist is compressed.

Although less than 10 percent of people with diabetes feel symptoms of carpal tunnel syndrome, about 25 percent of people with diabetes have some nerve compression at the wrist.[2]

Other focal neuropathies and proximal neuropathy are less common.

 # Who discovered diabetic neuropathy?

It was not until the 18th century that Western physicians started studying diabetes and its complications. Eventually, the works of the 19th century (de Calvi, Pavy) clearly established the link between diabetes mellitus and diabetic neuropathies. The epochal discovery of insulin in 1921 triggered a wide interest and more systematic approach to research of diabetic complications, leading to S. Fagerberger's conclusion that many of them share the underlying microvascular pathology.

3. AIM: Current Trends And Future Directions In Diabetic Neuropathy.

Figure 2: De Calvi Pavy who discovered Diabetic Neuropathy.

4. HISTORY OF DIABETIC NEUROPATHY

The clinical features of diabetes have been recognized over a thousand years ago.

However, the first description of diabetic neuropathy was by Rollo in 1798 when he described pain and paresthesia in the legs of a diabetic patient.

Pavy described a 'pain of a burning and unremitting nature' in 1887, Diabetic neuropathy by causing an insensitive neuropathic foot causes considerable morbidity.

In UK, 2% of all diabetic patients had active foot ulcers and 2.5% were amputees.

Neuropathy is a significant cause of diabetic foot lesions.

The primary mechanism initiating nerve damage is hyperglycemia. There is good evidence that achieving normoglycemia can reduce the frequency of neuropathy. A diverse array of

clinical presentation is possible as different nerve fiber populations may be affected in different manners.

The acute neuropathies generally recover while the chronic neuropathies follow an insidious irreversible course. In research studies, at least one measure each from clinical symptoms, examinations, electrodiagnostic studies, quantitative sensory testing should be performed in order to evaluate diabetic neuropathy.

However, clinical examination alone may suffice for identification of the high risk foot in clinical practice. Therapy for painful neuropathy is with tricyclic antidepressants, phenytoin, carbamazepine and topical capsaicin.

Diabetic neuropathy is a cause of significant morbidity in terms of amputations and prolonged hospitalization.

Early diagnosis and institution of appropriate preventive care can prevent many of these problems.

This may include measures varying from simple foot care advice to provision of special footwear.

Hence a multidisciplinary team approach to screening for neuropathy and preventing foot lesions is an essential component of any diabetes.

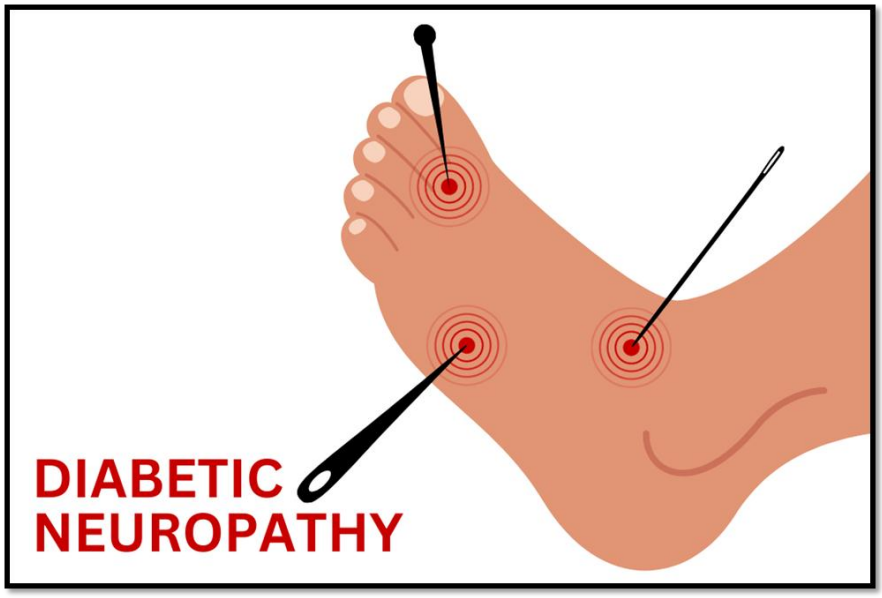

Figure 3: High risk foot in clinical practice.

5. TYPES OF DIABETIC NEUROPATHY

Four main types of neuropathy can impact on the nervous system, including:

- **Peripheral symmetric neuropathy:** This affects the feet and hands. It is the most common form of diabetic neuropathy.
- **Autonomic neuropathy:** This occurs in the nerves that control involuntary functions of the body, such as digestion, urination, or heart rate.
- **Thoracic and lumbar root, or proximal, neuropathy**: This damages nerves along a specific distribution in the body, such as the chest wall or legs.
- **Mononeuropathies**: These can affect any individual nerve.

Peripheral neuropathy

Peripheral neuropathy that affects the feet can make it difficult for a person to stand and walk. It can increase the risk of falling.

When a person cannot feel heat, cold or injury, this can lead to new problems.

For example, a blister on the foot can become ulcerated because the person did not feel pain in the early stages. As the infection progresses, gangrene can develop.

Eventually, amputation may be necessary.

Autonomic neuropathy

Autonomic neuropathy (**AN** or **AAN**) is a form of polyneuropathy that affects the non-voluntary, non-sensory nervous system (i.e., the autonomic nervous system), affecting mostly the internal organs such as the bladder muscles, the cardiovascular system, the digestive tract, and the genital organs.

These nerves are not under a person's conscious control and function automatically.

Autonomic nerve fibers form large collections in the thorax, abdomen, and pelvis outside the spinal cord.

They have connections with the spinal cord and ultimately the brain, however.

Most commonly autonomic neuropathy is seen in persons with long-standing diabetes mellitus type 1 and 2.

In most—but not all—cases, autonomic neuropathy occurs alongside other forms of neuropathy, such as sensory neuropathy.

Autonomic neuropathy is one cause of malfunction of the autonomic nervous system (referred to as dysautonomia), but not the only one; some conditions affecting the brain or spinal cord also may cause autonomic dysfunction, such as multiple system atrophy, and therefore, may cause similar symptoms to autonomic neuropathy.

 # Proximal neuropathy (diabetic polyradiculopathy)

This type of neuropathy often affects nerves in the thighs, hips, buttocks or legs. It can also affect the abdominal and chest area. Symptoms are usually on one side of the body, but may spread to the other side.

 # Mononeuropathy (focal neuropathy)

Mononeuropathy refers to damage to a single, specific nerve. The nerve may be in the face, torso, arm or leg.

 # Other types

There are many types of neuropathies.

Proximal neuropathy can lead to pain in the lower body, often on one side, and weakness in the legs. Symptoms of focal neuropathy can vary widely, depending on the nerve affected. Focal neuropathy and cranial neuropathy can both lead to visual disturbances, such as double vision. People with diabetic neuropathy often do not realize they have it until the symptoms are more advanced.

6. SYMPTOMS OF DIABETIC NEUROPATH:

 # Peripheral neuropathy

1. Numbness or reduced ability to feel pain or temperature changes.
2. Tingling or burning feeling.
3. Sharp pains or cramps.
4. Muscle weakness.
5. Extreme sensitivity to touch — for some people, even a bedsheet's weight can be painful.
6. Serious foot problems, such as ulcers, infections, and bone and joint damage.

 # Autonomic neuropathy

1. A lack of awareness that blood sugar levels are low (hypoglycemia unawareness)

2. Drops in blood pressure when rising from sitting or lying down that may cause dizziness or fainting (orthostatic hypotension)
3. Bladder or bowel problems.
4. Slow stomach emptying (gastroparesis), causing nausea, vomiting and sensation of fullness and loss of appetite.
5. Difficulty swallowing.
6. Changes in the way the eyes adjust from light to dark or far to near
7. Increased or decreased sweating.
8. Problems with sexual response, such as vaginal dryness in women and erectile dysfunction in men.

 # Proximal neuropathy (diabetic polyradiculopathy)

1. Severe pain in the buttock, hip or thigh.
2. Weak and shrinking thigh muscles.
3. Difficulty rising from a sitting position.
4. Chest or abdominal wall pain.

 # Mononeuropathy (focal neuropathy)

1. Difficulty focusing or double vision.
2. Paralysis on one side of the face.
3. Numbness or tingling in the hand or fingers.
4. Weakness in the hand that may result in dropping things.
5. Pain in the shin or foot.
6. Weakness causing difficulty lifting the front part of the foot (foot drop)
7. Pain in the front of the thigh.

7. CLASSIFICATION

A. Diffuse neuropathy

Distal Symmetrical Peripheral Neuropathy

- Primarily small-fiber neuropathy
- Primarily large-fiber neuropathy
- Mixed small- and large-fiber neuropathy (most common)

Autonomic Cardiovascular

- Reduced Heart Rate Variability

- Resting tachycardia
- Orthostatic hypotension
- Sudden death (malignant arrhythmia)

Gastrointestinal

- Diabetic gastroparesis (gastropathy)
- Diabetic enteropathy (diarrhea)
- Colonic hypomotility (constipation)

Urogenital

- Diabetic cystopathy (neurogenic bladder)
- Erectile dysfunction
- Female sexual dysfunction

Sudomotor dysfunction

- Distal hypohydrosis/anhidrosis,
- Gustatory sweating

Hypoglycemia unawareness

Abnormal pupillary function.

B. Mononeuropathy (mononeuritis multiplex) (atypical forms)

Isolated cranial or peripheral nerve (e.g., Cranial Nerve III, ulnar, median, femoral, peroneal) Mononeuritis multiplex (if confluent may resemble polyneuropathy).

C. Radiculopathy or polyradiculopathy: (atypical forms)

Radiculoplexus neuropathy (a.k.a. lumbosacral polyradiculopathy, proximal motor amyotrophy) Thoracic radiculopathy.

D. Nondiabetic neuropathies

Common in diabetes

Pressure palsies

Chronic inflammatory demyelinating polyneuropathy

Radiculoplexus neuropathy

Acute painful small-fiber neuropathies (treatment-induced)

8. DIAGNOSIS

To diagnose diabetic neuropathy, you will need a physical exam and tests. During the physical exam, your healthcare provider may check your muscle strength and reflexes. Your provider may also check how your nerves respond to:

- Position.
- Vibration.
- Temperature.
- Light touch.

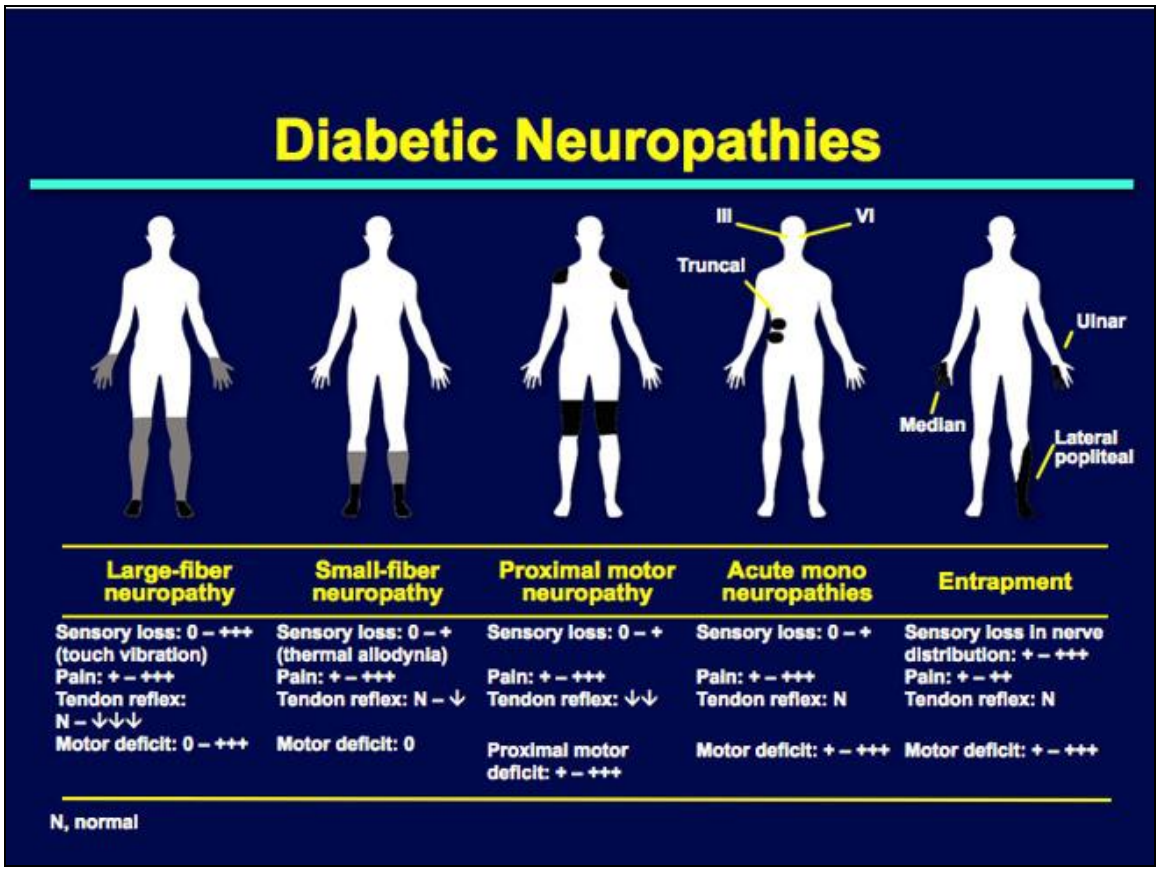

Figure 4: Staging.

You may also have tests, such as

- Ultrasound to check for problems with the bladder.
- X-rays and other tests to check for stomach problems.
- Electrocardiogram (ECG) to look for changes in your heart's rhythm.
- Nerve conduction studies to check flow of electrical current through a nerve.
- Electromyography (EMG) to see how muscles respond to electrical impulses.
- Nerve biopsy to remove a sample of nerve for testing.

Other possible causes of Neuropathy includes

- Autoimmune disorders (e.g. Guillain-Barré syndrome, systemic lupus erythematosus, and rheumatoid arthritis)
- Inherited disorders (e.g. Charcot-Marie-Tooth Disease)
- Infections (e.g. chicken pox, HIV, hepatitis c and Lyme disease)
- Alcoholism
- Vitamin deficiency (e.g. vitamins B1, B6, B12, vitamin E and niacin)
- Trauma
- Toxins (e.g. heavy metals and industrial chemicals)
- Medications (e.g. some antibiotics or chemotherapy)
- Hypothyroidism
- Vascular disorders.

9. STAGING SCALE OF DIBETIC NEUROPATHY

A doctor may break down the stages of kidney disease, depending on the GFR, which also represents the percentage of effective kidney function.

Stage 1: Kidney damage present but normal kidney function and a GFR of 90% or above.

Stage 2: Kidney damage with some loss of function and a GFR of 60–89%.

Stage 3: Mild to severe loss of function and a GFR of 30–59%.

Stage 4: Severe loss of function and GFR of 15–29%.

Stage 5: Kidney failure and a GFR of under 15%.

- N0 - No neuropathy.
- N1a - Signs but no symptoms of neuropathy.
- N2a - Symptomatic mild diabetic polyneuropathy; sensory, motor, or autonomic symptoms; patient able to heel walk.
- N2b - Severe symptomatic diabetic polyneuropathy, and patient unable to heel walk.
- N3 - Disabling diabetic polyneuropathy.

10. DIBETIC NEUROPATHY TREATMENT

There are four main components of diabetic neuropathy treatment:

- Control of blood sugar levels
- Lifestyle interventions, specifically diet and exercise
- Care for the feet to prevent complications

- Control of pain caused by neuropathy

Although there is no cure for diabetic neuropathy, use of these treatments can improve painful symptoms and prevent complications.

Control blood sugar levels — An important treatment for diabetic neuropathy is to control blood sugar levels.

Symptoms of pain and burning may improve when blood glucose sugar improves.

If blood sugar levels are not adequately controlled with the current treatment regimen, a different regimen may be recommended.

- For people with type 1 diabetes, this may mean taking more frequent insulin injections or using an insulin pump.
- For people with type 2 diabetes, this may mean taking an additional oral medication or starting insulin injections.

Diet and exercise in type 2 diabetes — The American Diabetes Association recommends lifestyle interventions, specifically diet and exercise, as the first line in treating diabetic neuropathy in type 2 diabetes.

The goal is to achieve and maintain a normal body weight with a nutrient-dense diet low in saturated fats and high in whole grains, vegetables, fruits, and lean meats. Exercise should consist of at least 150 minutes of moderate-to-vigorous physical activity, such as brisk walking, at least three times per week.

Muscle-strengthening activities that involve all major muscle groups are recommended two or more days per week. Sedentary activities (eg, sitting at a desk) should be interrupted every 30 minutes by brief periods of standing, walking, or other physical activities.

Care for the feet — People with neuropathy do not always feel pain when there is a wound or injury on the foot. As a result, daily foot care is necessary to monitor for changes in the skin (such as cracks or wounds), which can increase the risk of infection. The American Diabetes Association recommends that people with diabetes have a comprehensive foot examination once per year and a visual examination of the feet at each visit (usually every three to four months). Foot examinations are described in detail separately.

Control pain — Neuropathic pain can be difficult to control and can seriously affect your quality of life. Neuropathic pain is often worse at night, seriously disrupting sleep.

Fortunately, only a small percentage of people with diabetic neuropathy experience pain. Pain resolves without treatment in some people over a period of weeks to months, especially if the episode of pain developed after a sudden change in health (eg, an episode of diabetic ketoacidosis, a significant weight loss, or a significant change in blood glucose control).

There are several medications that are useful for the treatment of diabetic neuropathy and have been approved by the US Food and Drug Administration (FDA), including duloxetine and pregabalin. Other medications are also useful, including tricyclic medications (eg, amitriptyline), gabapentin, tramadol, and alpha-lipoic acid.

Tricyclic antidepressants — There are several tricyclic antidepressants available for the treatment of chronic pain, including amitriptyline, nortriptyline, and desipramine.

Clinical trials have shown that tricyclic antidepressant drugs are effective for patients with painful diabetic neuropathy. The dose of tricyclic antidepressants used to treat diabetic neuropathy is typically much lower than that used to treat depression.

These medications are usually taken at bedtime, starting with a low dose and gradually increasing over a period of several weeks. People with heart disease should not take amitriptyline or nortriptyline.

Tricyclic medications can be taken with gabapentin and pregabalin but should not be taken with duloxetine. Side effects can include dry mouth, sleepiness, dizziness, and constipation.

Duloxetine — Duloxetine is an antidepressant that is often effective in relieving pain caused by diabetic neuropathy. In short-term clinical trials, duloxetine was more effective than placebo.

However, the long-term effectiveness and safety of duloxetine for diabetic neuropathy is uncertain.

There are no trials comparing duloxetine with other drugs for the treatment of diabetic polyneuropathy.

Duloxetine is usually taken by mouth once per day on a full stomach, although in some cases it is taken twice per day. It should not be taken by people who take other antidepressant medications.

Side effects can include nausea, sleepiness, dizziness, decreased appetite, and constipation.

Gabapentin — Gabapentin is an anti-seizure medication. It is usually taken by mouth three times per day. Side effects can include dizziness and confusion.

Gabapentin can be taken with a tricyclic antidepressant or duloxetine. In some cases, gabapentin can be taken at night to prevent pain during sleep.

Pregabalin — Pregabalin is an anti-seizure medication, similar to gabapentin. Pregabalin is taken by mouth, starting at bedtime at a low dose and then gradually increasing to three times per day over a period of several weeks. Side effects can include dizziness, sleepiness, confusion, swelling in the feet and ankles, and weight gain.

It may be possible to become addicted to pregabalin, and changes in dosing should be monitored carefully.

Pregabalin can be taken with duloxetine or tricyclic antidepressants but not with gabapentin.

Anesthetic drugs — Lidocaine is an anesthetic drug that may be recommended if other treatments have not improved pain. It is applied to the painful area in a patch, which slowly releases the medication over time.

Patches should stay in place for no more than 12 hours in any 24-hour period.

Alpha-lipoic acid — Alpha-lipoic acid (ALA) is an antioxidant medication. Several short-term trials showed that it was helpful in relieving pain caused by diabetic neuropathy. Thus, ALA may be recommended to people with diabetic neuropathy who do not improve with or who cannot tolerate other treatments.

However, longer-term studies are still needed to confirm its safety and effectiveness.

In the United States, ALA is available without a prescription as a dietary supplement. It is usually taken by mouth once per day.

Drug Name	Dosing Range	Adverse Effects	Special Considerations
Gabapentin	300-3,600 mg daily in 3 divided doses	Dizziness, somnolence, GI upset, peripheral edema	Dosage adjustments in renal impairment
Pregabalin	50-300 mg daily in 2 or 3 divided doses	Dizziness, somnolence, weight gain, peripheral edema	Dosage adjustments in renal impairment
Tricyclic antidepressants (amitriptyline, desipramine, nortriptyline)	10-150 mg daily; usually dosed at bedtime due to drowsiness	Dry mouth, blurred vision, constipation	First choice in patients with underlying insomnia or depression; avoid in patients with cardiac conduction abnormalities and in those at risk of suicide; anticholinergic effects are worse with amitriptyline use; avoid in elderly due to risk of falls
Duloxetine	60-120 mg daily	Nausea, somnolence, dizziness, decreased appetite, constipation	Avoid in hepatic impairment; avoid in CrCl <30 mL/min
Oxycodone	*Immediate release:* 10-30 mg every 4 h *Controlled release:* 10-30 mg every 12 h	Constipation, somnolence, dizziness, nausea, vomiting, itchiness	Risk of addiction, physical dependence, and tolerance
Tramadol	50-100 mg every 4-6 h (max dose 400 mg daily)	Constipation, somnolence, dizziness, nausea, vomiting, itchiness	Risk of addiction, physical dependence, and tolerance; avoid use in those with seizures
Morphine	*Immediate release:* 10-30 mg every 4-6 h *Controlled release:* 15-30 mg every 12-24 h	Constipation, somnolence, dizziness, nausea, vomiting, itchiness	Risk of addiction, physical dependence, and tolerance
Lidocaine	Apply patch to affected area; patch may remain in place up to 12 h; remove patch for 12 h	Skin irritation	Used as adjunct therapy to oral medications
Capsaicin	Apply topically to affected area 3-4 times daily	Stinging and burning sensation	Used as adjunct therapy to oral medications

CrCl: creatinine clearance; GI: gastrointestinal; max: maximum.
Source: References 4, 8, 12.

Figure 5: Drugs used in Diabetic Neuropathy.

11. PREVENTION OF DIBETIC NEUROPATHY

To lower your risk of developing diabetic nephropathy:

See your health care team regularly to manage diabetes. Keep appointments to check on how well you are managing your diabetes and to check for diabetic nephropathy and other complications. Your appointments might be yearly or more often.

Treat your diabetes. With good treatment of diabetes, you can keep your blood sugar levels in the target range as much as possible.

This may prevent or slow diabetic nephropathy.

Manage high blood pressure or other medical conditions. If you have high blood pressure or other conditions that raise your risk of kidney disease, work with your health care professional to control them.

Take medicines you get without a prescription only as directed. Read the labels on the pain relievers you take. This might include aspirin and nonsteroidal anti-inflammatory drugs, such as naproxen sodium (Aleve) and ibuprofen (Advil, Motrin IB, others).

For people with diabetic nephropathy, these types of pain relievers can lead to kidney damage.

Stay at a healthy weight. If you're at a healthy weight, work to stay that way by being physically active most days of the week. If you need to lose weight, talk with a member of your health care team about the best way for you to lose weight.

Don't smoke. Cigarette smoking can damage kidneys or make kidney damage worse.
If you're a smoker, talk to a member of your health care team about ways to quit.
Support groups, counselling and some medicines might help.

 # NEW TREATMENT IN DIBETIC NEUROPATHY

An extremely important recent FDA approval was just announced authorizing spinal cord stimulation (SCS) for the treatment of painful diabetic neuropathy. We expect this to help the lives of thousands. Dr. Winne's enthusiasm is apparent, as this new device may alleviate nerve pain more effectively and reliably than previous methods.

 # APPROVAL

Nevro Corp, a medical device company, received FDA approval for HFX, its Senza system for treating chronic pain associated with PDN. Approval was based on the system's demonstrated safety and efficacy in the SENZA-PDN trial published in JAMA Neurology.

It was shown that high-frequency, or 10 kHz, SCS is safe and effective for people suffering from extreme pain and for those whose medication does not provide the necessary relief. After a year, patients reported clear, sustained benefits–less pain, improved sleep, and better quality of daily life. This may mean that some patients can leave their mediations (and accompanying side effects) behind.

PDN can now be treated with stimulators, which Dr.Winne has been doing slightly in the past. As he tells us, "Now, painful diabetic, peripheral neuropathy has been studied and now approved to be treated with stimulators, which we've kind of been doing a little bit over the years, and I've been talking to various patients about doing it, but it's never been fully

approved. Not that we can't do it, not that Medicare wouldn't pay for it, but now they (*i.e.*, Medicare) definitely will." This is excellent news to patients who desperately need this treatment.

 # How It Works

Here's a quick summary of the device's ultimate goal: When you stick this wire in someone's back, you stimulate the spinal cord, and that inhibits their pain.

Delivering 10,000 electric pulses per second, HFX does not allow the painful sensation to be relayed up to the brain.

The use of HFX begins with a test. Before implantation, the wires are temporarily placed on the intended spot on the body and connected to an external control box. You can test it for one to two weeks in order to see how it feels and if you like it.

Unlike surgery, HFX is minimally invasive and totally reversible. If the pain improves within a few years, patients can have the system removed. HFX may be a viable option for people with non-operative conditions or who are too ill for surgery. "If an 85-year-old lady who is not a good surgical candidate, either because her disease is too extensive or she's too ill, that spinal cord stimulator is certainly a lot less than basic procedure and option for her," explains Dr. Winne. Richard P. Winne. The HFX spinal cord stimulation device was approved by the FDA with a specific indication for treating painful diabetic Neuropathy (PDN) in 2023.

Figure 6: Dr. Richard P Winnie discovered the HFX spinal cord stimulation device in the year 2023.

12. RISK FACTOR FOR DIBETIC NEUROPATHY

Globally, Diabetes mellitus (DM) is one of the foremost non-communicable diseases that currently affects 463 million adults (20–79 years); a total that is set to reach 700 million by 2045.

In Saudi Arabia, Al Rubeaan et al found that the prevalence of diabetes among Saudis aged ≥30 years was 25.4% with 40.3% being unaware of their disease. Type 2 diabetes mellitus (T2DM) is a disorder of glucose metabolism that involves the regulation of insulin secretion, insulin sensitivity, gluconeogenesis, and glucose uptake at the cellular level. Dysregulation of one or more of these previously mentioned processes due to genetic or environmental factors can result in altering glucose metabolism causing DM.

The enormous impact of diabetes, being secondary to its high prevalence, is also significantly related to the high frequency of chronic complications that can affect any organ system in the body. In most societies worldwide, diabetes is considered to be the leading cause of vision loss, amputation, renal dialysis, and high mortality secondary to coronary artery disease (CAD), thereby making it one of the world's most important causes of disability and economic growth loss.

Diabetes risk factors in those the Gulf Cooperation Council (GCC) countries including Saudi Arabia are almost similar in which overweight and obesity are considered to be the most prominent risk factor. It is estimated that the prevalence of overweight ranges between 25% and 50% and the prevalence of obesity ranges between 10% and 50% and is found to be relatively higher in women showing an increase with age.[5] It has been reported that neuropathy is a common complication of diabetes, affecting up to 50% of patients.

The most common diabetes-related microvascular complications are diabetic peripheral neuropathy (DPN) and diabetic autonomic neuropathy, and they can result in a significant increase in morbidity, such as chronic pain, foot ulcerations, amputations, and mortality.

In a recently published preliminary report, it was found that subjects with DPN had higher body mass index and waist circumference than subjects without DPN.

Also, the association of markers of inflammation with microvascular and cardiovascular disease among diabetes has been previously reported. This is because inflammatory activity is increased in individuals with diabetes.

Besides, as reported by Pinzur et al there is no doubt that foot ulcers strongly correlated with morbid obesity. Previous studies showed a significant correlation between the early development of DPN and BMI.

There is a scarcity of data regarding the association between risk factors and neuropathy among T2DM patients in Saudi Arabia; therefore, we conducted this study in a trial to fill the literature gap in this regard.

13. CONCLUSION

The results herein showed a high prevalence of diabetic neuropathy among T2DM patients in Saudi Arabia. This study identified severe hyperglycemia and hyperlipidemia were significantly associated with increased risks of diabetic neuropathy among T2DM patients with longer duration of diabetes.

This suggested the measures aimed at the prevention, control and treatment of DPN development and emphasizes the importance of implementing a health program to educate diabetic patients about the development and prevention of macro vascular complications in T2DM patients with longer duration of diabetes.

Sensorimotor and cardiovascular neuropathies are common in diabetic patients. Apart from strict glycaemic control, no further therapeutic approach exists in the prevention of this phenomenon. The reasons that only some patients with nerve lesions develop neuropathic pain are still unknown. Risk factors such as age, gender, pain intensity before and after the lesion, and emotional and cognitive features indicate that there are multiple factors other than the nerve lesion itself that contribute to the manifestation of chronic pain.

Diagnosis and symptomatic treatment are essential for these patients as painful sensorimotor neuropathies are associated with poor quality of life and autonomic neuropathies are associated with increased cardiovascular mortality.

Intensive diabetes therapy, intensive multifactorial cardiovascular risk reduction and lifestyle intervention are recommended in patients with CAN. The symptomatic treatment of sensory symptoms includes TCAs, SNRIs, gabapentin, pregabalin and opioids. Other treatment strategies are not so effective.

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14. REFRENCES

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