

PATHOPHYSIOLOGY, DIAGNOSIS AND MANAGEMENT OF DIABETIC NEUROPATHY: A REVIEW

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Abstract-Diabetic neuropathies are a family of nerve disorders caused by chronic effect of diabetes. It is the most common complication and greatest source of morbidity and mortality in diabetics. The main risk factor for diabetic neuropathy is hyperglycemia. It can affect nerves throughout the body, causing numbness and sometimes pain in the hands, arms, feet, or legs, and problems with the digestive tract, heart, sex organs, and other body systems. The pathology of diabetic neuropathy involves oxidative stress, advanced glycation end products, polyol pathway flux and protein kinase C activation; all contribute to microvascular disease and nerve dysfunction. Management of Diabetic neuropathy first involves bringing blood glucose levels within the normal range. Its treatment includes pain relief and other medications as needed, depending on the type of nerve damage. Foot care is an important part of treatment. Untreated injuries increase the risk of infected foot sores and amputation.

Keywords: Neuropathy, Hyperglycemia, Peripheral Nerves, Microvasculature, Foot amputation.

1. Introduction

Diabetes Mellitus is associated with several short term and long term complications. The most common type of long term complications include nerve damaging disorders known as diabetic neuropathies whose prevalence is estimated to be 25% within diabetic patients [1-4]. In 2010, approximately 132 million people in the world were found to be affected from diabetic neuropathy [5]. About 60 to 70 percent of people with diabetes have some form of neuropathy. It is a family of nerve disorders that can affect nerves throughout the body, causing numbness and sometimes pain in the hands, arms, feet, or legs, and problems with the digestive tract, heart, sex organs, and other body systems. The symptoms of diabetic neuropathy have been visualized in patients before they are diagnosed with diabetes. Chronic nature of diabetes increases the likelihood of having diabetic neuropathy. It may affect the sensory, motor as well as autonomic nerves. The nerve damage due to diabetes may result into loss of sensation and make a patient prone to developing skin ulcers that can become infected and may not heal. This serious complication of diabetes can lead to loss of a foot, a leg, or even life. Diabetic neuropathy is implicated in 50–75% of nontraumatic amputations. Duration of diabetes, age, cigarette smoking, hypertension, height, and hyperlipidemia are risk factors for diabetic neuropathy.

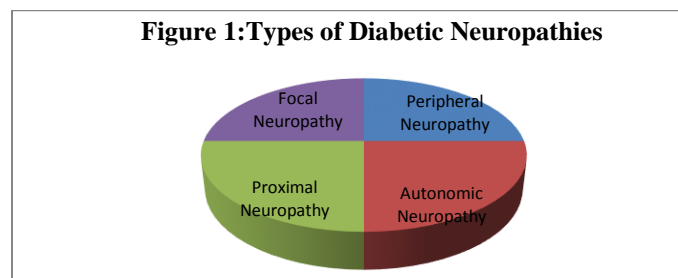
2. Signs and Symptoms

Diabetic neuropathy can affect all organs and systems as it affects all peripheral nerves including sensory, motor and autonomic. A patient can have sensorimotor and autonomic neuropathy or any other combination. Symptoms of diabetic neuropathy depend on the type of neuropathy and nerves which are affected. They may include muscle weakness and muscle wasting, numbness and tingling of extremities, trouble with balance, indigestion, nausea, dizziness, difficulty in swallowing, vision changes, speech impairment, urinary incontinence, erectile dysfunction in men or vaginal dryness in women, burning or electric pain in the sole and dysesthesia. Sudden and severe pain is felt in case of focal neuropathy. Symptoms that are not due to neuropathy, but often accompany it, include weight loss and depression.

3. Types of diabetic neuropathies

Diabetic neuropathy can be classified as peripheral, autonomic, proximal or focal, each affects different parts of the body in various ways [6] [Figure 1]. The most common type of diabetic neuropathy is peripheral neuropathy characterized by pain or loss of feeling in the toes, feet, legs, hands, and arms. Autonomic neuropathy affects visceral organs and causes changes in digestion, bowel and bladder function, sexual response, and perspiration. It can also affect the nerves that serve the heart and control blood pressure, as well as nerves in the lungs and eyes. Proximal neuropathy causes pain in the thighs, hips, or buttocks and leads to weakness in the legs. Focal neuropathy results in the sudden weakness of one nerve or a group of nerves, causing muscle weakness or pain. It may affect eyes, facial muscles, ears, pelvis and lower back, chest, abdomen, thighs, legs and feet.

Figure 1: Types of Diabetic Neuropathies



3.1 Peripheral neuropathy

When there is persistence of signs or symptoms of peripheral nerve dysfunction in diabetics after the exclusion of other causes, the pathological condition can be stated as diabetic Peripheral neuropathy. This type of neuropathy causes nerve damage in the arms, hands, legs and feet and also known as distal symmetric neuropathy or sensorimotor neuropathy. It is more common in the patients with poorly managed diabetes and may affect sensory, motor or autonomic nerves. A study conducted in South India reflected that 19.1% type 2 diabetic patients had peripheral neuropathy [7]. Diabetic peripheral neuropathies are subcategorized into two types- acute sensory neuropathy and chronic sensorimotor neuropathy. These two types of neuropathies differ in the signs and mode of onset. The sensory neuropathy is characterized by the symptoms like numbness or tingling in the feet and pain or discomfort in the feet or legs—including prickly, sharp pain or burning feet whereas motor neuropathy is accompanied by muscle weakness coupled with loss of muscle tone in the feet and lower legs, loss of balance and changes in foot shape. Dry feet and cracked skin are the signs of peripheral autonomic neuropathy. Since nerve conduction velocity is inversely dependent on nerve length therefore, longer nerve fibers are affected to a greater degree than shorter ones. Consequently, they are at risk of developing ulcers and infections on the feet and legs, which can lead to amputation [8]. Similarly, these patients may have multiple fractures of the knee, ankle or foot, and develop a Charcot joint. Progressive loss of motor function results in loss of the interosseous muscle function that leads to contraction of the digits, so-called hammer toes. The mode of onset of acute sensory neuropathy is rapid and characterized by severe burning pain along with aching. But recovery can be there within 12 months if proper management plans are followed. In contrast to acute sensory neuropathy, the chronic sensorimotor neuropathy onset is gradual and characterized by burning pain, absence of ankle/knee reflexes along with numbness. Its symptoms may persist intermittently for years and may lead to foot ulceration and amputation. The chronic sensorimotor neuropathy is more prevalent in type 2 diabetic patients.

3.2 Autonomic neuropathy

Nerves serving the heart, lungs, blood vessels, bone, adipose tissue, sweat glands, gastrointestinal system and genitourinary system constitute autonomic nervous system. Autonomic neuropathy can affect any of these visceral nerves and hence, can affect vital organs. The most commonly recognized autonomic dysfunction in diabetics is orthostatic hypotension, or fainting when standing up. In the case of diabetic autonomic neuropathy, it is due to the failure of the heart and arteries to appropriately adjust heart rate and vascular tone to keep blood continually and fully flowing to the brain. This symptom is usually accompanied by a loss of respiratory sinus arrhythmia – the usual change in heart rate seen with normal breathing. Gastrointestinal tract manifestations include gastroparesis characterized by slow emptying of stomach. Severe gastroparesis can lead to persistent nausea and vomiting, bloating, and loss of appetite. Gastroparesis can also make blood glucose levels fluctuate widely, due to abnormal food digestion. Problems with the digestive system can lead to weight loss. Autonomic neuropathy often affects the organs that control urination and sexual function. Nerve damage can prevent the bladder from emptying completely, allowing bacteria to grow in the bladder and kidneys and causing urinary tract infections. When the nerves of the bladder are damaged, urinary incontinence may result because a person may not be able to sense when the bladder is full or control the muscles that release urine. Autonomic neuropathy can also gradually decrease sexual response in men and women, although the sex drive may be unchanged. A man may be unable to have erections or may reach sexual climax without ejaculating normally. A woman may have difficulty with arousal, lubrication, or orgasm. Autonomic neuropathy can also affect the nerves that control sweating. When nerve damage prevents the sweat glands from working properly, the body cannot regulate its temperature as it should. Nerve damage can also cause profuse sweating at night or while eating. Finally, autonomic neuropathy can affect the pupils of the eyes, making them less responsive to changes in light. As a result, a person may not be able to see well when a light is turned on in a dark room or may have trouble driving at night.

3.3 Proximal neuropathy

Proximal neuropathy is also referred as lumbosacral plexus neuropathy, femoral neuropathy, or diabetic amyotrophy and characterized by pain in the lower limb area such as thighs, hips, buttocks and legs resulting into weakness in the legs. The patient shows inability to go from a sitting to a standing position without help. It is reported commonly in case of aged type 2 diabetic patients.

3.4 Focal neuropathy

It generally affects the nerves of head area, torso and legs. Patients may show inability to focus the eye, double vision, aching behind one eye, paralysis on one side of the face called Bell's palsy, severe pain in the lower back or pelvis, pain in the front of a thigh, pain on the outside of the shin or inside of the foot, chest or abdominal pain that is sometimes mistaken for heart disease, a heart attack, or appendicitis. The focal neuropathy of the third cranial nerve namely oculomotor nerve that is most common. This nerve controls all the muscles that move the eye except for the lateral rectus and superior oblique muscles. It also serves to constrict the pupil and open the eyelid. The onset of diabetic third nerve palsy is usually abrupt, beginning with frontal or periorbital pain and then diplopia. All the muscles innervated by the third nerve may be affected. The sixth nerve, the abducens nerve, which innervates the lateral rectus muscle of the eye, is also commonly affected but fourth nerve the trochlear nerve that innervates the superior oblique muscle, which moves the eye downward involvement, is unusual. Focal neuropathy is painful and unpredictable and occurs most often in older adults with diabetes. People with diabetes also tend to develop nerve compressions, also called entrapment syndromes [9]. One of the most common is carpal tunnel syndrome, which causes numbness and tingling of the hand and sometimes muscle weakness or pain.

4. Pathogenesis

Diabetic neuropathy development involves a no. of factors such as metabolic, neurovascular, autoimmune, lifestyle, hereditary and mechanical factors [Table 1].

1. Metabolic factors	High blood glucose, long duration of diabetes, abnormal blood fat levels and possibly low levels of insulin.
2. Neurovascular factors	Involving to damage to the blood vessels that carry oxygen and nutrients to nerves (Microvascular disease)
3. Autoimmune factors	Inflammation in nerves
4. Lifestyle factors	Smoking or alcohol use
5. Hereditary factors	Increase susceptibility to nerve disease
6. Mechanical factors	Mechanical injury to nerves, such as carpal tunnel syndrome

Microvascular disease or Small blood vessel dysfunction occurs early in diabetes. The narrowing of small blood vessels leads to capillary basement membrane thickening and endothelial hyperplasia which contribute to diminished oxygen tension and hypoxia. It results into neuronal ischemia which is a well-established characteristic of diabetic neuropathy. Blood vessel opening agents (e.g., ACE inhibitors, α 1-antagonists) can lead to substantial improvements in neuronal blood flow, with corresponding improvements in nerve conduction velocities. Hyperglycemic condition in the diabetic patients may lead to glycosylation of proteins within cells. Increased levels of glucose within cells cause a non-enzymatic covalent bonding with proteins, which alters their structure and inhibits their function. Some of these glycosylated proteins have been implicated in the pathology of diabetic neuropathy and other long-term complications of diabetes. The polyol pathway also called the sorbitol/aldose reductase pathway appears to be implicated in diabetic complications, especially in microvascular damage to the retina, kidney and nerves [10-12].

5. Diagnosis

Diabetic peripheral neuropathies which may be asymptomatic in up to 50% of cases, is one of the most important complications of diabetes. It is the most likely diagnosis for someone with diabetes who has pain in a leg or foot, although it may also be caused by vitamin B₁₂ deficiency or osteoarthritis [13]. A 2010 review in the Journal of the American Medical Association's "Rational Clinical Examination Series" evaluated the usefulness of the clinical examination in diagnosing diabetic peripheral neuropathy [14]. Nerve conduction tests may show reduced functioning of the peripheral nerves, but seldom correlate with the severity of diabetic peripheral neuropathy and are not appropriate as routine tests for the condition [15]. All diabetic patients, regardless of their type of diabetes, duration of diabetes, or age, require careful clinical examination of the lower extremities and feet at least once a year. The tests like nerve conduction studies or electromyography may be performed to assess the magnitude of diabetic neuropathy. Nerve conduction studies check the transmission of electrical current through a nerve. Electromyography shows how well respond to electrical signals transmitted by nearby nerves muscles. Ultrasound uses sound waves to produce an image of internal organs. An ultrasound of the bladder and other parts of the urinary tract, for example, can be used to assess the structure of these organs and show whether the bladder empties completely after urination.

6. Management of diabetic neuropathies

The first step in the management of diabetic neuropathy involves bringing of blood glucose levels within the normal range to help prevent further nerve damage. Regular Blood glucose monitoring, meal planning, physical activity and diabetes medicines or insulin will help control blood glucose levels. The tricyclic and anticonvulsant agents remain first line drugs for the management of diabetic peripheral neuropathies. One notable side effect of tricyclic antidepressants is cardiac toxicity, which can lead to fatal abnormal heart rhythms. Additional common side effects include dry mouth, difficulty sleeping, and sedation. Anticonvulsants like Phenytoin, Carbamazepine, Gabapentin and Pregabalin are widely used for treatment of neuropathic symptoms [16, 17]. American Association of Clinical Endocrinologists, American Academy of Neurology, European Federation of Neurological Societies, and the National Institute of Clinical Excellence recommend antiepileptic drugs such as pregabalin, as first-line treatment for painful diabetic neuropathy [18]. The most common side effects associated with antiepileptic drugs use include sleepiness, dizziness, and nausea. The serotonin-norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine are recommended in multiple medical guidelines as first or second-line therapy for diabetic peripheral neuropathies. A 2017 systematic review and meta-analysis of randomized controlled trials concluded there is moderate quality evidence that duloxetine and venlafaxine each provide a large benefit in reducing diabetic neuropathic pain [19, 20]. The only three medications approved by the United States FDA for diabetic peripheral neuropathy are the antidepressant duloxetine, the anticonvulsant pregabalin, and the long-acting opioid tapentadol [21]. Opioid medications are recommended as second or third-line treatment for diabetic peripheral neuropathies [Table 2].

1. Tricyclic Antidepressants	Amitriptyline, Imipramine, and Desipramine
2. Antidepressants,	Duloxetine, Venlafaxine, Bupropion, Paroxetine and Citalopram
3. Anticonvulsants	Pregabalin, Gabapentin, Carbamazepine, and Lamotrigine
4. Opioids	Controlled-Release Oxycodone, An Opioid and Tramadol (Ultram)

Eating small, frequent meals; avoiding fats; and eating less fiber relieve mild symptoms of gastroparesis such as indigestion, belching, nausea, or vomiting. When symptoms are severe, drugs like erythromycin, tetracycline and metoclopramide are generally prescribed to speed up digestion and relieve nausea, diarrhea or other bowel problems. People with neuropathy need to take special care of their feet. The nerves to the feet are the longest in the body and are the ones most often affected by neuropathy. Loss of sensation in the feet means that sores or injuries may not be noticed and may become ulcerated or infected. Smoking increases the risk of foot problems and amputation. Medical devices like

Monochromatic infrared photo energy treatment has been shown to be an effective therapy in reducing and often eliminating pain associated with diabetic neuropathy. The studied wavelength of 890nm is able to penetrate into the subcutaneous tissue where it acts upon a specialized part of the cell called the cytochrome C. The infrared light energy prompts the cytochrome C to release nitric oxide into the cells. The nitric oxide in turn promotes vasodilation which results in increased blood flow that helps nourish damaged nerve cells. Once the nutrient rich blood is able to reach the affected areas (typically the feet, lower legs and hands) it promotes the regeneration of nerve tissues and helps reduce inflammation thereby reducing and/or eliminating pain in the area. Physical therapy can be an effective and alternative treatment option for patients with diabetes[22]. Certain physiotherapy techniques can help alleviate symptoms brought on from diabetic neuropathy such as deep pain in the feet and legs, tingling or burning sensation in extremities, muscle cramps, muscle weakness, sexual dysfunction, and diabetic foot. Exercise programs, along with manual therapy, will help to prevent muscle contractures, spasms and atrophy[23, 24]. These programs may include general muscle stretching to maintain muscle length and a person's range of motion. General muscle strengthening exercises will help to maintain muscle strength and reduce muscle wasting [25]. Aerobic exercise such as swimming and using a stationary bicycle can help peripheral neuropathy, but activities that place excessive pressure on the feet (e.g. walking long distances, running) may be contraindicated[26].

7. Conclusion

Diabetic neuropathy is a many-faceted complication of diabetes that can be managed symptomatically with an array of drugs. Glycemic control remains the foundation of prevention and the prerequisite of adequate treatment. There is a need for research and development in the field of pharmaceuticals and technology so that more effective drugs and treatments can be available to treat the complications of diabetic neuropathy.

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