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A REVIEW ON DIABETIC NEUROPATHY

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Abstract:
Diabetic neuropathy is a complication of diabetes that effects the nerves and it is the most common neuropathy in industrialized countries, and it is associated with a wide range of clinical manifestations. When we have diabetes, high blood sugar levels can cause damage tothe nerves in your body over time. This damage can lead to various symptoms and problems.diabetic neuropathy can also effects the nerves that control your internal organs, leading to problems with digestion, sexual function, and even the functioning of your and blood vessels explores the diverse range of medications aimed at managing symptoms and slowing disease progression, highlighting the effectiveness of different drug classes, including analgesics, anticonvulsants, and antidepressants, in alleviating neuropathic pain.
Keywords: Diabetes mellitus, hyperglycemia, diabetic neuropathy, peripheral neuropathy.

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INTRODUCTION:

Diabetic neuropathy is the most common neuropathy in industrialized countries, and it is associated with a wide range 0f clinical manifestations. The vast majority of patients with clinical diabetic. The vast majority of patients with clinical diabetic neuropathy have a distal symmetrical form of the disorder that progresses following a fiber length dependent pattern, with sensory and autonomic manifestations predominating. Diabetes affect approximately 246 million people worldwide, it is estimated that 20-30 million people worldwide are affected by symptomatic diabetic neuropathy. Growing rates of obesity and the associated increase in theprevalence of type 2 diabetes could cause these figures to double by the year 2030. The prevalence of diabetic neuropathy also increases with time and poor glycemic control, and severe diabetic polyneuropathy can develop in young adults within a few months after the onset of type 1 diabetes if the diabetes is poorly controlled.

DIABETES:

Diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), which leads over time to serious damage to the heart, blood vessels, eyes, kidneys and nerves. The most common is type 2 diabetes, usually in adults, which occurs when the body becomes resistant to insulin or doesn't make enough insulin. In the past 3 decades the prevalence of type 2 diabetes has risen dramatically in countries of all income levels. Type 1 diabetes, once known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition in which the pancreas produces little or no insulin by itself. For people living with diabetes, access to affordable treatment, including insulin, is critical to their survival. There is a globally agreed target to halt the rise in diabetes and obesity by 2025.

TYPES OF DIABETES

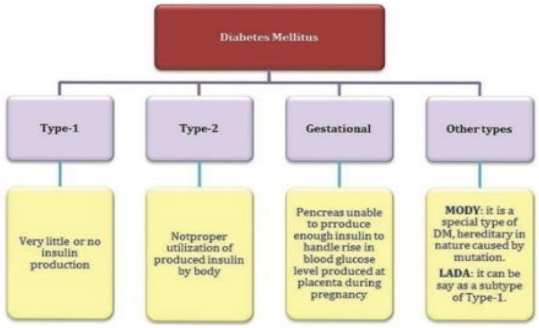

Fig: 01 types of diabetes

TYPE 1 DIABETES:

The body does not produce insulin. Some people may refer to this type as insulin-dependentdiabetes, juvenile diabetes, or early-onset diabetes. People usually develop type 1 diabetes before their 40th year, often in early adulthood or teenage years.Type 1 diabetes is nowherenear as common as type 2 diabetes. Approximately 10% of all diabetes cases are type 1. Patients with type 1 diabetes will need to take insulin injections for the rest of their life. They must also ensure proper blood-glucose levels by carrying out regular blood tests and following a specialdiet.

TYPE 2 DIABETES:

The body does not produce enough insulin for proper function, or the cells in the body do notreact to insulin (insulin resistance). Approximately 90% of all cases of diabetes worldwide are type 2. Somepeople may be able to control their type 2 diabetes symptoms by losing weight, following a healthy diet, doing plenty of exercise, and monitoring their blood glucose levels. However, type 2 diabetes is typically a progressive disease.

GESTATIONAL DIABETES:

This type affects females during pregnancy. Some women have very high levels of glucose in their blood, and their bodies are unable to produce enough insulin to transport all of the glucose into their cells, resulting in progressively rising levels of glucose. Diagnosis of gestational diabetes is made during pregnancy. The majority of gestational diabetes patients can controltheir diabetes with exercise and diet. Between 10 to 20 percent of them will need to take some kind of blood-glucose controlling medications. Undiagnosed or uncontrolled gestational diabetes can raise the risk of complications during childbirth.

OTHER TYPES OF DIABETES:

MODY: Maturity-onset diabetes of the young (MODY) is the name given to a collection of different types of inherited forms of diabetes that usually develop in adolescence or early adulthood. MODY was given that the name in the past because it acted more like adult type of diabetes (Type 2 Diabetes) but was found in young people.

LADA: Latent autoimmune diabetes in adults (LADA) is a type of diabetes that starts in adulthood and slowly gets worse over time. Like type 1 diabetes, LADA happens when the pancreas stops making insulin. That's usually because an autoimmune process is damaging cells in the pancreas. But unlike type 1 diabetes, in LADA, the

process happens slowly. So people who have LADA often don't need to take insulin right away.

DIABETIC NEUROPATHY:

Diabetic neuropathy (DN) is a most common complication of diabetes mellitus, caused by low response of blood flow and Hyperglycaemia leading to Nerve damage. Diabetic Neuropathy affect nearly 66% of type1 and 59% of type2 diabetic patient and 20% of all diabetic patients suffer from chronic neuropathic pain (NP). International Association for the study of pain (IASP) defined Diabetic Neuropathy-"Pain initiated or caused by a primary lesion or dysfunction in the nervous system". Diabetic neuropathy characterizes a dynamic fluctuation between neuronal falling apart and regeneration. Neuropathies are a family of nerve disorders caused by diabetes. It is regular and unbearable Microvascular complication of both type 1 and type 2 diabetes. Up to 50% of every single one patient with diabetes arise neuropathy and the popularity of heartrending neuropathy ranges from 10 to 20% of patients with diabetes. Diabetic patient over time can develop, nerve impairment throughout the body. Path physiology of Neuropathy including elevated hexamine shunt, aldose reductase activation, decreased nerve myoinositol content, activation of protein kinase C, activation of poly ADPribose polymerase, impaired insulin/C peptide action, and formation of advanced glycation end products (AGEs). Nerve destruction produces symptoms such as pain, tingling, or numbness-loss of feeling-in the hands, arms, feet and legs. The maximum rate of neuropathy in those cases in which, people had diabetes for at least 25year.

CLASSIFICATION OF DIABETIC NEUROPATHY

Chronic Hyperglycaemia can affect any part of the nervous system. Sensory, autonomic, and motor neurons of the peripheral nervous system are vulnerable to the adverse effects of Hyperglycaemia in diabetic patients. Various classifications for diabetic neuropathy have been proposed in recent years. Nevertheless, there is no universally accepted classification. Some of the suggested classifications are based on etiology, pathological or topographical features, and a classification based upon the clinical manifestation is most useful in clinical practice.

Classification of diabetic neuropathy according to clinical presentation is shown in table: 01

A. GENERALIZED NEUROPATHIES
Distal symmetric polyneuropathy Autonomic neuropathy (cardiovascular, gastrointestinal, urogenital, sudomotor) Acute sensory neuropathy
B. FOCAL NEUROPATHIES
Isolated Cranial neuropathies (e.g., Cranial nerves III, VII, VI, IV) Isolated peripheral nerve neuropathies (e.g., ulnar, median, femoral, peroneal nerve) Entrapment neuropathies (e.g., Carpal tunnel syndrome, Ulnar neuropathy) Other mononeuropathies (Phrenic mononeuropathy) Mononeuropathy multiplex
C. MULTIFOCAL NEUROPATHIES
Diabetic radiculoplexus neuropathies lumbosacral radiculoplexus neuropathy thoracic radiculoneuropathy cervical radiculoplexus neuropathy

A. GENERALIZED NEUROPATHY

A generalized type of neuropathy, known as polyneuropathy, is the most common type of diabetic neuropathy. Other types of neuropathy can also affect people with diabetes but will not be discussed here. Signs and symptoms of diabetic neuropathy include loss of sensationand/or burning pain in the feet.

❖ DISTAL SYMMETRIC POLYNEUROPATHY:

Distal symmetric polyneuropathy is the most common form among diabetic neuropathies accounting for about 75% of the diabetic neuropathies. The disease's course is chronic and progressive. DSPN predisposes diabetic patients to variable degrees of pain, motor dysfunction, postural instability, gait abnormalities, nerve palsies, ulcers, burns, infections, gangrene, and Charcot's disease. DSPN is the most common cause of foot ulceration and lower extremity amputation. It is also a major contributor to falls and fractures. Neuropathic pain can cause physical and psychosocial impairment, disability, and reduced health-related quality of life. A minority number of patients are seen with anorexia, depression, and weight loss.

SYMPTOMS OF DISTAL SYMMETRIC POLYNEUROPATHY:

In most cases symptoms are distal, symmetrical, and increase at night. Paranesthesia's and hyperesthesia's are frequent. Patients often describe symptoms as prickling, deep aching, sharp, and burning.

❖ AUTONOMIC NEUROPATHY:

Autonomic neuropathy affects the nerves that control the heart, regulate blood pressure, and control blood glucose levels. Autonomic neuropathy also affects other internal organs, causing problems with digestion, respiratory function, urination, sexual response, and vision. In addition, the system that restores blood glucose levels to normal after a hypoglycemic episodemay be affected, resulting in loss of the warning symptoms of hypoglycemic.

SYMPTOMS OF AUTONOMIC NEUROPATHY:

- Loss of bladder control
- leading to infection or incontinence
- Dizziness
- light headedness or fainting because of a loss of control over blood pressure
- Diarrhoea
- constipation or incontinence related to nerve damage in the intestines or digestive tract
- Difficulty eating or swallowing.

❖ ACUTE SENSORY DIABETIC NEUROPATHY

Acute sensory diabetic neuropathy is a form of nerve damage that occurs suddenly in individuals with diabetes. Unlike the more common chronic neuropathies that develop over several years, this condition manifests with a rapid onset of symptoms, usually over a few days to weeks. It predominantly affects the sensory nerves, causing a range of distressing symptoms.

SYMPTOMS OF ACUTE SENSORY DIABETIC NEUROPATHY:

The hallmark of acute sensory diabetic neuropathy is severe sensory disturbances in the lower limbs, particularly the feet. Some of the common symptoms include:

- Intense Pain.
- Tingling and Numbness.
- Sensitivity to Touch.
- Muscle Weakness.

B. FOCAL NEUROPATHY

Focal neuropathy appears suddenly and affects specific nerves, most often in the head, torso,or leg. Focal neuropathy may cause, inability to focus the eye, double vision, aching behind one eye. Focal neuropathy is painful and unpredictable and occurs most often in older adultswith diabetes. However, it tends to improve by itself over weeks or months and does not cause long-term damage. People with diabetes also tend to develop nerve compressions, also calledentrapment syndromes. One of the most common is carpal tunnel syndrome, which causes numbness and tingling of the hand and sometimes muscle weakness or pain. Other nerves susceptible to entrapment may cause pain on the outside of the shin or the inside of the foot.

SYMPTOMS OF FOCAL NEUROPATHY:

- carpal tunnel syndrome, which causes pain, numbness, and tingling in your thumb, index finger, and middle finger, and sometimes weakness of your grip.
- Ulnar entrapment, which causes pain, numbness, and tingling in your little and ring fingers.

❖ ISOLATED CRANICAL NEUROPATHIES:

Nerves power your entire body, but those nerves can be damaged by injury or an illness such as diabetes. Neuropathy is a disorder that causes nerve damage and affects your ability to feel and move. Exactly how your body and your movement are affected depends on where in thebody the damaged

nerves are located. When nerves in the brain or brainstem are affected, it is called cranial neuropathy.
The cranial nerves are those that arise directly from your brain or brainstem and often affect areas like the face and eyes. Some of the different types of cranial neuropathies include:
Bell's palsy, Microvascular cranial nerve palsy, Third nerve palsy, Fourth nerve palsy, Sixth nerve palsy.

SYMPTOMS OF ISOLATED CRANICAL NEUROPATHIES:
Different types of neuropathies can cause different symptoms, based on which nerves are damaged and where they are located. Generally, neuropathies can cause:

- Pain
- A tingling sensation
- Numbness
- Skin that feels sensitive to the touch
- Weak or paralyzed muscles

❖ ISOLATED PERIPHERAL NERVE NEUROPATHEIS:
Peripheral neuropathy happens when the nerves that are located outside of the brain and spinal cord (peripheral nerves) are damaged. This condition often causes weakness, numbness, and pain, usually in the hands and feet. It also can affect other areas and body functions including digestion and urination. The peripheral nervous system sends information from the brain and spinal cord, also called the central nervous system, to the rest of the body through motor nerves. The peripheral nerves also send sensory information to the central nervous system through sensory nerves.

SYMPTOMS OF ISOLATED PERIPHERAL NERVE NEUROPATHEIS:
Symptoms depend on the type of nerves affected. Nerves are divided into:

- Sensory nerves that receive sensation, such as temperature, pain, vibration, or touch, from the skin.
- Motor nerves that control muscle movement.
- Autonomic nerves that control functions such as blood pressure, sweating, heart rate, digestion, and bladder function.

❖ ENTRAPMENT NEUROPATHIES:
Entrapment neuropathy is a condition in which a nerve becomes compressed, or entrapped, between two other structures in the body. Usually, the nerve is compressed between a ligament and a bone. Repetitive motion can cause the ligament and bone to press or rub against the nerve. Over time, this damages the myelin sheath, which is a layer of tissue that covers the outside of the nerve. The myelin sheath helps the nerve transmit electrical signals, so when it is damaged, the nerve can't function as well. The nerve's reduced ability to transmit signals causes symptoms of numbness, tingling, burning, or weakness in the fingers or other extremities.

SYMPTOMS OF ENTRAPMENT NEUROPATHIES:
The nerve's reduced ability to transmit signals causes symptoms of numbness, tingling, burning, or weakness in the fingers or other extremities. Although usually not serious, entrapment neuropathy can be painful and can seriously affect function if not treated.

❖ OTHER MONONEUROPATHIES:
Mono neuropathy is also called as phrenic neuropathy.The phrenic nerve provides the primary motor supply to the diaphragm, the major respiratory muscle. Phrenic nerve injury, such as may occur from cardiothoracic surgery, can lead to diaphragmatic paralysis or dysfunction. The presentation of phrenic nerve injury is non-specific, and the diagnosis may easily be missed.

SYMPTOMS OF OTHER MONONEUROPATHIES:
Symptoms that are including unexplained shortness of breath, recurrent pneumonia, anxiety, insomnia, morning headache, excessive daytime somnolence, fatigue, and difficulty weaning from mechanical ventilation.

❖ MONONEUROPATHY MULTIPLEX:
Mono neuropathy multiplex is a term used to describe a distinctive clinical presentation of progressive motor and sensory deficits in the distribution of specific peripheral nerves. MNM is essentially an asymmetrical, asynchronous sensory and motor peripheral neuropathy involving isolated damage to at least two separate limb or cranial nerves. Multiple nerves in random areas of the body can be affected simultaneously or sequentially. As the condition worsens, it becomes less multifocal and more symmetrical, mimicking distal dying-back symmetrical polyneuropathy.

SYMPTOMS OF MONONEUROPATHY MULTIPLEX:

- Loss of bladder or bowel control.
- Loss of sensation in one or more areas of the

body.
- Paralysis in one or more areas of the body.
- Tingling, burning, pain, or other abnormal sensations in one or more areas of the body.
- Weakness in one or more areas of the body.

C.MULTIFOCAL NEUROPATHIES:

Multifocal motor neuropathy is a progressive muscle disorder characterized by weakness in the hands, with differences from one side of the body to the other in the specific muscles involved. It affects men much more than women. The disorder is sometimes mistaken for amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. But unlike ALS, multifocal motor neuropathy is treatable. An early and accurate diagnosis allows individuals to recover quickly.

SYMPTOMS OF MULTIFOCAL NEUROPATHIES:

If you have MMN, you'll most likely notice the first symptoms in your hands and lower arms. Your muscles may feel weak and cramp up or twitch in a way you can't control. It may start in specific parts of the arm or hand, like the wrist or finger. Usually the symptoms are more severeon one side of your body. The disease may eventually affect your legs.

❖ DIABETIC RADICULOPLEXUS NEUROPATHIES:

The spectrum of diabetic Radiculoplexus neuropathies consists of three subtypes: lumbosacral, thoracic, and cervical radiculoplexusneuropathy. Radiculoplexus neuropathies share similar clinical, neurophysiological, and neuropathological characteristics can occur alone or in combination in people with diabetes. Painful unilateral or multiple asymmetrical neuropathies tend to occur in older patients with relatively mild or even unrecognized diabetes in radiculo plexus neuropathies pain followed by muscle weakness. Although pain is initially the worstsymptom, weakness and atrophy become the main problems.

SYMPTOMS OF DIABETIC RADICULOPLEXUS NEUROPATHIES:

A particular type of proximal diabetic neuropathy, lumbosacral radiculoplexus neuropathy (DLSRPN), presents with pelvic-femoral pain followed by weakness, beginning focally in the upper leg or thigh with spread to the contralateral limb, and variable weightloss.

❖ LUMBOSACRAL RADICULOPLEXUS NEUROPATHY:

Diabetic lumbosacral radiculoplexus neuropathy, also known as diabetic amyotrophic, is the most frequent subtype. It is a rare type of neuropathy affecting approximately 1% of middle-aged people with type 2 diabetes with mild impairment of glucose metabolism and absence of other microvascular complications. It usually begins abruptly and presents with severe, deep thigh pain, progressing to weakness and muscle atrophy. Symptoms present abruptly, unilaterally, and proximally. Lumbosacral radiculoplexus neuropathy is characterized by severe and often debilitating motor involvement manifesting with muscle weakness and atrophy.

SYMPTOMS OF LUMBOSACRAL RADICULOPLEXUS NEUROPATHY:

Lumbosacral radiculoplexus neuropathy is defined as (1) clinical symptoms of lower limb pain, weakness, and sensory loss in keeping with LRPN with neurologic examination findings beyond a single nerve or root distribution; (2) NCS/EMG in keeping with an axonal disorder of lumbosacral segments involving at least 2 nerves from at least 2.

❖ THORACIC RADICULONEUROPATHY:

Thoracic radiculopathy is a painful medical condition that affects both men and women alike. Pain, paresthesia, decreased sensation, and weakness are the major symptoms. Radiculopathy refers to the whole complex of symptoms that can be caused by irritation or compression of a nerve root in the spine.

SYMTOMS OF THORACIC RADICULO NEUROPATHY:

Pain is common with thoracic radiculopathy and can vary in location and intensity depending on the location and severity of the actual nerve irritation or injury the pain can be localized orpresent as:
- Scorching or shooting pain in the ribs, side, or abdomen
- Band-like pain
- Pain in the chest and torso

❖ CERVICAL RADICULOPLEXUS NEUROPATHY:

We therefore conclude that (i) diabetic cervical radiculoplexus neuropathy is a predominantly monophasic, upper limb diabetic neuropathy with pain followed by weakness and involves motor, sensory and autonomic fibres; (ii) the neuropathy begins focally and often evolves intoa multifocal or bilateral condition; (iii) the pathology of diabetic cervical radiculoplexus neuropathy demonstrates ischaemic injury often from microvasculitis; and (iv) diabetic cervical radiculoplexus neuropathy

shares many of the clinical and pathological features of diabetic lumbosacral radiculoplexus neuropathy, providing evidence that these conditions are best categorized together within the spectrum of diabetic radiculoplexus neuropathies.

SYMPTOMS OF CERVICAL RADICULOPLEXUS NEUROPATHY:

These illnesses usually present with abrupt onset of pain, followed by weakness and numbness that has unilateral or asymmetrical bilateral involvement often associated with weight loss. The pathogenesis of CRPN usually is ischemic nerve injury from microvasculitis.

EPIDEMIOLOGY OF DIABETIC NEUROPATHY:

Diabetic neuropathy is the most common neuropathy in resource abundant regions of the world.Prevalence is a function of disease duration, and a reasonable figure, based upon several large studies, is that approximately 50 percent of patients with diabetes will eventually develop neuropathy. In a landmark study, over 4400 patients with diabetes were serially evaluated over 25 years. Neuropathy was defined as decreased sensation in the feet and depressed or absent ankle reflexes. The onset of neuropathy correlated positively with the duration of diabetes mellitus and, by 25 years, 50 percent of patients had neuropathy. In a separate cross-sectional multicenter study of 6487 diabetic patients in the United Kingdom, the overall prevalence of diabetic neuropathy was 28.5 percent. There was a correlation with disease duration such that the prevalence reached 44 percent in patients between 70 and 79 years of age.

A population-based study of 329 adolescents with type 1 diabetes and 70 with type 2 diabetes found that the prevalence of diabetic polyneuropathy was significantly higher with type 2 compared with type 1 diabetes.

ETIOLOGY OF DIABETIC NEUROPATHY

The etiology of diabetic neuropathy, a common complication of diabetes, is multifactorial and not fully understood. It is believed to result from a combination of various factors, including:

- Hyperglycemia: Prolonged high blood sugar levels can damage the blood vessels thatsupply nerves with essential nutrients, leading to nerve damage.
- Advanced Glycation End Products (AGEs): Elevated glucose levels can lead to the formation of AGEs, which can accumulate in nerve tissues and contribute to nerve damage.
- Oxidative Stress: High blood sugar can increase oxidative stress in the body, damaging nerve cells and their supporting structures.
- Inflammation: Chronic inflammation in diabetes can also harm nerves and exacerbate neuropathic symptoms.
- Microvascular Changes: Diabetes can cause changes in the small blood vessels that supply nerves, reducing blood flow and nutrient delivery to nerve cells.
- Autoimmune Factors: Some researchers believe that autoimmune reactions may play a role in diabetic neuropathy.
- Genetic Predisposition: Genetics may make some individuals more susceptible to diabetic neuropathy.

The exact mechanisms and interactions of these factors in diabetic neuropathy are still anarea of active research, and the condition can manifest in different ways, including peripheral neuropathy, autonomic neuropathy, and other forms. Proper management of blood sugar levels, along with lifestyle changes and medications, is essential in preventing and managing diabetic neuropathy.

PATHOPHYSIOLOGY OF DIABETIC NEUROPATHY:

It is uncontrolled hi Severe early-onset polyneuropathy in insulin-dependent diabetes mellitus blood sugar damages nerves and interferes with their ability to send signals, leading to diabetic neuropathy. High blood sugar also weakens the walls of the small blood vessels (capillaries) that supply the nerves with oxygen and nutrients.

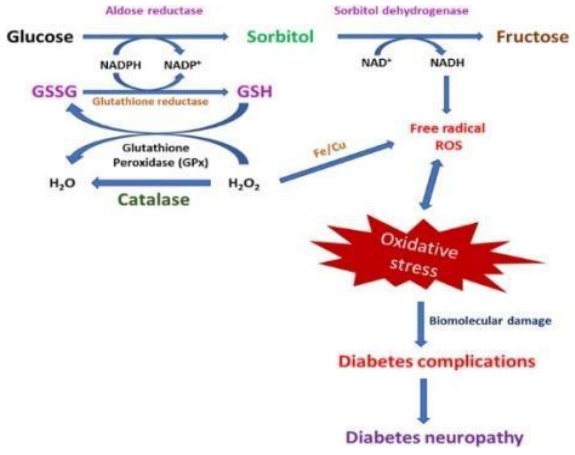

Fig: 02 pathophysiology of diabetic neuropathy

Insulin is the principle hormone that regulates the uptake of glucose from the blood into most cells of the body, especially liver, muscle, and adipose tissue. Therefore, deficiency of insulin or the insensitivity of its receptors plays a central role in

all forms of diabetes mellitus. The body obtains glucose from three main places: the intestinal absorption of food, the breakdown of glycogen, the storage form of glucose found in the liver and gluconeogenesis the generation of glucose from non-carbohydrate substrates in the body. Insulin plays a critical role in balancing glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen. Insulin is released into the blood by beta-cells (β-cells), found in the islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating.

RISK FACTORS OF DIABETIC NEUROPATHY:

The risk factors for diabetic peripheral neuropathy are the duration of diabetes, age, glycosylated haemoglobin 1c (HbA1c), diabetic retinopathy (DR), smoking, and body massIndex (BMI).

- **Poor blood sugar control:** Uncontrolled blood sugar increases the risk of every diabetes complication, including nerve damage.
- **Diabetes history:** The risk of diabetic neuropathy increases the longer a person has diabetes, especially if blood sugar isn't well controlled.
- **Kidney disease:** Diabetes can damage the kidneys. Kidney damage sends toxins into the blood, which can lead to nerve damage.
- **Being overweight:** Having a body mass index (BMI) of 25 or more may increase the risk of diabetic neuropathy.
- **Smoking:** Smoking narrows and hardens the arteries, reducing blood flow to the legs and feet. This makes it more difficult for wounds to heal and damagesthe peripheral nerves.

TABLE: 02 RISK FACTORS OF DIABETIC NEUROPATHY:

UNMODIFIABLE RISK FACTORS:
Advanced age Duration of diabetes Height
MODIFIABLE RISK FACTORS:
Poor glucose control[hdA1c,FPG]Obesity[BMI,weight] Abdominal obesity Dyslipidemia [high LDL,hypertriglyceridemia low HDL] Hypertension Smoking Heavy alcohol intake

COMPLICATIONS OF DIABETIC NEUROPATHY:

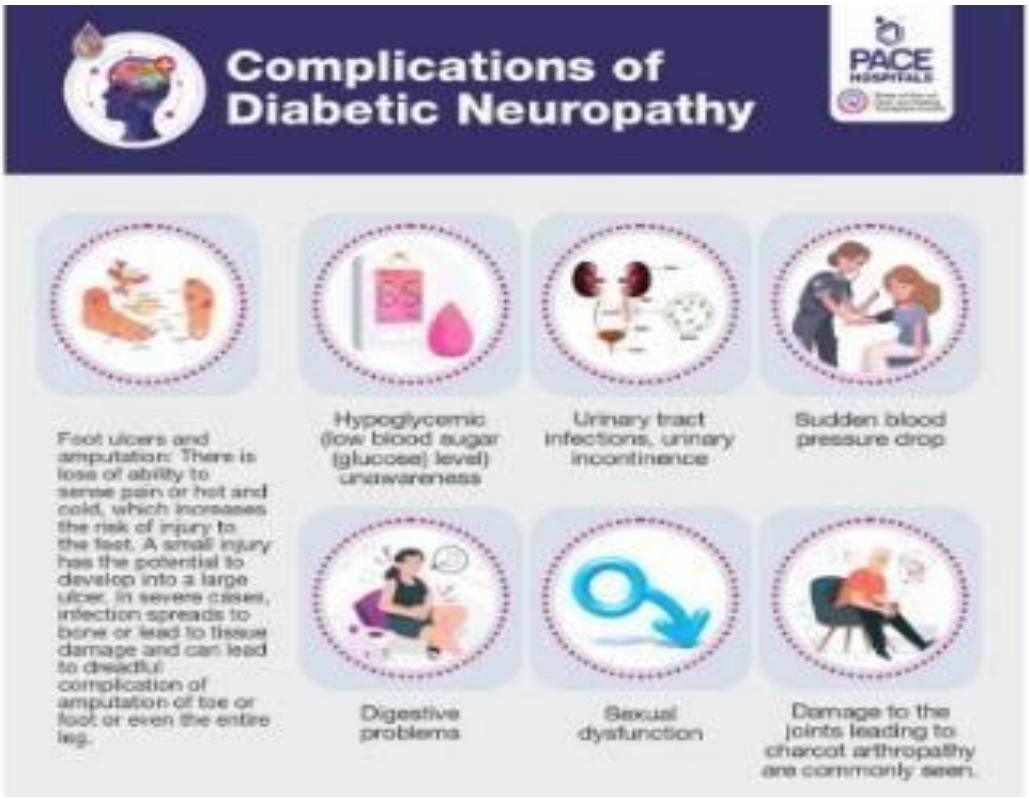

Fig: 3 complications of diabetic neuropathy

Diabetic neuropathy can cause a number of serious complications, including:

HYPOGIYCEMIA UNWARENESS**:** Blood sugar levels below 70 milligrams per deciliter (mg/dL) — 3.9 mill moles per liter (mmol/L) — usually cause shakiness, sweating and a fast heartbeat. But people who have autonomic neuropathy may not experience these warning signs.

LOSS OF TOE, FOOT or LEG: Nerve damage can cause a loss of feeling in the feet, so even minor cuts can turn into sores or ulcers without being noticed. In severe cases, an infection can spread to the bone or lead to tissue death. Removal (amputation) of a toe, foot or even part of the leg may be necessary.

URINARY TRACT INFECTIONS AND URINARY INCONTINENCE: If the nerves that controlthe bladder are damaged, the bladder may not empty completely when urinating. Bacteria can build up in the bladder and kidneys, damage causing urinary tract infections. Nerve can also affect the ability to feel the need to urinate or to control the muscles that release urine, leading to leakage (incontinence).

DIGESTIVE PROBLEMS: If nerve damage occurs in the digestive tract, constipation or diarrhea, or both are possible. Diabetes-related nerve damage can lead to gastroparesis, a condition in which the stomach empties too slowly or not at all. This can cause bloating and indigestion.

SUXUAL DYSFUNCTION: SHARP DROPS IN BLOOD PRESSURE: Damage to the nerves that control blood flow can affect the body's ability to adjust blood pressure. This can cause a sharp drop in pressure when standing after sitting or lying down, which may lead to lightheadednessand fainting.

Autonomic neuropathy often damages the nerves that affect the sex organs. Men may experience erectile dysfunction. Women may have difficulty with lubrication and arousal.

INCREASED OR DECREASED SWEATING: Nerve damage can disrupt how the sweat glands work and make it difficult for the body to control its temperature.

DIAGNOSIS OF DIABETIC NEUROPATHY:

Diabetic neuropathy is diagnosed by performing a physical exam and carefully reviewing your

symptoms and medical history.
Your health care provider typically checks your:

- Overall muscle strength and tone
- Tendon reflexes Sensitivity to touch, pain, temperature and vibration

Along with the physical exam, your health care provider may perform or order specific tests to help diagnose diabetic neuropathy, such as:

- FILAMENT TESTING: A soft nylon fiber (monofilament) is brushed over areas of your skin to test your sensitivity to touch.
- SENSORY TESTING: This non-invasive test is used to tell how your nerves respond to vibration and changes in temperature.
- NERVE CONDUCTION TESTING: This test measures how quickly the nerves in your arms and legs conduct electrical signals.
- ELECTROMYOGRAPHY: It isCalled needle testing, this test is often done along with nerve conduction studies. It measures electrical discharges produced in your muscles.
- AUTONOMIC TESTING: Special tests may be done to determine how your blood pressure changes while you are in different positions, and whether you're sweating is within the standard range.

MANAGEMENT OF DIABETIC NEUROPATHY:

There are the two of managements involved in diabetic neuropathy

1. Pharmacological management
2. Non pharmacological management

1. PHARMACOLOGICAL MANAGEMENT:

It is the management of symptoms through the use of medication. Pain modulation is a key treatment goal for diabetic peripheral neuropathy patients. Guidelines have recommended antidepressant, anticonvulsant, analgesic, and topical medications—both approved and off- label—to reduce pain in this population.

TABLE: 03 DRUG CHART FOR DIABETIC NEUROPATHY:

DRUG NAME	BRAND NAME	DOSEOF THE DRUG	INDICATION	ROUTE OF ADMINISTRATION
Amitriptyline	AMIFULL	25-100mg	Antidepressant	Oral
Desipramine	DESIPRAMINE HYDROCHLORIDE	10–25 mg	Antidepressant	Oral
Duloxetine (Cymbalta)	DUTOXIN	60mg	Antidepressant	Oral
Venlafaxine	VENLUSK	75-225mg	Antidepressant	Oral
Carbamazepine	MEZETOL	600mg	Anticonvulsant	Oral
Gabapentin	GABASIGN	900-3600mg	Anticonvulsant	Oral
Pregabalin (Lyrica)	NERVIG ESIC	150mg	Anticonvulsant	Oral
Valproate sodium	VALPORAX	500-1200mg	Anticonvulsant	Oral
Morphine sulfate (MS Contin)	MORPHINE SULPATE	15-30mg	Opioid analgesic	Oral &injection
Oxycodone CR (OxyContin)	OXYCODONE	120mg	Opioid analgesic	Oral
Dextromethorphan	DMR	40mg	Opioid analgesic	Oral (syrup)

AMITRIPTYLINE:
Mechanism of action: The mechanism of action of TCAs such as amitriptyline is unclear, but they are believed to inhibit the reuptake of serotonin and norepinephrine. In addition, they are known to antagonize N-methyl-d-aspartate (NMDA) receptors, which mediate hyperalgesiaand allodynia.
Adverse effects:
Nausea, vomiting, drowsiness.

DESIPRAMINE:
Mechanism of action: mechanism of action as amitriptyline in DPN patients, i.e., serotonin/norepinephrine reuptake inhibition (particularly norepinephrine blockade) and NMDA receptor antagonism. However, unlike amitriptyline, desipramine has a low affinity for cholinergic (muscarinic) receptors and is therefore associated with less-severe anticholinergic AEs.
Adverse effects:
Dry mouth, skin more sensitive to sunlight than usual, changes in appetite or weight,Constipation.

DULOXETINE:
Mechanism of action:
Duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake. Although the exact mechanism of action of the drug's central pain-inhibitory activity is unknown, it is believed to be related to the potentiation of serotonergic and noradrenergic activity in the central nervous system (CNS). The blockade of norepinephrine reuptake, in particular, is known to have a beneficial effect on neuropathic pain.
Adverse effects
Abdominal pain, Weight loss, Weakness.

VENLAFAXINE:
Mechanism of action:
The exact mechanism of venlafaxine's anti-depressant action is unknown, but it is thought tobe related to the potentiation of serotonin and norepinephrine in the CNS through inhibition of their reuptake. Venlafaxine is also thought to work centrally to decrease the perception of pain. Importantly, venlafaxine does not block muscarinic, histaminergic, or adrenergic receptors, thereby avoiding some adverse effects associated withTCAs.

Adverse effects:
Feeling dizzy, Feeling sleepy, Being unable to sleep (insomnia), Constipation.

CARBAMAZEPINE:
Mechanism of action:
Generally, carbamazepine decreases neuronal excitability or enhances inhibition by altering sodium, potassium, or calcium conductance or by affecting the δ-amino butiric acid (GABA), glutamate or other neurotransmitters that may be concerned in seizure activity.
Adverse effects
Headaches, Dry mouth, putting on weight.

GABAPENTIN:
Mechanism of action:
The precise mechanism of action by which gabapentin produces its analgesic effects is unknown, but animal studies suggest that its pain-modulating properties may be linked to therelease of GABA in spinal-cord pathways that modify pain perception.
Adverse effects:
Mood changes,
swollen arms and
legs, Blurred vision,
Dry mouth

PREGABALIN:
Mechanism of action:
Although pregabalin's precise mechanism of action is unknown, binding of the alpha2-delta subunit may be related to the drug's antinociceptive activity. Preclinical findings were consistent with a Mechanism of action that might involve the reduction of abnormal neuronal excitability through reduced release of the GABA neurotransmitter.
Adverse effects:
Blurred vision, drowsiness, trouble with thinking.

VALPROATE SODIUM:
Mechanism of action:
Valproate sodium's mechanism of action is believed, however, that its activity in epilepsy is related to increased brain concentrations of GABA.
Adverse effects:
Stomach pain, feeling or being sick, Diarrhoea, dry or sore mouth, or swollen gums.

MORPHINE SUIFATE:
Mechanism of action:
Like other medications in this class, morphine has an affinity for delta, kappa, and mu-opioidreceptors. This drug produces most of its analgesic effects by binding to the mu-opioid receptor within the central nervous system (CNS) and the peripheral nervous system (PNS).
Adverse effects:
Headache, nervousness, mood changes, small pupils.

OXYCODONE:
Mechanism of action:
Mechanism of action behind the analgesic effect of oxycodone is, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the drug's analgesic activity.
Adverse effects:
Nausea, Vomiting, constipation.

DEXTROMETHORPHAN:
Mechanism of action:
Dextromethorphan is a non-opioid cough suppressant. It is the methylated dextrorotatory analogue of levorphanol, a codeine analogue. Dextromethorphan acts centrally on the cough centre in the medulla and nucleus tracts solaris to increase the cough threshold.
Adverse effects:
Blurred vision, difficulty in urination, drowsiness.

2. NON-PHARMACOLOGICAL MANGEMENT:

Non-pharmacological management refers to the use of interventions and strategies that do not involve the administration of drugs or medications to address a particular condition or healthissue.

- Keep your blood pressure under control.
- Make healthy food choices
- Be active every day.
- Stop smoking.
- Avoid alcohol consumption
- Don't skip medication
- Don't take duel doses

COMBINATION THERAPY

combination therapy in neuropathic pain, including three high-quality studies highlighting the relevance of combining pregabalin with duloxetine, or gabapentin with opioids or TCAs forthe treatment of neuropathic pain. We identified three more recent double-blind RCTs of combination therapy, two of which included TCAs (108 patients). One high-quality study found that the combination of nortriptyline with morphine at moderate doses was more effective than monotherapy at higher doses for the treatment of peripheral neuropathic pain.

Both these studies concluded that the combination of TCAs with morphine or pregabalin was more effective than monotherapy, with a high final quality of evidence. One small double-blind active comparative study (14 patients per group) reported similar efficacies for methadone, oral ketamine and their combination in refractory neuropathic pain.

ALTERNATIVE MEDICINE

There are many alternative therapies that may help with pain relief on their own or in combination with medications. But check with your health care provider before using any alternative therapy or dietary supplement to make sure that you don't have any potential interactions.

- Capsaicin.
- Alpha-lipoic acid.
- Acetyl-L-carnitine.
- Transcutaneous electrical nerve stimulation
- Acupuncture.

CONCLUSION:

Diabetic neuropathy is the most debilitating complication that can cause significant morbidity and mortality in type 1 and type 2 diabetic patients. It is essential to detect symptoms or signs of diabetic neuropathy and determine risk factors as early as possible to implementinterventions and to prevent further neuronal damage. Increasing awareness and knowledge among healthcare professionals about the management of diabetic foot complications is vital to prevent lower leg.

REFERENCES:

1) International Diabetes Federation [http://www.idf.org/]
2) Pirart J (1978) Diabetes mellitus and its degenerative complications: a prospective study of 4400 patients observed between 1947 and 1973. Diabetes Care 1: 168-188,253-263.
3) Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329: 977-986.
4) Martin CL et al. (2006) Neuropathy among the Diabetes Control and Complications Trial Cohort 8 years after trial completion. Diabetes Care 29: 340-344.
5) Said G et al. (1998) uncommon early onset neuropathy in diabetic patients. J Neurol 245: 61- 68.
6) Diabetes – world health organization [WHO]
7) Hossam A.shouipsinai university on Jan 02 2015 diabetes mellitus.
8) Thaifa MS, Roshna S, Arya US and Aparna G Babu on A review on diabetes mellitus and diabetic neuropathy: A plantbased approach Journal of Pharmacognosy and Phytochemistry 2017; 6(3): 506-510.
9) WHO expert committee on diabetes

mellitus.second report. Geneva: WHO, 1980. Technical report series 646.
10) IDF. IDF Diabetes Atlas. 8th Edition ed. Web; 2017 [cited 2020 Jun 1]. Available from: https://www.idf.org/e-library/welcome.html
11) Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. Nat Rev Dis Primers. 2019; 5(1):41. DOI: 10.1038/s41572-019-0092-1.
12) Vinik AI, Nevoret ML, Casellini C, et al. Diabetic neuropathy. Endocrinol Metab Clin North Am. 2013; 42(4):747–787.
13) Pirart J. [Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973 (3rd and last part) (author's transl)]. Diabetes Metab. 1977;3(4):245–256
14) Rf Br H, Dabelea D, D'Agostino RB Jr, et al. The SEARCH for Diabetes in Youth Study: Rationale, Findings, and Future Directions. Diabetes Care. 2014;37(12):3336–3344.
15) Jaiswal M, Divers J, Dabelea D, et al. Prevalence of and risk factors for diabetic peripheral neuropathy in youth with Type 1 and Type 2 diabetes: search for diabetes in youth study. Diabetes care. 2017; 40 (9):1226–1232. DOI: 10.2337/dc17-0179.
16) . Abbott CA, Malik RA, van Ross ER, et al. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the. UK Diabetes Care. 2011; 34 (10):2220–2224. DOI: 10.2337/dc11-1108.
17) Daousi C, MacFarlane IA, Woodward A, et al. Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. Diabet Med. 2004; 21(9):976–982.
18) Sadosky A, Hopper J, Parsons B. Painful diabetic peripheral neuropathy: results of a survey characterizing the perspectives and misperceptions of patients and healthcare practitioners. Patient. 2014; 7(1):107–114.
19) Palumbo PJ et al. (1978) Neurologic complications of diabetic mellitus: transient ischemic attack, stroke and peripheral neuropathy. In Advances in Neurology, vol 19, 593-601 (Ed Schoenberg BS) New York: Raven Press.
20) De Freitas MRG et al. (1992) Diabetic neuropathy. I—epidemiology, classification, clinical and electrophysiological aspects. A study of 210 cases [Portuguese]. Rev Brasileira Neurol 28: 69- 73.
21) Said G (1981) Progressive centripetal degeneration in polyneuropathies [French]. Rev Neurol 137: 573-58
22) J.J. Duby, K.R. Campbell, M.S. Setter, R.J. White, K.A. RasmussenDiabetic neuropathy: an intensive review Am J Health Syst Pharm, 61 (2) (2004), pp. 160-173R. PopBusui, A.J.M. Boulton, E.L. Feldman, V. Bril, R. Freeman, R.A. Malik, *e t al*. Diabetic neuropathy: a position statement by the American Diabetes Association Diabetes Care, 40 (1) (2017), pp. 136-154.
23) A.I. Vinik, M.L. Nevoret, C. Casellini, H. Parson Diabetic neuropathy Endocrinol Metab Clin North Am, 42 (4) (2013), pp. 747-787.