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Diabetic Neuropathy: A Comprehensive Review of Mechanisms and Therapies

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Abstract:

The main purpose of this review is to study the risk factor / pathogenesis, prevalence, clinical manifestations, diagnosis and treatment for Diabetic Neuropathy. It also emphasises the role of pharmacist in counselling the patient who is suffering from Diabetic neuropathy. Methods: A review on focusing diagnosis, symptoms, pathogenesis and treatment of Diabetic Neuropathy was conducted. The record of Google, ResearchGate, Nature, Watermark. silver chair, onlinelibrary. wley, sciencedirect, pubmed annual reviews, were also searched. Content: In 2021, across India. a large-scale survey was conducted, as per their result, it was found that over 43 percent of the respondents are suffering from diabetes mellitus and their age is above in years. Diabetes mellitus is the most common cause of neuropathy. In the USA, it is estimated that. 11.6% of the Dos population had diabetes. As per 2024 statistics 8.7M adults have undiagnosed diabetes, 29.3 million have diagnosed diabetes and 115.9 million have pre-diabetes. Diabetic neuropathy is a serious diabetes. complication that may affect 50% of people who are suffering from diabetes. India has estimated that 100 million people (i.e. 1 in 10 Indians) are officially diagnosed with diabetes, which makes it the second most affected in the world after China. Neuropathy occurs in both non-insulin dependent diabetes mellitus and insulin dependent diabetes. It may develop sooner after diagnosis in non-insulin dependent diabetes mellitus. Generally diabetic neuropathy is a type of nerve damage that can occur by diabetes; due to the highly increased level of blood glucose level It mostly affects the legs and feet. Medications are selected by considering the type of diabetic neuropathy symptoms and side effects. Even if rapid pain relief is necessary.

Keywords: Diabetic neuropathy, hyperglycemia, neuropathic pain, glycemic control, peripheral neuropathy, autonomic neuropathy

1. INTRODUCTION

Diabetic neuropathy is considered the most common long-term complication of diabetes. In general, Neuropathy is a nerve problem, that causes pain, numbness, tingling, swelling or muscle weakness indifferent parts of the body. Diabetic peripheral neuropathy is a most common form of diabetic neuropathy. Symptoms depend on the area of nerve damage. and it includes motor changes such as weakness. It also includes sensory symptoms such as feeling of numbness, tingling, burning, discomfort or shooting pain.

When the nerves are damaged then messages cannot be sent properly, which may lead to the change in Sensation or feeling1798, Rollo described the diabetic neuropathy.

Described the pain and paraesthesia in the legs of the Diabetic patient. In 19th Century, De Calvi, Pavy established the link between diabetes mellitus and Diabetic neuropathy. Later in 1921, the Epochal discovery of insulin triggered a wide interest in the research of diabetic complications. In 1884, Bouchard described the loss of tendinous reflexes in lower limbs and in 1885. id Pavy describes the presence of spontaneous symptoms such as pain and hyperesthesia. Motor symptoms were documented by Buzzard in 1890. In 1893 Leyden suggested the first diabetic Neuropathy classification and subdivided it in sensory and motor manifestations. In 1890 Auche was one among other who mentioned the cases of paralysis which are occurring during diabetes. Auche drew attention to the fact that Bouchard has reported in 1884. The course that the knee jerks are often absent in diabetic patients. Thus in 1890, the clinical Picture of peripheral diabetic neuropathy has been documented. Thus, the review focuses on the study of diagnosis, Symptoms, pathogenesis and treatment of diabetic Neuropathy. Patients who are suffering from Diabetic Peripheral Neuropathy (DPN). Patients who are suffering From Diabetic Peripheral Neuropathy experiences greater Level of pain which corresponds with higher symptom Level of depression, anxiety, sleep. Problem. Diabetic Peripheral neuropathic treatment is challenging and for Many patients no effective therapies are available. DN is a progressive disease and symptoms get worse over time. The study of types of diabetic neuropathy is important to acquire the knowledge for diagnosis, symptoms, prevention and treatment of diabetic neuropathy.

1.1 CAUSES OF DIABETIC NEUROPATHY

i Prolonged exposure to higher-than-normal glucose levels certainly damages the nerves, causing neuropathy.

ii There are certain medications also that include some anti-cancer drugs, which are associated with bringing on neuropathy.

iii High levels of triglycerides, key blood fat which is measured during a cholesterol check may develop the nerve damage.

A combination of other casual factors includes:

1) Smoking.
2) A person having chronic liver or kidney disease.
3) Vitamin B deficiency.
4) Alcohol use.
5) High blood pressure.

1.2 RISK FACTORS

Chronic diabetes is a major risk factor for diabetic Neuropathy. Factors which may influence the diabetic Neuropathy are:

1) High cholesterol levels.
2) Obesity
3) Alcohol consumption.
4) Vitamin C deficiency.
5) Chronic liver and kidney diseases.

2. CLASSIFICATION

There are four major types of Diabetic Neuropathies seen in people. They are

i PERIPHERAL NEUROPATHY

The most common form of diabetic neuropathy is peripheral neuropathy. Peripheral neuropathy includes a wide range of clinical pathologies probably presenting with peripheral nervous system dysfunction. Patients with peripheral experience a degree of numbness tingling, aching, weakness of limbs, hyperalgesia, burning sensation and pain. It usually affects the feet and legs. There are many causes of peripheral neuropathy, Diabetic Peripheral Neuropathy (DPN) is a most Prevalent subtype that can lead to complications ranging from paraesthesia to loss of limb and life. The exact cause of DPH is not known. Genetic, social and lifestyle factors

such as chronic alcohol consumption and Smoking may cause diabetic peripheral neuropathy. Insulin resistance may be caused due to continual high blood serum glucose, which promotes inflammation and cell damage. In this first, autonomic nerve fibres and distal sensory fibres are damaged that leads to the loss of protective sensation in the skin and foot joints.

SIGNS AND SYMPTOMS.

Symptoms range from mild to severe and may include

1) Numbness.
2) Tingling.
3) Burning sensation.
4) Extreme tenderness to touch.
5) Muscle weakness.

6) Loss of balance or coordination.
7) Insensitivity to hot and cold temperatures.

ii AUTONOMIC NEUROPATHY

Diabetic autonomic neuropathy is a common complication of diabetes. Autonomic neuropathy refers to the category of nerve damages affecting the autonomic nervous system. The autonomic nerves are those nerves that control an involuntary process in the body, such as breathing, Heart rate, blood pressure, respiration and digestion. If there is a high level of sugar and fat in the blood that damages the nerves that control and internal organs then The Diabetic Autonomic Neuropathy occurs. Diabetic autonomic neuropathy is also associated with an increased risk of cardiovascular mortality. Diabetic autonomic neuropathy. Includes Major Clinical manifestations such as resting tachycardia, exercise Intolerance, orthostatic hypotension, constipation, Impaired neurovascular function,brittle diabetes and Hypoglycaemic autonomic failure. When nerves are damaged it affects the messages sent between the brain and other organs and areas of the autonomic nervous system. These areas may include the heart, blood vessels and sweat glands. Diabetic autonomic neuropathy caused due to diabetes, autoimmune disease, irregular protein builds up some viruses and bacteria and certain medications including some drugs used in cancer Treatment. Symptoms and treatment are based on which nerves are damaged.

SIGN AND SYMPTOMS

Signs and symptoms depend on the nerve being damaged.

1) Urinary problems: - Such as difficulty in starting a urination, loss of bladder control.
2) Sexual difficulties: These include ejaculation problems. Among women, the difficulties include vaginal dryness.
3) Difficulty in digestion It includes loss of appetite, diarrhoea, constipation nausea, vomiting, difficulty in swallowing.
4) Problems with sweating, either excessive or too little
5) Sluggish pupil reaction: - There is a problem adjusting from light to dark and. 'seeing well when driving at night."
6) Exercise intolerance.

iii PROXIMAL NEUROPATHY

Proximal neuropathy is also called Dabetic Polyradiculopathy Or Diabetic amyotrophy. Diabetic Proximal Neuropathy is a motor neuropathy, it affects one's movement. Proximal neuropathy may cause sudden severe pain in the thigh, hips, buttocks, and legs. In proximal neuropathy usually one side of the body has

been affected, but may spread to the other side as well. In. Proximal neuropathy weakness in legs has been reported. A Person suffering from non-insulin dependent diabetes mellitus appears to have an earlier onset of diabetic Proximal Neuropathy symptoms rather than the persons who are suffering from insulin dependent diabetes mellitus. (IDDM).The symptoms of proximal neuropathy are more Prevalent in the persons with type- 2 diabetes in older adults' proximal neuropathy is. More Prevalent. An individual who is suffering from diabetes may develop Diabetic proximal neuropathy due to various factors. The factors that causesthe nerve damage are hypertension, smoking, poor weight. Management of obesity, poor glycemic control. An infrequent and impaired type of nerve damage in your hip, buttock or Thigh. Proximal neuropathy is more prevalent in men than women. High blood Glucose, also called blood gloves sugar and also high levels of fat such as triglycerides in the blood from diabetes can damage your nerves and small blood vessels that nourish your nerves leading to proximal neuropathy. Proximal Neuropathy can cause severe weight. Many patients with proximal neuropathy recover spontaneously with the passage of time.

SIGN AND SYMPTOMS

The symptoms are typically one-sided, but may spread to the opposite side as well.

1) Patient experiences pain in the hip, thigh or buttock.
2) Severe stomach ache
3) Difficulty in rising from a sitting position.
4) Weight loss
5) swelling in the abdomen
6) Weak thigh muscle.

iv FOCAL NEUROPATHY

Diabetic focal neuropathy is also known as. Mononeuropathy. It is a type of diabetic neuropathy in which only one nerve gets damaged at a time. Mostly it damages the nerves of hands, legs and head. Diabetic focal neuropathy is very painful and it happens very frequently. This kind of damage to nerves is less similar to peripheral or autonomic neuropathy. Diabetic Focal Neuropathy or Mononeuropathy has two types, they are as follow

a) Cranial mononeuropathy.

b) peripheral mononeuropathy

CRANIAL MONONEUROPATHY

- Cranial mononeuropathy is the most common form of diabetic neuropathy. In cranial mononeuropathy any cranial nerve may be affected mostly the Oculomotor nerve and extra ocular muscles are affected.
- Cranial mononeuropathy involves a separate cranial nerve.
- Mostly it occurs in older patients. The term cranial was first described in 1903 by Dieakufoy.
- Based on the nerve that has been affected, the symptoms are noted. These include,

1) Doubled vision.
2) One eyelid drooping.
3) Headache or eye pain.

PERIPHERAL MONONEUROPATHY.

Peripheral mononeuropathy is one of the type of focal mononeuropathy. It is a nerve related disorder where only a single nerve is damaged. In this condition, the nerve that is used to transport the messages from brain to peripheral body is damaged. Peripheral mononeuropathy and peripheral neuropathy are the common neurological disorder. Diagnosis can often be difficult it requires medical testing to ensure the appropriate diagnosis.

DIAGNOSIS INCLUDES

1) Medical history
2) Physical and neurological exam
3) Body fluid tests

SIGN AND SYMPTOMS.

Inheritance Mononeuropathy may cause

1) Problems focusing.
2) One-sided paralysis of your face. It is called Bell's palsy.
3) Numbness or tingling in your hand or fingers

3. PATHOGENESIS OF DIABETIC NEUROPATHY

Chronic Hyperglycemia

↓

Activation of Metabolic Pathways

(Polyol pathway, AGE formation, PKC activation, Hexosamine pathway)

↓

Polyol Pathway Activation

(Increase Sorbitol accumulation → Osmotic stress → decrease in Myo-inositol → Decrease Na^+/K^+-ATPase)

↓

Advanced Glycation End Products (AGEs)

Protein cross-linking + RAGE activation

↓

Oxidative Stress

Increase Reactive oxygen species → Mitochondrial dysfunction

↓

Protein Kinase C (PKC) Activation

Decrease Nitric oxide → Vasoconstriction → Increase Vascular permeability

↓

Microvascular Dysfunction

Basement membrane thickening → Decrease Endoneurial blood flow

↓

Nerve Ischemia & Hypoxia

↓

Inflammation & Loss of Neurotrophic Factors

Increase Cytokines (TNF-α, IL-6) + Decrease NGF

↓

Nerve Structural Damage

Axonal degeneration + Demyelination

↓

Diabetic Neuropathy

4. DIAGNOSIS OF DIABETIC NEUROPATHY

An early detection of diabetic neuropathy and the institution of appropriate management is the key in the management of patients who are suffering from diabetes. Diagnosis of diabetic neuropathy is based on the history, clinical examination, and supporting laboratory tests. Healthcare providers can usually diagnose diabetic neuropathy by performing a physical exam. Health care provider checks:

- Overall muscle strength and tone.
- Tendon reflexes
- Pain, Vibration & Temperature Sensitivity

Besides the physical exam, health care providers may perform specific tests that could help to diagnose diabetic neuropathy.

These Tests are

a. FILAMENT TEST

It is also called a monofilament test. It helps in diagnosing diabetic neuropathy by checking nerve damage and loss of feeling in the feet. In this test, a small strand of nylon is used known as a monofilament. This filament is attached to a plastic base and brushed over the skin in order to test the sensitivity to touch. Mono filament is placed on the sole of his foot, perpendicular to the skin and at that time the patient may be asked to close his eyes or look away. The patient is asked to say "yes" if he feels. If the patient can't feel the filament, when it bends, then it should be considered as a sign of insensitivity.

b. SENSORY TEST

It is a non-invasive test, used for diagnosis of diabetic neuropathy, which diagnoses the neuropathy by estimating how nerve responds to changes in temperature and vibration. It is a part of the physical exam; it includes checking tendon reflexes, muscle strength, and sensation to touch.

c. ELECTROMYOGRAPHY

It is also called needle testing. It is also used for diagnosis of diabetic neuropathy. In this test, the electrical activity of muscle is measured by inserting a small needle into a muscle. This test is often done along with nerve conduction studies. Primarily the type-2 diabetes patients are evaluated by Electromyography. EMG may be useful for managing diabetic neuropathy.

d. NERVE CONDUCTION STUDIES TESTING

This test helps to determine the function and ability of electrical conduction of nerves. Nerve conduction study measures how quickly nerve in the arms and legs conduct electrical signals. If the patient has symptoms such as Numbness or tingling in their arms, legs, hands, Face or feet, then the health care provider recommends a nerve Conduction Test.

e. AUTONOMIC TESTING

Special tests may be done to determine how your blood pressure and heartbeat change while you are in different positions. Various cardiovascular tests include heart rate tests, deep breathing tests, Orthostatic hypotension test, and lying to standing tests. Other tests include gastrointestinal tests, quantitative Sudomotor axon reflex tests, Urinalysis, bladder function tests and ultrasounds. Along with those tests, a blood test is also performed for diagnosis of Diabetic Neuropathy. Blood tests are performed to determine electrolyte levels, vitamin B12 Levels, urea levels and glucose levels in the blood. Kidney and liver function tests are also performed.

5. NON PHARMACOLOGICAL MANAGEMENT

Non-pharmacological management of diabetic neuropathy has often focused on weight loss through exercise, dietary modification and annual foot examination.

a) IMPROVED GLYCEMIC CONTROL

High glucose level in blood is the main cause of diabetic neuropathy. Enhanced glucose levels in patients with Type 1 diabetes that reduces progression of diabetic Neuropathy. To improve glycemic control, eat a healthy diet that is rich in protein, fibers and low in fats and carbohydrates. For glycemic control, eat whole grains, fruits and Vegetables.

b) EXERCISE

Exercise is the most important factor for reducing the progression of diabetic neuropathy. Exercise mostly focused on weight loss. It improves blood flow, lowers increased blood sugar levels. It may keep your heart healthy. It reduces neuropathic pain and also reduces oxidative stress. Exercise may promote micro vascular dilation.

c) LIFE STYLE CHANGES

Diabetic neuropathy is caused by smoking and consumption of alcohol. Excessive intake of smoking and alcohol may lead to poor circulation in your feet that causes the pain.

d) FOOT CARE

Proper foot care is necessary for the persons suffering from diabetic neuropathy. Check regularly for cracks in the Skin. Also, lock signs of infection such as redness, swelling. If the infection of the foot becomes critical

then immediately meet the doctor for the treatment. Use the proper and clean footwear to keep the foot safe. Regular washing of your feet is necessary.

e) ACUPUNCTURE

It is also an important treatment that helps to reduce the progression of diabetic neuropathy. Acupuncture is one of the non-pharmacological treatments for diabetic neuropathic pain. Acupuncture helps to treat chronic migraine, as well as fibromyalgia and musculoskeletal pain-related problems. Acupuncture is safe in reducing the symptoms of peripheral neuropathy. It does not have any adverse effects. Acupuncture may be done by a certified practitioner; this technique involves the insertion of thin needles into specific points on the body. The points at which needles are inserted are known as acupoints. Then these needles readjust your body's energy. It also promotes your body to release natural chemicals to fight for the symptoms.

6. PHARMACOLOGICAL MANAGEMENT

Pain diabetic neuropathic pain is managed pharmacologically. There are various types of drugs used in the treatment of diabetic neuropathy. A variety of drugs were sanctioned by the U.S FDA for managing pain or treating diabetic neuropathy (DN) This Includes

ANTICONVULSANTS

These are the pharmacological agents used in the treatment of convulsions. They are otherwise known as antiepileptic drugs. Many of your antiepileptic drugs are used as a first line drugs in the treatment of diabetic neuropathy.

7. DRUGS USED FOR TREATMENT OF DIABETIC NEUROPATHY INCLUDE

I. Carbamazepine

Carbamazepine is a first-generation anticonvulsant drug that helps to treat diabetic neuropathy or Diabetic peripheral Neuropathy. It treats partial Seizure, plus it is used as a third line for diabetic neuropathy.

II. PREGABALIN

The National Institute for Clinical Excellence recommends antiepileptic drugs like pregabalin as a first line treatment for PDN. Pregabalin is effective in comparison with placebo in reducing neuropathic pain. pregabalin is small but the effect of pregabalin is small.

III. GABAPENTIN

Gabapentin is a structural analogue of Gamma Amino Butyric Acid. GABA is inhibitory neurotransmitter present in the central nervous system. Certain individuals with moderate or severe neuropathic pain should be treated with gabapentin that provide the pain relief. It has a rapid onset of action.

IV. SEROTONIN-NOREPINEPHRINE RE UPTAKE INHIBITORS (SNRI)

Serotonin norepinephrine reuptake inhibitors like venlafaxine and duloxetine are recommended as a first or second-line therapy for DPM. Duloxetine is a selective inhibitor of reuptake of 5HT and norepinephrine. Because of its dual effect, it has been recommended for use in reducing diabetic neuropathic pain. Venlafaxine is also used for reducing neuropathic pain. It has a little anticholinergic activity. Duloxetine is more effective in reduction of neuropathic pain than the venlafaxine.Duloxetine may result in side effects consisting of dizziness, Headache, and sleepiness. Venlafaxine may lead to Nausea, constipation, and insomnia.

V. TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants are also used in the treatment of painful diabetic neuropathy. It is considered as a first line treatment, effect of TCA for patients with DPN has been shown by Clinical trials. Amitriptyline is the most widely used TCA for treatment of DPN. Nortriptyline and desipramine might be considered as safe in older adults due to its fewer adverse effects than amitriptyline. Long term use of TCA increases the risk of dementia due to their anticholinergic effect.

VI. OPIOIDS

Opioids are used for the treatment of moderate severe diabetic neuropathic pain. But because of their addiction and several adverse effects, opioids are not recommended as a first line of treatment for diabetic neuropathic pain. Sometimes oxycodone is used in reducing the pain. Oxycodone appears to be no more effective than placebo. The SNAI properties are present in tramadol and tapentadol.

VII. ANTIARRHYTHMICS

These are also used in the treatment of diabetic neuropathic pain. Mexiletine belongs to the class of 1B antiarrhythmic drug. It is a structural analogue of lidocaine. Patients suffering from diabetic neuropathic pain, experiences significant pain relief at night after taking a high dose of Mexiletine i.e 675 mg/day.

8. DISCUSSION

Diabetic neuropathy (DN) is one of the most prevalent and disabling consequences of diabetes mellitus, and it affects both Type 1 and Type 2 diabetic patients. It is a heterogeneous group of disorders, and it is caused due to nerve fiber damage induced by hyperglycemia and associated abnormalities of metabolism and blood vessels. Regardless of the advances in the management of diabetes, diabetic neuropathy remains a significant reason for morbidity and increased health care load all across the globe. Diabetic neuropathy involves a complicated pathogenesis. Chronic hyperglycemia regulates various biochemical pathways; these pathways interact with and regulate each other. They include the activity of the polyol pathway, the generation of advanced glycosylation end products (AGEs), the activity of protein kinase C (PKC), and others. These processes are responsible for microvascular damage, which leads to a failure in blood flow to the nerves. Another process associated with diabetes neuropathy and that plays a prominent part during pathogenesis is oxidativestress.CONCLUSION:

Diabetic neuropathy is among the most prevalent and severe complications arising from diabetes mellitus, attributed to the prolonged periods of high blood glucose concentrations. The condition influences the peripheral as well as the autonomic nervous system, as manifested by various symptoms, including pain, numbness, paraesthesia, loss of protective sensation, and autonomic dysfunction. Such symptoms greatly influence the quality of life, increasing the risk of foot ulcerations, infections, as well as the potential for amputations. Diabetic neuropathy has complex pathophysiologic mechanisms that include oxidative damage, activation of the polyol pathway, advanced glycosylation end- products, inflammation, and ischaemia. Early disease diagnosis is very important because, by the time a patient presents with clinical symptoms and other diagnostic criteria, the nerve damage would have become irreversible. Glycemic control is very important in preventing this complication as well as slowing its progression. Diabetic neuropathies can be managed by a multidisciplinary approach, including tight control of blood sugar levels. Pain management using pharmacologic therapy, lifestyle interventions, and educating diabetic patients. New approaches targeting the mechanisms involved in causing diabetic neuropathy, together with palliation, have enhanced outcomes for these patients; however, a cure from diabetic neuropathies is not always possible. Thus, in conclusion, diabetic neuropathy is a condition that is complex and progressive in nature and requires immediate diagnosis, constant monitoring, and tailored treatment. Greater awareness and research efforts can possibly contribute to lowering the incidence of this complication and improving the lives of patients suffering from diabetes mellitus.

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