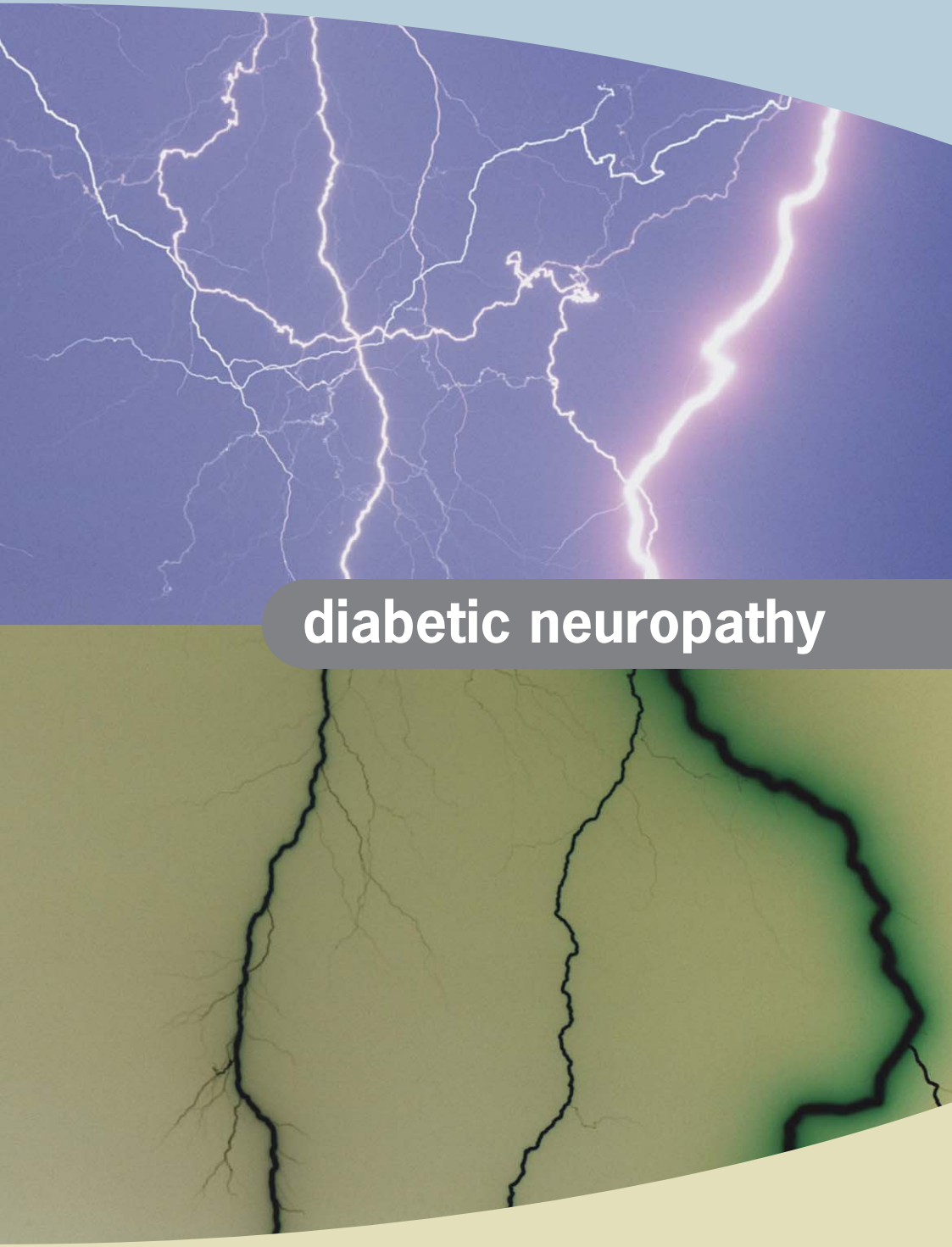
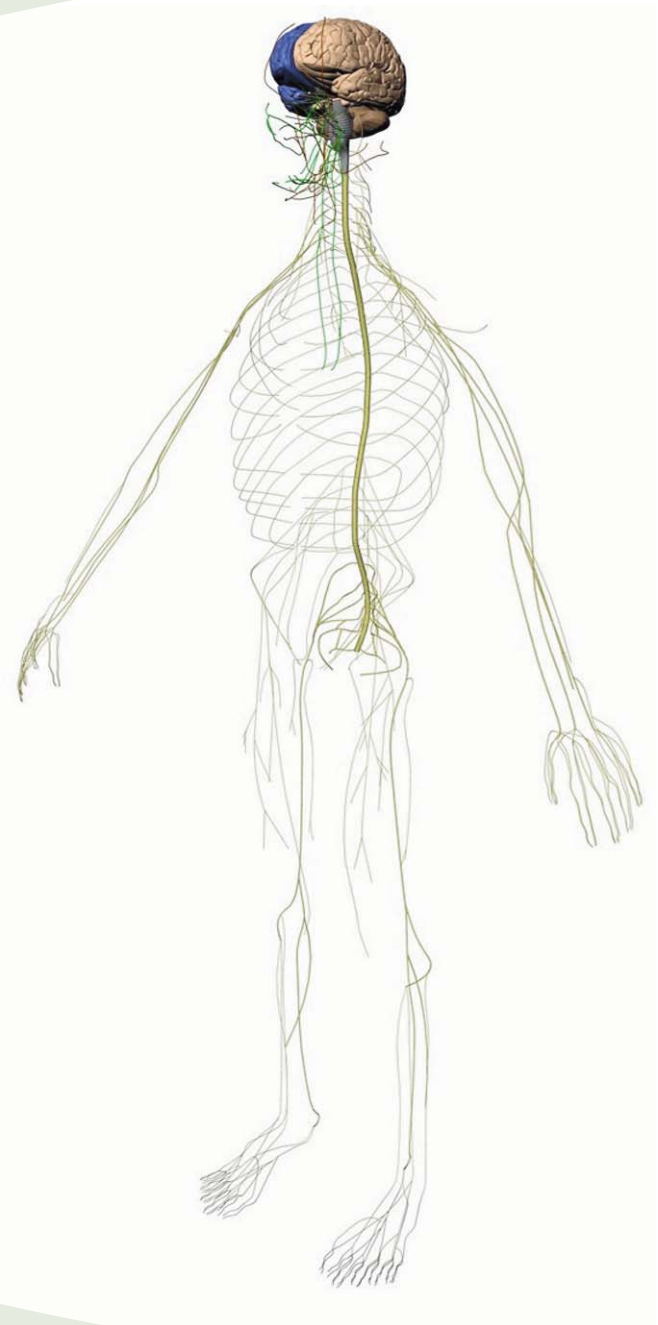


diabetic neuropathy



1 how does the nervous system work?

Nerves carry messages between the brain and other parts of the body through impulses, also known as nerve impulses. Collectively, these nerves are known as the nervous system.

Some nerves tell the brain what is going on in the body. For example, if your finger comes in close contact to a flame or if you step on a nail, the sensory nerves in that area transmit the feeling of pain to your brain. In turn, the nervous system sends another signal, which provokes a motor response so as to avoid the cause of pain.

There are three types of peripheral nerves: motor, sensory and autonomic.

The peripheral motor nerves send impulses to the muscles allowing them to move.

Sensory nerves convey information about texture, temperature, and pain to the brain.

Autonomic nerves are involuntary and control vital body functions such as blood pressure, heart rate, and movements of the digestive system or sweating.

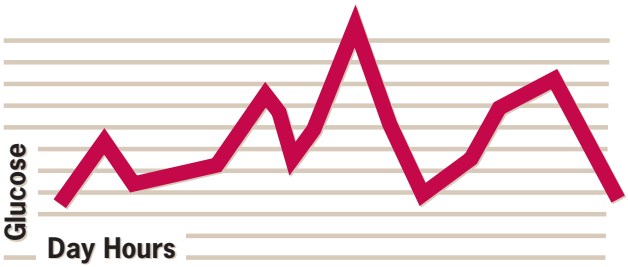
The symptoms of diabetic neuropathy can widely vary depending of the location and type of nerves that are affected.

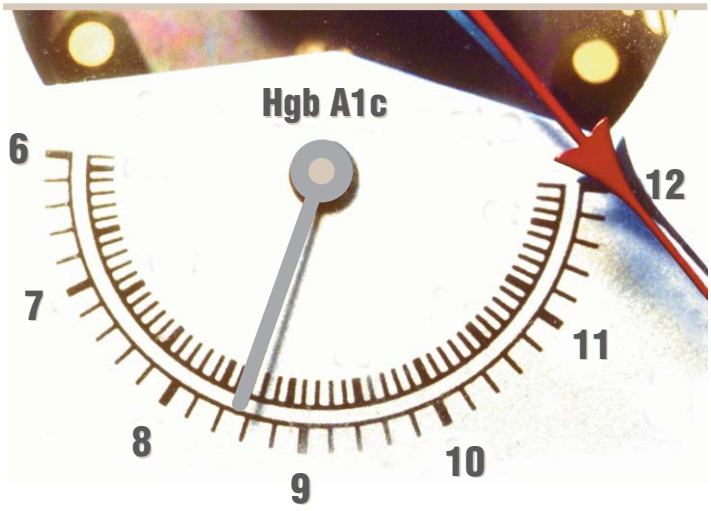
2 what is diabetic neuropathy?

Diabetic neuropathy is a disorder caused by diabetes that affects the nerves found throughout our bodies. These nerves connect the spine to the muscles, skin, blood vessels and the other organs found in our bodies. As such, diabetic neuropathy can affect any part of the body.

Affected nerves can send erroneous messages to the brain. For example, in the case of neuropathy affecting the legs, the brain can send continuous messages stimulating them and sending pain sensations, cramps, tingling etc. On the other hand, the affected nerves might not send signals to the brain when it should, like when we hit ourselves with a hammer and nail or when our shoes fits too tightly, situations that can result in serious lesions.

Neuropathy can occur in either type of diabetes. Neuropathy increases the longer you have diabetes type 1 but is a more common complication in diabetes type 2 where more than 50% of the patients are affected starting from the beginning of their illness or even before they have been diagnosed.


Glucose
Day Hours


Hgb A1c
6
7
8
9
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11
12

3 causes

It's not known what causes diabetic neuropathy. The following is a list of factors that are thought to cause diabetic neuropathy:

Metabolic causes

Such as high blood glucose levels, long duration of diabetes, insufficient levels of insulin, abnormal blood fat levels, or accumulation of certain substances that are toxic to the nerves.

Neurovascular causes

Leading to damage to the blood vessels that carry oxygen and nutrients to nerves.

Autoimmune causes

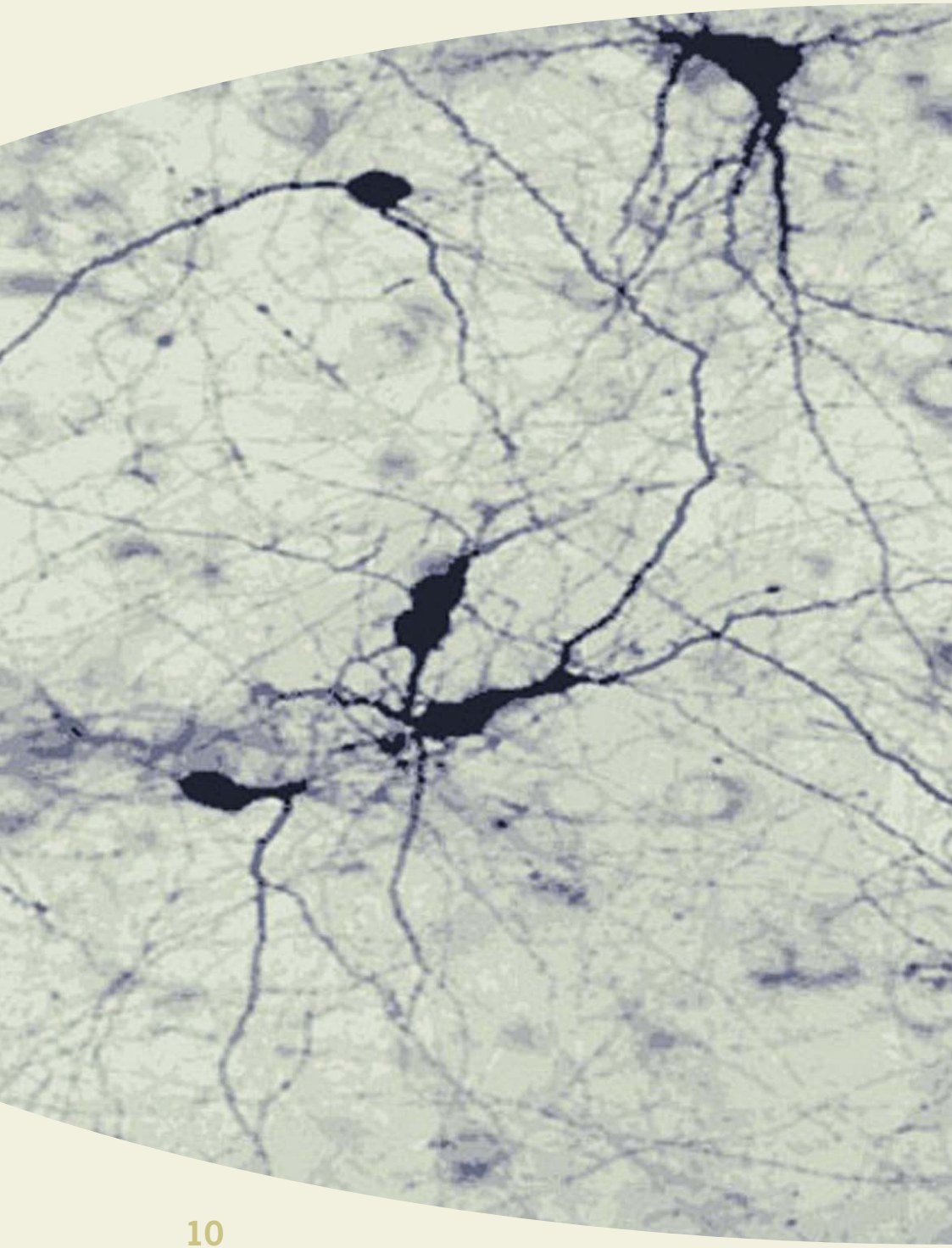
That cause inflammation in the nerves.

Environmental causes

Ssuch as the use of alcohol and tobacco.

Genetic causes

That increase susceptibility to nerve disease.



4 types of diabetic neuropathy and symptoms

In a broad sense, we can talk about three main types of diabetic neuropathy depending on the nervous system fibers that are affected:

a. motor **b. sensory** **c. autonómic**

a. motor neuropathy

Motor neuropathy is uncommon but can cause muscular weakness or even paralysis of the affected nerves. It predominantly affects the cranial nerves which are responsible for facial and ocular muscle movement. Symptoms can include double vision, headaches, and paralysis of half the face. More rarely, thigh muscles are affected causing muscular weakness and atrophy causing difficulty getting up from a chair and even difficulties walking.

b. sensory neuropathy

Sensory neuropathy is the most common of the mentioned neuropathies. Its symptoms vary from pain, pins and needles, tingling, and cramps in the extremities. Sensory neuropathy generally afflicts the legs symmetrically, with increased symptoms at night.

Sensory neuropathy is important not only because of the suffering it causes but because it is the most frequent cause of non-traumatic lower extremity amputations as it increases the risk of foot ulcers and infections. Sensory neuropathy increases the risk of foot ulcers and infections because of the diminished sensation making it difficult to distinguish between coldness, heat, or even pain. This patient population carries the risk of vascular problems in their legs making them more susceptible to infections. Their wounds tend to heal slowly and if not treated on time, can lead to amputations.

When the nerves that innervate with the muscles in the feet are affected, they tend to loose strength. The feet are unable to maintain normal foot structure. This leads to displacement of the bones within the feet. As a result, foot deformities and fractures can occur. This is known as Charcot foot.

c. autonomic neuropathy

It can affect any of the organs in the body, however, the organs most frequently affected are summarized in following table:

autonomic neuropathy symptoms

System	*Symptoms*
Cardiovascular	Pallor Dizziness Fatigue Fainting
Gastrointestinal	Constipation Fecal incontinence Diarrhea Nausea and vomiting
Genitourinary	Urinary incontinence Erectile dysfunction retrograde ejaculation Lack of lubrication Urinary tract infections
Dermatological	Alterations in sweat Hot flashes, etc…

digestive system

stomach

Can occur in 5-12% of people that have diabetes. Women are affected more often than men. It can cause a condition called diabetic gastroparesis where the stomach doesn't empty normally. Many times, this complication isn't diagnosed until the symptoms are obvious. Symptoms can vary from bloating, nausea, vomiting, blood sugar control variability with hypoglycemia after meals and late episodes of hyperglycemia.

small intestine

Disrupts the functioning of the small intestine which generally manifests as episodes of chronic diarrhea, including nocturnal episodes, that alternate with phases of constipation.

large intestine

Generally causes very intense constipation that doesn't respond well to traditional laxatives. Many resort to using enemas. This neuropathy is frequently associated with cardiovascular autonomic neuropathy.

anal sphincter

The muscle nerves that control the sphincter are affected and can cause incontinence which is aggravated by the fact that it's usually associated with diarrhea as the small intestine is affected as well.

genitourinary system

It is known as a neurogenic bladder and is caused by nerve dysfunction of the bladder. The nerves don't respond appropriately to pressure changes in the bladder when full. It becomes difficult to know when you need to use the restroom and can even cause accidental leakage of urine. When voiding, the bladder does not empty completely. There is always a small amount of urine residual left which makes you susceptible to frequent urinary tract infections.

sexual function

In males, nerve dysfunction of the mechanisms involved with an erection can lead to decreased sexual response. Generally, the sexual desire is maintained. This disorder tends to appear slowly and progressively over time.

In women, the vaginal nerves can impede adequate lubrication during sexual intercourse leading to difficulties with penetration. In addition, sensation in the genital area can be lost.

cardiovascular system

postural hypotension

Our autonomic nervous system has pressure receptors located in the blood vessels that, when functioning normally, allow for blood pressure changes with positional changes. These mechanisms falter in some people with this type of autonomic neuropathy, causing various nuisances with postural changes. Symptoms vary from simple dizzy spells, in particular, when getting up from the bed, to sudden fainting episodes which can cause dangerous falls.

heart

If the nerves in the heart are affected, the heart beats faster and at different speeds, causing arrhythmias. Autonomic neuropathy can also eliminate or diminish the pain caused by coronary disease and is one reasons why diabetics so frequently suffer from painless heart attacks.

skin

The nerves that regulate sweat of the gland activity tend to be affected leading to symptoms such as dry skin. Since the natural system of hydration falters, cracks and possible skin infections may occur, especially in the feet. Short episodes of profuse sweating can occur at night or with meals.

hypoglycemic unawareness

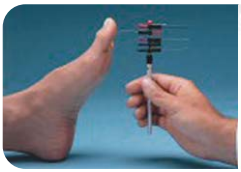
Autonomic neuropathy can influence how our body responds to low blood sugar levels and is one of the causes of hypoglycemic unawareness especially in people that have had diabetes for a long time.

5 diagnosis

Some patients see the doctor because of pain or changes in the sensitivity of their feet or legs. Others see the doctor because of vomiting, diarrhea, constipation, dizziness or sudden loss of consciousness.

Diabetic neuropathy can be diagnosed based on the above-mentioned symptoms and with a physical exam during which the physician uses a simple device to check muscular strength, reflexes, vibratory sensation, temperature, etc.

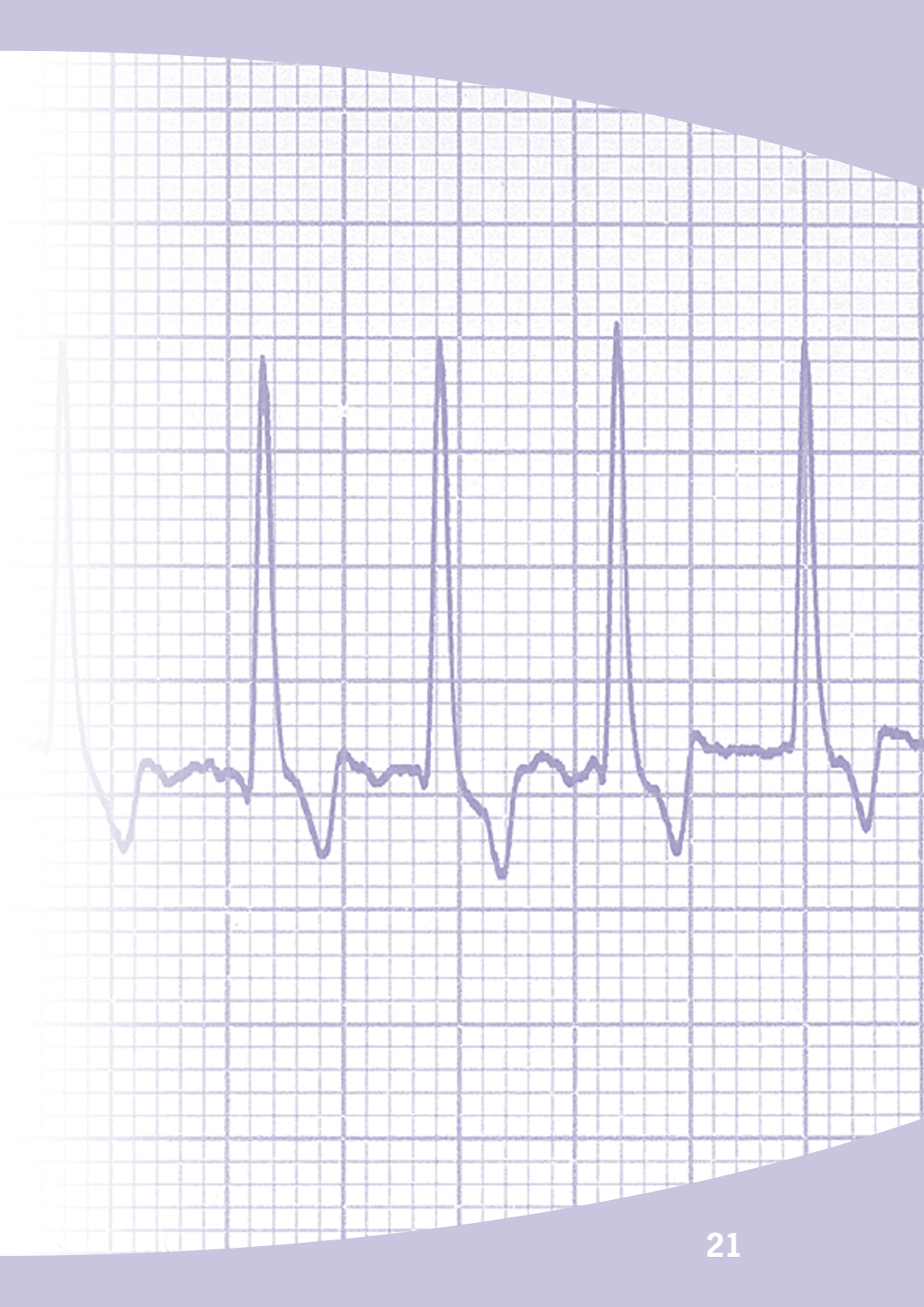
The monofilament test is a quick and easy test used to detect diabetic neuropathy and should be performed at least every year. The test consists of a nylon filament that applies 1 gram of pressure before bending. If the nylon is not felt at the various areas of the feet, this would indicate diminished sensitivity or a loss of sensitivity perception. Special precautions would need to be taken as a loss of the protective sensation significantly increases the risk of ulcers and other problems with the feet.



There are a variety of other tests that can be performed. Some are more sophisticated, such as electromyography that records muscular responses to electric impulses. Nerve conduction velocity studies measure the transmission of nerve impulses. Biothesiometry measures and records vibratory sensitivity.

In order to diagnose autonomic neuropathy, heart rate variability tests are performed to check how the heart responds to deep breathing, posture changes and blood pressure changes. Gastric emptying studies record gastric contractions similar to how an EKG is done for the heart.

These studies along with the physician's clinical observations confirm the diagnosis while ruling out other possible causes for your symptoms.



6 treatment

Studies are being done to help discover treatments that reestablish nervous system function that has been damaged by diabetic neuropathy. Currently, there is no cure to recover damaged nerve function, however, there are methods and certain medications to help control symptoms and avoid pain. There is no magic treatment that exists that works for everyone. Treatment should be individualized depending on the type of neuropathy, the intensity, location of pain, and the personal characteristics of each person.

As no treatment is perfect for this type of pain, your physician should clearly explain the limitations of treatment and that many times, patients experience only partial relief of pain. In this manner, false expectations will be avoided and a climate of confidence created. In addition, your physician should explain that the medication dosage is individual and progressive. It may take a few weeks to obtain therapeutic levels of medication in the bloodstream. As such, one should wait a month before switching medications.

Obtaining adequate control of your diabetes and above all, stabilizing blood sugars can help or at least diminish the symptoms caused by neuropathy.

a. treatments for sensory neuropathy

Aside from the stabilization and optimization of blood sugar control as mentioned above, it is essential that treatment includes meticulous foot care aimed at protecting insensitive feet from sustaining injury.

The current principal treatments are summarized in the following table:

drugs useful in diabetic neuropathy

Antidepressants	*Tricyclics:*
	Amitriptyline and Impramina
	Velataxina
	*Cymbalta**
Antiepileptics	*Gabapentin*
	Topiramate
	Valproate
Opiates	*Pregabalin**
	Tramadol
Others	*Oxycodone, etc.*
	Capsaicin cream
	Mexiliteno
	Ac alpha lipoic

* Unique to the specific indication approved treatments in Diabetic Neuropathy

Medications are available to help alleviate pain, reduce burning, numbness and tingling. Some medicines are known for treating other pathologies but also help treat issues related to nervous system disorders. Among the options, medications are used to treat:

- **pain > analgesics**
- **depression > antidepressants**
- **seizures > anticonvulsants**

Topical treatments: Capsaicin is applied as a cream in mild cases of neuropathy and can alleviate the sensation of pain and heat. Some local discomfort may occur but should lessen with time.

analgesics

Aspirin and anti-inflammatory drugs such as ibuprofen can be used however their effectiveness is limited. Opiates should be avoided whenever possible because of their side effects and, above all, because long-term use leads to dependency.

antidepressants

Above all, the tricyclic antidepressants such as Imipramine and Amitriptyline have been used for many years and in some cases helps relieve pain. The benefit could be related to the pain perception threshold and is not related to the improvement of depression.

Other antidepressants used include Duloxetine and Venlafaxine which act upon the levels of certain hormonal substances (serotonin and norepinephrine) which are thought to be related to pain.

anticonvulsants and opiates

Carbamazepine and Phenytoin were used for many years with relative success but have since been discontinued because of their side effects and toxicity. More recently, Gabapentin has been used. Gabapentin has the advantage of being well tolerated, even at larger doses, and is quite effective in reducing cramps and tingling.

Pregabalin is a similar substance that can help with pain in some patients that suffer from neuropathic pain. It is thought that Pregabalin acts by blocking receptors in the affected nerve cells.

Topamax is also used and it has the advantage of promoting weight loss. There are no studies comparing the effectiveness of these medications nor do we have studies about how these medications interact. However, in the future, when studies do become available, they may constitute future treatments.

Opiates would only be used in extreme cases and in general would be used in patients referred to the Pain Unit.

non-pharmalogical methods

Non-invasive stimulation techniques or high voltage galvanic stimulation, acupuncture etc, may be helpful in some cases to help alleviate pain. In reality, few respond to these treatments. At the same time, few specialists are against trying such measures.

b. treatments for autonomic neuropathy

gastroparesis

Gastroparesis is very difficult to treat but it can be alleviated by following a series of steps. Firstly, all vegetables high in fiber should be eliminated from the diet. It's better to eat pureed or mashed proteins and drink at least 2 cups of water with each meal.

In most cases, these measures should accompany drug therapy such Metoclopramide, Erythromycin, Domperidone or a combination of them.

Rarely, surgery is needed to perform a jejunostomy and place a feeding tube, or more recently, implantation of a gastric pacemaker that stimulates contractions and gastric emptying.

postural hypotension

Physical measures such as standing up slowly or moving your legs around before standing can improve dizziness and feeling faint during postural changes. Wearing elastic stockings or increasing salt consumption can help in other cases. In the exceptional case, the use of medications like Fludrocortisone, which is a hormone, can help your body retain salt.

neurogenic bladder

Early management of a neurogenic bladder is remembering to void every 3-4 hours. Applying pressure with your hands to the lower part of the abdomen helps reduce the amount of residual urine left in the bladder after urination and in turn helps decrease the risk of developing a urinary tract infection. Rarely, medications such as Urecholine are needed to help the bladder contract and empty.

small intestine

As we mentioned before, in the majority of cases, disturbances of the small intestine include diarrhea which can alternate with periods of constipation. These issues respond well to daily treatments with Diphenoxylate, Loperamide, ect. When symptoms don't improve with these medications, broad spectrum antibiotics such a Tetracycline can be used.

skin

Daily use of hydrating lotions, especially in the lower extremities, helps to prevent dry skin which can lead to cracked and chapped areas or ulcers. Early and adequate treatment of fungal infections of the skin and nails should be employed.

sexual dysfunction

In the male population, the Phosphosdiesterase-5 inhibitors (Sildenafil, Tadalafil, Vardenafil) have been used with much success, although results may vary. In those patients that cannot take the above listed medications, other less frequently used methods that have been helpful include mechanical emptying devices, injection of vasoactive substances (Phentolamine, Prostaglandin, Papaverine) and rarely surgery for implantation of inflatable prosthetic device.

The role that diabetic neuropathy plays in women that present with sexual dysfunction is less clear. When sexual dysfunction exists, sexual relations becomes a challenge due to decreased vaginal lubrication. The use of lubricants can help relieve dryness.

hypoglycemia unawareness

They can be very difficult to treat but outcomes can be improved by following series of step:

a. Modify insulin therapy to try and avoid hypoglycemia, especially hypoglycemic episodes below 54mg%. It has been seen that the body's contraregulatory systems deteriorate when levels drop below this level.

b. Utilization of insulin pumps. It has been shown that the number and severity of hypoglycemic episodes decreases by avoiding slow acting insulin.

c. Continuous monitoring of blood sugars. In reality, the current systems available are semi-invasive which measure the amount of glucose within interstitial fluid. These systems are certainly feasible however their usage is limited by the high costs associated with product utilization. We can assume that these costs will decrease as new systems become commercialized, as do most technologic products with time. Diabetes causing significant limitations and decreased quality of life will be a thing of the past with these advances.

Translated by Sarah Folan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