

## DIABETIC NEUROPATHY– A REVIEW

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## ABSTRACT

**Objective/Purpose:** The main objective of this review is to study the risk factor / pathogenesis, prevalence, clinical manifestations, diagnosis and treatment for Diabetic Neuropathy. It also emphasizes the role of pharmacist in counselling the patient who is suffering from Diabetic neuropathy. **Methods:** A review focusing on 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.

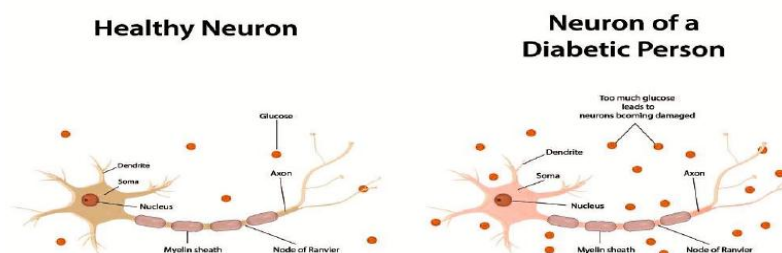
**KEYWORDS:** Diabetes mellitus, Diabetic neuropathy (DN), Diabetic Peripheral neuropathy (DPN).

## • INTRODUCTION

Diabetic neuropathy is considered. as a most common long-term complication of diabetes. In general, neuropathy is a nerve problem, that causes pain, numbness, tingling, swelling or muscle weakness in different 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 feeling.

## Diabetic Neuropathy



In 1798, Rollo described the diabetic neuropathy. He 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, treatment of diabetic neuropathy.

- **Causes of diabetic neuropathy**

- 1) Prolonged exposure to higher than normal glucose levels certainly damages the nerves, causing neuropathy.
- 2) Certain medications, including some anti- cancer drugs are also associated with. bringing on neuropathy.
- 3) 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 include**

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

- 5) High blood pressure.

- **Risk factors**

- Chronic diabetes is a major risk factor for diabetic neuropathy. Factors that may influence diabetic neuropathy are:

- 1) High cholesterol levels.
- 2) Obesity
- 3) Alcohol consumption.
- 4) Vitamin & deficiency
- 5) Chronic liver and kidney disease.

- **Classification**

In people with diabetes, there are four main types of neuropathies.

- 1) **Peripheral neuropathy**

- **Introduction**

Peripheral neuropathy is a most common form of diabetic 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 blond 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.

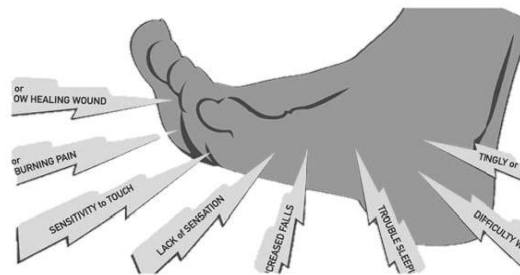
- **Signs and Symptoms**

Symptoms can be mild to severe.

**They include**

- 1) Numbness
- 2) Tingling
- 3) Burning sensation.
- 4) Extreme sensitivity to touch.
- 5) Muscle weakness
- 6) Loss of balance or coordination
- 7) Insensitivity to hot and cold temperatures.

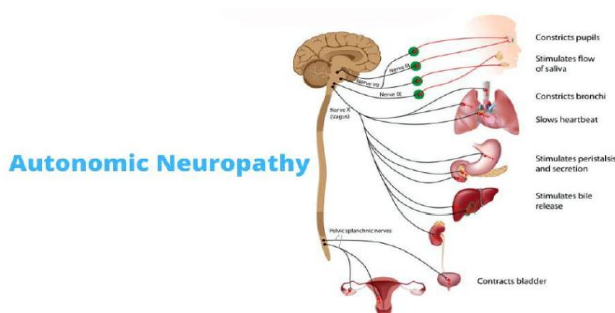
- Patients suffering from peripheral neuropathy experiences symptoms more often at night.



## 2) Autonomic neuropathy

Diabetic autonomic neuropathy is a common complication of diabetes. Autonomic neuropathy belongs to nerve damage that affects the autonomic nervous

system. 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 buildup some viruses and bacteria and certain medications including some drugs used in cancer treatment (Chemotherapy). Symptoms and treatment are based on which nerves are damaged.

### ▪ Sign and Symptoms

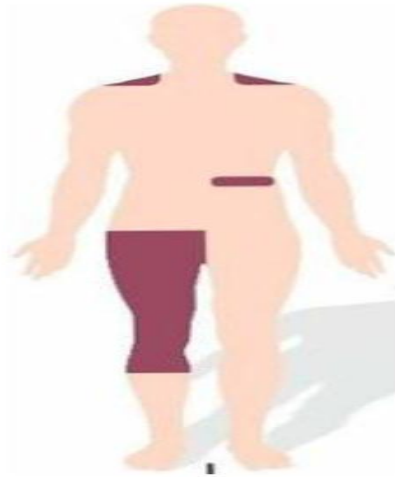
- Signs and symptoms are based on the nerve being damaged.

- Symptoms include;

- 1) Urinary problems: - Such as difficulty in starting a urination, loss of bladder control.
- 2) Sexual difficulties: It includes ejaculation problems. In women, problems include vaginal dryness.
- 3) Difficulty in digestion It includes loss of appetite, diarrhoea, constipation nausea, vomiting, difficulty in swallowing.
- 4) Sweating problems such as excess or too little sweating
- 5) Sluggish pupil reaction: - In this condition, it is difficult to adjust from light to dark and. 'seeing well when driving at night.
- 6) Exercise intolerance.

### 3) Proximal neuropathy

Proximal neuropathy is also known as Diabetic Polyradiculopathy. This type of neuropathy is also called diabetic amyotrophy. Diabetic Proximal Neuropathy is a motor neuropathy that affects one's movement. Proximal neuropathy may lead to 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 is also reported.



A Person suffering from non-insulin dependent diabetes mellitus (NIDDM) 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 cause the nerve damage are hypertension, smoking, poor weight management or obesity, poor glycaemic control, a 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 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 may lead to significant weight loss. A large number of people suffering from proximal neuropathy improve over time.

#### ▪ Sign and Symptoms

Symptoms are usually on one side of the body, but may also spread to the other side.

#### Patient experiences

- 1) Severe pain in the hip and thigh or buttock.
- 2) Severe stomach pain
- 3) Difficulty in rising from a sitting position.
- 4) Weight loss
- 5) Swelling in the abdomen
- 6) Weak thigh muscle.

#### 4) 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 nerve of hands, legs and head are damaged. Diabetic focal neuropathy is very painful and it occurs frequently. This type of nerve damage is less similar to peripheral or autonomic neuropathy. There are two types of mononeuropathy, they are as follows;

- A) Cranial mononeuropathy
- B) Peripheral mononeuropathy.



#### A) 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 extraocular muscles are

affected. Cranial mononeuropathy involves a separate cranial nerve. It mostly occurs in older patients. In 1903, Dieakufoy first described the term cranial mononeuropathy. On the basis of affected nerve, symptoms are observed

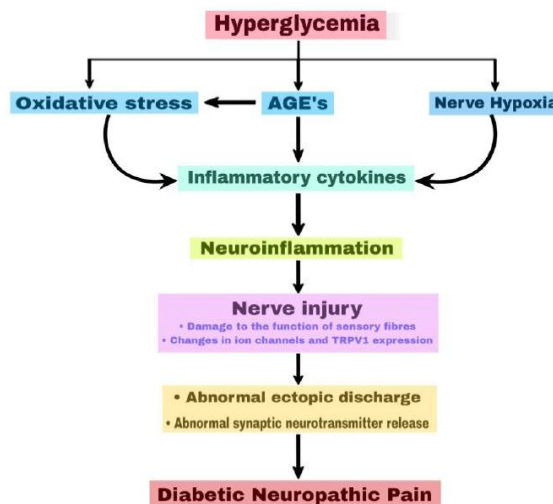
Symptoms include,

- 1) Doubled vision
- 2) Drooping of one eyelid.
- 3) Headache or eye pain.

### B) Peripheral mononeuropathy

Peripheral mononeuropathy is a type 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.

#### • Pathogenesis of diabetic neuropathy



A variety of factors has been postulated to bring out the pain associated with diabetic neuropathy including, hyperglycaemia, oxidative stress, Advance Glycation End product (AGE's), nerve hypoxia, and neuroinflammation. In the development of diabetic neuropathic pain, hyperglycaemia plays an important role. In the study of animals and non-diabetic individuals, it has been demonstrated that hyperglycaemia can cause the decrease in pain threshold.

Other than hyperglycaemia, there are some factors that may result in the generation of DNP. Hyperglycaemia may lead to an increase in production of AGE and cause a decrease in regeneration of glutathione. Glutathione depletion can be a sign of oxidative stress. When disposal of intracellular glucose is decreased, substitute pathways are activated which may cause oxidative stress and also cause nerve injury. Within diabetic nerves, in oxidative stress, hyperglycaemia plays a key role. In sensory nerves, hyperglycaemia evokes the nerve hypoxia, which causes them to be an alteration of their function and electrical stability. Then the production of inflammatory cytokines and growth factors. are caused by AGE's, Oxidative stress and hypoxia. It again causes neuroinflammation and nerve injury, neuropathic pain, also known as nerve pain, can be correlated with damage

### Diagnosis includes

- 1) A medical history
- 2) Physical and neurological exam
- 3) Body fluid tests

#### ▪ Sign and Symptoms

Mononeuropathy may lead to:

- 1) Difficulty in focusing.
- 2) Paralysis on one side of your face. it is known as Bell's palsy.
- 3) Numbness or tingling in your hand or fingers.

to sensory fibres. These sensory fibres include AS fibres and C fibres. They lead to the change in voltage gated ion Charmel distribution and expression and conduct the nerve impulses.

Hyperglycaemia, hypoxia, AGE's and oxidative stress mediated damage in glial cell and neuron as well as successive activation of proinflammatory cascades may eventually leads to an abnormal ectopic discharges and release of abnormal synaptic neurotransmitter. Due to this, it prompted the development of neuropathic pain.

#### • Diagnosis of diabetic neuropathy

An early identification of diabetic neuropathy and the commencement of appropriate management is necessary for 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.
- Sensitivity to pain, vibration, and temperature.



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

#### These tests are

##### 1) Filament test

It is also known as a monofilament test. It helps to diagnose diabetic neuropathy by checking nerve damage and loss of feeling in the feet. In this test, a small strand of nylon called a monofilament is used. This filament is attached to a plastic base and brushed over the skin to test the Sensitivity to touch. Mono filament is placed on the sole of their foot, perpendicular to the skin and at that time, the patient may be asked to close their 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.

##### 2) Sensory testing

It is a non-invasive test, used for. diagnosis of diabetic neuropathy. It diagnoses the diabetic 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.

##### 3) Electromyography (EMG)

It is also known as 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. FMCG is frequently. performed in conjunction with nerve. conduction studies. This tests the nerve function by measuring conduction speed and how nerve fibres are functioning.

Primarily the type-2 diabetes patients are evaluated by EMG. EMG may be useful for managing diabetic neuropathy.

##### 4) 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.

##### 5) Autonomic testing

It is a test performed for diagnosis of diabetic autonomic neuropathy. Autonomic tests include.

- a) Cardiovascular tests such as heart rate tests, deep breathing tests, Orthostatic hypotension test and lying to standing tests
- b) Other tests such as 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.

#### Treatment

Diabetic neuropathy has a no specific cure. Aim of the treatment is to;

- Relieve pain
- Slow progression
- Manage complication.

Diabetes Control and complications Trial (DCCT) found that, intensive therapy for insulin dependent diabetes mellitus particularly reduces the progression of diabetic neuropathy and other related complication.

The 30% risk of Diabetic Peripheral Neuropathy has been reduced by intensive therapy. There are both non pharmacological and pharmacological managements available, but they do not cure the diabetic neuropathy they can relieve the pain, manage the complication and reduce the progression.

##### ▪ Non pharmacological management

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

##### 1) Improved glycaemic control

High glucose level in blood is the main Cause of diabetic neuropathy. Enhanced glucose control in patients with type 1 diabetes that reduces progression of diabetic neuropathy.

To improve glycaemic control, eat a healthy diet that is rich in protein, fibres and low in fats and carbohydrates. For glycaemic control, eat whole grains, fruits and vegetables.

##### 2) Exercise

Exercise is a most important factor for reducing the progression of diabetic neuropathy Exercise mostly focused on weight loss. Exercise can improve blood flow, lowers an increased blood sugar. Exercise may keep your heart healthy. Exercise can reduce neuropathic pain. and also reduce oxidative stress. Exercise may promote microvascular dilation.

##### 3) Life-style changes

Smoking and alcohol consumption are the causes of diabetic neuropathy. Excessive smoking and alcohol consumption may lead to the poor circulation in your feet, that causes the pain.

##### 4) Foot care

Proper foot care is important for people who are suffering from diabetic neuropathy. Check regularly for cracks in the Skin. Also look signs of infection such as redness, swelling. If foot infection becomes critical, then

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

#### ▪ **Acupuncture**

Acupuncture is also an important treatment that helps to reduce the progression of diabetic neuropathy. It is one of the non-pharmacological treatments for diabetic neuropathic pain. Acupuncture helps to treat chronic migraine as well as fibromyalgia, musculoskeletal pain related problems. Acupuncture is safe to reduce the symptoms of peripheral neuropathy. It does not have any adverse effects.

Acupuncture may be done by a certified practitioner; this technique involves 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 the body to release natural chemicals to fight the symptoms.

#### ▪ **Pharmacological management**

Pharmacological treatments are used to manage the pain diabetic neuropathic pain. There are various types of drugs which are used in the treatment of diabetic neuropathy. The U.S FDA sanctioned a variety of drugs for managing pain or treating diabetic neuropathy (DN).

#### **This includes**

##### **1) Anticonvulsants**

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

#### **Drugs used to treat diabetic neuropathy include**

##### **a) Carbamazepine**

Carbamazepine is a first-generation anticonvulsant drug that helps to treat diabetic neuropathy (DN) or Diabetic Peripheral Neuropathy (DPN). It is used to treat partial seizure as well as used as third line treatment for diabetic neuropathy.

##### **b) Pregabalin**

National Institute for Clinical Excellence recommends antiepileptic drugs such as pregabalin as a first line treatment for PDN. Pregabalin is more effective than placebo for reducing neuropathic pain. pregabalin is small but the effect of pregabalin is small.

##### **c) Gabapentin**

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

#### **2) Serotonin-norepinephrine reuptake inhibitors (SNRI)**

Serotonin norepinephrine reuptake inhibitors such as venlafaxine and duloxetine are recommended as a first- or second-line therapy for DPN. Duloxetine is a selective inhibitor of reuptake of 5HT and norepinephrine. Due to 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 cause side effects such as dizziness, headache and sleepiness. Venlafaxine may lead to nausea, constipation and insomnia.

#### **3) Tricyclic antidepressants**

Tricyclic antidepressants are also used in the treatment of painful diabetic neuropathy. Tricyclic antidepressants are 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.

#### **4) Opioids**

Opioids are also used to treat moderate to severe diabetic neuropathic pain. But due to their addiction, several adverse effects, opioids are not recommended as a first line treatment for diabetic neuropathic pain. Sometimes Oxycodone is used in reducing the pain. Oxycodone appears to be not more effective than placebo. Tramadol and tapentadol have SNAI properties.

#### **5) 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.

#### **CONCLUSION**

Diabetic neuropathy is a nerve disorder, caused by various factors which are typically similar to diabetes, such as poor blood sugar control, high level of triglycerides and cholesterol. Early diagnosis is necessary for mitigation, adequate treatment, preventing progression of diabetic neuropathy and severe complications. For treatment it is necessary to obtain the clinical history through physical examination, laboratory test and some neurological tests. Treatment helps to control the progression of diabetic neuropathy firstly by improving glycaemic control and exercise. A good

glucose level reduces the progression of diabetic neuropathy. A variety of drugs are used in the treatment of diabetic neuropathy.

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