



## Recent trends in diagnosis criteria, clinical features and management diabetic neuropathy-a nerve disease

Debjit Bhowmik<sup>1</sup>, K.P.Sampath kumar<sup>2</sup> and Lokesh Deb<sup>3</sup>

<sup>1</sup>Department of Pharmaceutical sciences, Karpagam University, Coimbatore

<sup>2</sup>Coimbatore Medical College Coimbatore, Tamilnadu

<sup>3</sup>Department of Biotechnology, Institute of Bioresources and Sustainable Development, Imphal.

### ARTICLE INFO

#### Article history:

Received: 15 August 2011;

Received in revised form:

19 October 2011;

Accepted: 4 November 2011;

#### Keywords

Diabetes Neuropathy,  
Sensory neuropathy,  
Autonomic neuropathy,  
Motor neuropathy.

### ABSTRACT

Diabetic neuropathy is a type of nerve damage that is seen in people who have diabetes. This makes it difficult for the nerves to carry messages to the brain and parts of the body. Diabetic neuropathy can result in numbness or painful tingling in different parts of the body. Diabetic neuropathy can affect any part of the nervous system. This nerve disorder should be suspected in all patients with type 2 diabetes and in patients who have had type 1 diabetes for more than five years. About 60 to 70 percent of people with diabetes have some form of neuropathy. People with diabetes can develop nerve problems at any time, but the risk increases with age and duration of the disease. The highest rates of neuropathy occur among people who have had diabetes for at least 25 years and among people who have trouble controlling their blood sugar levels, as well as those with high levels of blood fat and blood pressure and those who are overweight. Diabetic neuropathy is long-term damage to the nerve fibres. It happens when high blood glucose levels are present over several years. In diabetes, the form it usually first takes is reduced sensation in the feet. The nerve damage affects each foot equally and eventually spreads up the legs. Poor sensation in your feet makes them more prone to injury. Combined with poor circulation this can easily lead to ulcers and infections. As community Pharmacist becomes a consultant for patients who are put on therapy. He counsels the patients about the disease process and simultaneously role of drugs. He informs the patient of drug interactions and adverse reactions.

© 2011 Elixir All rights reserved.

### Introduction

Diabetic neuropathy is a debilitating disorder that occurs in nearly 50 percent of patients with diabetes. It is a late finding in type 1 diabetes but can be an early finding in type 2 diabetes. The primary types of diabetic neuropathy are sensor motor and autonomic. Neuropathy is a common name for complications affecting the nervous system. Acute neuropathy (neuritis) usually disappears once the diabetes is under control. It often presents as a burning sensation in the feet and is especially bad at night and can interrupt sleep. Chronic neuropathy has more serious implications. An early sign of diabetic neuropathy is a lack of ability to feel vibrations, for example from a tuning fork. This test can be carried out during your annual diabetes check-up. The same sort of nerve damage can occur in the hands. This is uncommon, and is always accompanied by problems in the feet and legs. Unfortunately; this type of nerve damage is permanent. Once it's happened, it isn't improved by better control of diabetes. Other types of nerve damage seen in diabetes include paralysis involving single nerves and some painful types of neuralgia (nerve pain). These nerve conditions can be improved by good diabetes control. The morbidity and mortality of diabetes is due to the development of both macrovascular and microvascular complications. Macrovascular complications including myocardial infarction, stroke, and large vessel peripheral vascular disease are 2 to 4 times more prevalent in individuals with diabetes. The underlying common factor in macrovascular complications is the ability of the diabetic condition to accelerate atherogenesis. Atherogenesis is a

multifactorial response of vessels to injury; both insulin resistance and elevated lipid levels, common in diabetes, are primary triggers of atherogenic injury. The endothelium in diabetic arteries is also more prone to atherogenic injury, likely due to decreased production of endothelial nitric oxide, known to be antiatherogenic, and increased production of plasminogen activator inhibitor-1 (PAI-1). While macro-vascular complications are common among diabetics, diabetes-specific microvascular complications will eventually affect nearly all individuals with diabetes. Diabetic retinopathy is the most common cause of adult blindness in the United States. Ninety percent of diabetics present evidence of retinopathy within 15 years of disease onset and approximately 25,000 new cases of diabetes-related blindness are reported per year. Diffuse neuropathy is treated by bringing blood glucose levels under control. This can help to prevent problems from this diabetic complication. Diet, exercise or medication may be adjusted to reach these goals. Exercise can be particularly effective, helping the patient to improve circulation, strengthen muscle and lose weight. Smoking should be stopped and the amount of alcohol consumed should be reduced. Taking regular care of your feet and skin is essential.

### Types of Diabetes Neuropathy

**There are three broad types of neuropathy: sensory, autonomic and motor:**

Sensory neuropathy (or peripheral neuropathy, usually just called neuropathy) affects the nerves that carry information to

the brain about sensations from various parts of the body - how hot or cold something is, what the texture of something feels like, the pain caused by a sharp object or heat, etc. This is the most common form of diabetic neuropathy.

Autonomic neuropathy affects the nerves that control involuntary activities of the body, such as the action of the stomach, intestine, bladder and even the heart.

Motor neuropathy- affects the nerves that carry signals to muscles to allow motions like walking and moving fingers. This form of neuropathy is very rare in diabetes.

Sensory neuropathy can lead to pain, numbness or tingling in the extremities and, ultimately, an inability to feel heat, cold, pain or any other sensation in affected areas. Autonomic neuropathy can lead to impotence in men, bladder neuropathy (which means the bladder is unable to empty completely), diabetic diarrhea, or bloated stomach. Motor neuropathy can lead to muscle weakness. If you are diagnosed with neuropathy, your physician may use terms to describe the type that you have based on whether only one side of your body is affected (asymmetric) or both sides (symmetric). If only one kind of nerve is affected, your doctor may say you have mononeuropathy. If several nerves are affected, the term polyneuropathy may be used.

**Distal Neuropathy** - is a form of sensory neuropathy that affects the hands or feet. It can be asymmetric but is usually symmetric, and is the most frequently diagnosed type of neuropathy

**Femoral neuropathy** -- is painful sensory neuropathy that centers in the thigh muscles. It can be asymmetric or symmetric.

Diabetic amyotrophy - is motor neuropathy that affects the thigh nerves, with resulting weakness often in addition to or instead of pain. It can be symmetric or asymmetric.

**Gastroparesis** -- is autonomic neuropathy that affects the stomach, preventing it from emptying normally. It can result in ulcer-like symptoms, vomiting, bloating, and poor absorption of food resulting in malnutrition and hypoglycemic episodes as food fails to be absorbed at the anticipated rate. High blood sugars can later result when the meal finally makes its way through the system.

**Diabetic diarrhea** - is autonomic neuropathy that results in an erratic functioning of the small intestine. This can cause unformed stools to be passed. If the nerves which communicate with the sphincter muscles (which control passing a bowel movement) are not working properly, stool can pass without warning, and/or without being able to control when it comes out, resulting in fecal incontinence. Constipation also can result when the large intestine is involved and the stool remains in the large intestine too long.

**Bladder neuropathy** - occurs when the bladder nerves no longer respond normally to pressure as the bladder fills with urine, and do not enable the bladder to empty completely. Some urine continually stays in the bladder, leading to urinary tract infections. Symptoms of this problem include cloudy urine, painful urination, low back pain and fever.

**Postural hypotension** - is autonomic neuropathy that results in low blood pressure when standing. In people with postural hypotension, the pulse does not go up to compensate for the change in blood pressure, so fainting and dizziness can result.

**Charcot joint**- is also called neuropathic arthropathy and occurs when the bones in the feet fracture or "powder" and the foot becomes misaligned. The foot becomes deformed as a result of the lack of nerve stimulation, which causes the muscles to lose

the ability to support the foot properly. Walking makes it worse. People who already have neuropathy in their feet and have lost sensation are at a greater risk of developing this.

Unilateral foot drop - occurs when the foot can't be picked up because a nerve in the leg has been damaged either by blood vessel disease or compression.

**Impotence** - is caused by autonomic neuropathy and/or sensory neuropathy, and/or blood vessel disease that leads to an inability to have and maintain an erection in men.

#### **Causes of Diabetic Neuropathy**

The causes are probably different for different types of diabetic neuropathy. Researchers are studying how prolonged exposure to high blood glucose causes nerve damage. Nerve damage is likely due to a combination of factors:

- ❖ metabolic factors, such as high blood glucose, long duration of diabetes, abnormal blood fat levels, and possibly low levels of insulin
- ❖ neurovascular factors, leading to damage to the blood vessels that carry oxygen and nutrients to nerves
- ❖ autoimmune factors that cause inflammation in nerves
- ❖ mechanical injury to nerves, such as carpal tunnel syndrome
- ❖ inherited traits that increase susceptibility to nerve disease
- ❖ lifestyle factors, such as smoking or alcohol use

#### **Symptoms Diabetic Neuropathy**

Symptoms depend on the type of neuropathy and which nerves are affected. Some people with nerve damage have no symptoms at all. For others, the first symptom is often numbness, tingling, or pain in the feet. Symptoms are often minor at first, and because most nerve damage occurs over several years, mild cases may go unnoticed for a long time. Symptoms can involve the sensory, motor, and autonomic – or involuntary – nervous systems. In some people, mainly those with focal neuropathy, the onset of pain may be sudden and severe.

Symptoms of nerve damage may include

- ❖ numbness, tingling, or pain in the toes, feet, legs, hands, arms, and fingers
- ❖ wasting of the muscles of the feet or hands
- ❖ indigestion, nausea, or vomiting
- ❖ diarrhea or constipation
- ❖ dizziness or faintness due to a drop in blood pressure after standing or sitting up
- ❖ problems with urination
- ❖ erectile dysfunction in men or vaginal dryness in women
- ❖ weakness

Symptoms that are not due to neuropathy, but often accompany it, include weight loss and depression.

#### **Pathophysiology of Diabetic Neuropathy**

The factors that cause diabetic neuropathy have not been understood completely. However, there are a number of factors that are considered to be responsible for this damage. Some of the proposed theories for the occurrence of diabetes neuropathy include:

**Metabolic theory:** This proposes that diabetes causes increase in the glucose in the nerves, which causes saturation of the normal glycolytic pathway. This results in increase of sorbitol and fructose that decrease the nerve activity and inhibits the transmission through nerves.

**Vascular Theory:** As per this theory endoneurial ischemia is formed that increases the vascular resistance to the hyperglycemic blood. This results in nerve damage.

Altered neurotrophic support theory: The neurotrophic factors are responsible for the maintenance and development of the responsive elements of the nerves. If there is alteration in these systems then it can result in nerve damage.

Laminin theory: Lack of the glycoprotein Laminin can result in nerve damage.

Autoimmune theory: IF there is any alteration in the immunogenic system then it can result in nerve damage.

Diabetic neuropathy is seen to occur more frequently in male patients suffering from diabetes rather than female patients. Moreover it is seen to occur in patients where diabetes is severe.

#### **Risk Factors of Diabetic Neuropathy**

- ❖ Smoking
- ❖ Aged over 40 years
- ❖ History of periods of poor glycaemic control
- ❖ Prevalence increases with increased duration of diabetes
- ❖ People with signs of neuropathy are likely also to have evidence of diabetic nephropathy and diabetic retinopathy
- ❖ Hypertension
- ❖ Ischemic heart disease

#### **Diagnosis of Diabetic Neuropath**

##### **Foot exams**

Experts recommend that people with diabetes have a comprehensive foot exam each year to check for peripheral neuropathy. People diagnosed with peripheral neuropathy need more frequent foot exams. A comprehensive foot exam assesses the skin, muscles, bones, circulation, and sensation of the feet. Your doctor may assess protective sensation or feeling in your feet by touching your foot with a nylon monofilament – similar to a bristle on a hairbrush – attached to a wand or by pricking your foot with a pin. People who cannot sense pressure from a pinprick or monofilament have lost protective sensation and are at risk for developing foot sores that may not heal properly. The doctor may also check temperature perception or use a tuning fork, which is more sensitive than touch pressure, to assess vibration perception.

##### **Other tests**

The doctor may perform other tests as part of your diagnosis.

- ❖ Nerve conduction studies or electromyography are sometimes used to help determine the type and extent of nerve damage. Nerve conduction studies check the transmission of electrical current through a nerve. Electromyography shows how well muscles respond to electrical signals transmitted by nearby nerves. These tests are rarely needed to diagnose neuropathy.
- ❖ A check of heart rate variability shows how the heart responds to deep breathing and to changes in blood pressure and posture.
- ❖ 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 show how these organs preserve a normal structure and whether the bladder empties completely after urination.

#### **Treatment of Diabetic Neuropathies**

The first treatment step is to bring blood glucose levels within the normal range to help prevent further nerve damage. Blood glucose monitoring, meal planning, physical activity, and diabetes medicines or insulin will help control blood glucose levels. Symptoms may get worse when blood glucose is first brought under control, but over time, maintaining lower blood glucose levels helps lessen symptoms. Good blood glucose control may also help prevent or delay the onset of further problems. As scientists learn more about the underlying causes of neuropathy, new treatments may become available to help

slow, prevent, or even reverse nerve damage. As described in the following sections, additional treatment depends on the type of nerve problem and symptom. If you have problems with your feet, your doctor may refer you to a foot care specialist.

Pain relief

Doctors usually treat painful diabetic neuropathy with oral medications, although other types of treatments may help some people. People with severe nerve pain may benefit from a combination of medications or treatments. Talk with your health care provider about options for treating your neuropathy. Medications used to help relieve diabetic nerve pain include

- ❖ tricyclic antidepressants, such as amitriptyline, imipramine, and desipramine (Norpramin, Pertofrane)
- ❖ other types of antidepressants, such as duloxetine (Cymbalta), venlafaxine, bupropion (Wellbutrin), paroxetine (Paxil), and citalopram (Celexa)
- ❖ anticonvulsants, such as pregabalin (Lyrica), gabapentin (Gabarone, Neurontin), carbamazepine, and lamotrigine (Lamictal)
- ❖ opioids and opioid-like drugs, such as controlled-release oxycodone, an opioid; and tramadol (Ultram), an opioid that also acts as an antidepressant

Duloxetine and pregabalin are approved by the U.S. Food and Drug Administration specifically for treating painful diabetic peripheral neuropathy.

You do not have to be depressed for an antidepressant to help relieve your nerve pain. All medications have side effects, and some are not recommended for use in older adults or those with heart disease. Because over-the-counter pain medicines such as acetaminophen and ibuprofen may not work well for treating most nerve pain and can have serious side effects, some experts recommend avoiding these medications. Treatments that are applied to the skin – typically to the feet – include capsaicin cream and lidocaine patches (Lidoderm, Lidopain). Studies suggest that nitrate sprays or patches for the feet may relieve pain. Studies of alpha-lipoic acid, an antioxidant, and evening primrose oil have shown that they can help relieve symptoms and may improve nerve function. A device called a bed cradle can keep sheets and blankets from touching sensitive feet and legs. Acupuncture, biofeedback, or physical therapy may help relieve pain in some people. Treatments that involve electrical nerve stimulation, magnetic therapy, and laser or light therapy may be helpful but need further study. Researchers are also studying several new therapies in clinical trials

#### **Gastrointestinal problems**

To relieve mild symptoms of gastroparesis – indigestion, belching, nausea, or vomiting – doctors suggest eating small, frequent meals; avoiding fats; and eating less fiber. When symptoms are severe, doctors may prescribe erythromycin to speed digestion, metoclopramide to speed digestion and help relieve nausea, or other medications to help regulate digestion or reduce stomach acid secretion. To relieve diarrhea or other bowel problems, doctors may prescribe an antibiotic such as tetracycline, or other medications as appropriate. Dizziness and weakness Sitting or standing slowly may help prevent the light-headedness, dizziness, or fainting associated with blood pressure and circulation problems. Raising the head of the bed or wearing elastic stockings may also help. Some people benefit from increased salt in the diet and treatment with salt-retaining hormones. Others benefit from high blood pressure

medications. Physical therapy can help when muscle weakness or loss of coordination is a problem.

#### Urinary and sexual problems

To clear up a urinary tract infection, the doctor will probably prescribe an antibiotic. Drinking plenty of fluids will help prevent another infection. People who have incontinence should try to urinate at regular intervals—every 3 hours, for example – since they may not be able to tell when the bladder is full.

To treat erectile dysfunction in men, the doctor will first do tests to rule out a hormonal cause. Several methods are available to treat erectile dysfunction caused by neuropathy. Medicines are available to help men have and maintain erections by increasing blood flow to the penis. Some are oral medications and others are injected into the penis or inserted into the urethra at the tip of the penis. Mechanical vacuum devices can also increase blood flow to the penis. Another option is to surgically implant an inflatable or semirigid device in the penis. Vaginal lubricants may be useful for women when neuropathy causes vaginal dryness. To treat problems with arousal and orgasm, the doctor may refer women to a gynecologist.

#### Foot care

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. Circulation problems also increase the risk of foot ulcers.

More than half of all lower-limb amputations in the United States occur in people with diabetes – 86,000 amputations per year. Doctors estimate that nearly half of the amputations caused by neuropathy and poor circulation could have been prevented by careful foot care.

#### Follow these steps to take care of your feet:

- Clean your feet daily, using warm – not hot – water and a mild soap. Avoid soaking your feet. Dry them with a soft towel and dry carefully between your toes.
- Inspect your feet and toes every day for cuts, blisters, redness, swelling, calluses, or other problems. Use a mirror – laying a mirror on the floor works well – or get help from someone else if you cannot see the bottoms of your feet. Notify your health care provider of any problems.
- Moisturize your feet with lotion, but avoid getting the lotion between your toes.
- After a bath or shower, file corns and calluses gently with a pumice stone.
- Each week or when needed, cut your toenails to the shape of your toes and file the edges with an emery board.
- Always wear shoes or slippers to protect your feet from injuries. Prevent skin irritation by wearing thick, soft, seamless socks.
- Wear shoes that fit well and allow your toes to move. Break in new shoes gradually by first wearing them for only an hour at a time.
- Before putting your shoes on, look them over carefully and feel the insides with your hand to make sure they have no tears, sharp edges, or objects in them that might injure your feet.

#### Conclusion

Diabetic neuropathy in the form of autonomic neuropathy may likewise affect the digestive system, the heart, and the reproductive organs. Proximal neuropathy affects the hips, thighs, and or buttocks area. Blood glucose control is the most

effective (and simplest) treatment for neuropathy. A patient's blood glucose level has to be maintained within the standard range in order to put off additional nerve damage. The doctor may design a program that helps the patient monitor his or her blood glucose, plan meals around the goal, and exercise specifically for the condition. Some patients are advised to take either insulin injections or oral drugs that help manage blood glucose levels. Aspirins and non-steroidal anti-inflammatory drugs may also be prescribed to lessen pain. Some doctors also administer electronic nerve stimulation to impede pain. Combinations of relaxation training, hypnosis, acupuncture, and biofeedback are also sometimes used. Community Pharmacist who can properly guide the optimal management for each individual patient

#### Reference

- 1) Greene DA, Sima AF, Pfeifer MA, Albers JW. Diabetic neuropathy. *Annu Rev Med.* 1990;41:303–17.
- 2) Olaleye D, Perkins BA, Bril V. Evaluation of three screening tests and a risk assessment model for diagnosing peripheral neuropathy in the diabetes clinic. *Diabetes Res Clin Pract.* 2001;54:115–28.
- 3) Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. *Diabetes Care.* 2003;26:1553–79.
- 4) Stevens MJ, Raffel DM, Allman KC, Schwaiger M, Wieland DM. Regression and progression of cardiac sympathetic dysinnervation complicating diabetes: an assessment by C-11 hydroxyephedrine and positron emission tomography. *Metabolism.* 1999;48:92–101.
- 5) Consensus development conference on the diagnosis of coronary heart disease in people with diabetes: 10–11 February 1998, Miami, Florida. American Diabetes Association *Diabetes Care.* 1998;21:1551–9.
- 6) May O, Arildsen H. Assessing cardiovascular autonomic neuropathy in diabetes mellitus: how many tests to use? *J Diabetes Complications.* 2000;14:7–12.
- 7) Frykberg RG, Armstrong DG, Giurini J, Edwards A, Kravette M, Kravitz S, et al. Diabetic foot disorders: a clinical practice guideline. American College of Foot and Ankle Surgeons. *J Foot Ankle Surg.* 2000;395 suppl:S1–60.
- 8) Sommer TC, Lee TH. Charcot foot: the diagnostic dilemma [published correction appears in *Am Fam Physician* 2002;65:2436–8]. *Am Fam Physician.* 2001;64:1591–8.
- 9) Valdovinos MA, Camilleri M, Zimmerman BR. Chronic diarrhea in diabetes mellitus: mechanisms and an approach to diagnosis and treatment. *Mayo Clin Proc.* 1993;68:691–702.
- 10) Wald A. Incontinence and anorectal dysfunction in patients with diabetes mellitus. *Eur J Gastroenterol Hepatol.* 1995;7:737–9.
- 11) Chu NV, Edelman SV. Erectile dysfunction and diabetes. *Curr Diab Rep.* 2002;2:60–6.
- 12) Minhas S, Eardley I. Diabetes mellitus and impotence. In: Carson CC 3d, Kirby RS, Goldstein I, eds. Textbook of erectile dysfunction. Oxford, England: Isis Medical Media, 1999:541–50.
- 13) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. Diabetes Control and Complications Trial Research Group. *N Engl J Med.* 1993;329:977–86.
- 14) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK

Prospective Diabetes Study (UKPDS) Group [published correction appears in *Lancet* 1999;354:602]. *Lancet*. 1998;352:837-53.

15) American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care*. 2005;28(suppl 1):S4-36.

16) Effect of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. *Ann Neurol*. 1995;38:869-80.

17) American Association of Clinical Endocrinologists medical guidelines for the management of diabetes mellitus: the AACE system of intensive diabetes self-management 2002 update. *Endocrine Practice*. 2002;8(suppl 1):41-65.

18) Hollingshead TS. Pathophysiology and treatment of diabetic foot ulcer. *Clin Podiatr Med Surg*. 1991;8:843-55.

19) Armstrong DG, Lavery LA. Diabetic foot ulcers: prevention, diagnosis and classification. *Am Fam Physician*. 1998; 57:1325-321337-8.

20) Mayfield JA, Reiber GE, Sanders LJ, Janisse D, Pogach LM, American Diabetes Association. . Preventive foot care in diabetes. *Diabetes Care*. 2004;27(suppl 1):S63-4.

21) National Diabetes Education Program. Feet can last a lifetime. Screening form for diabetes foot disease. Accessed online February 13, 2005, at: <http://ndep.nih.gov/resources/feet/screenfo.htm>.

22) Frykberg RG. Diabetic foot ulcers: pathogenesis and management. *Am Fam Physician*. 2002;66:1655-62.