Diabetic Neuropathy

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3.1 Introduction

Diabetic neuropathy (DN) is a common complication of diabetes that typically presents symmetrically in both lower limbs. It affects both the sensory and motor nerves and is a significant cause of lower extremity amputation. DN is an uncontrollable complication of diabetes, and its prevalence within 1 year of diagnosis ranges from 7 to 50% in diabetics 25 years and older. The presence of cardiovascular autonomic neuropathy (CAN) dramatically shortens a patient's lifespan and increases mortality [1]. Complete loss of sensation in the lower extremities occurs in 1–2% of patients with diabetes, which therefore increases the risk of amputation. Despite efforts to make an early diagnosis and prevent the progression of DN, there is no effective treatment currently available except for the strict control of blood glucose.

3.2 Classification

Many different types of neuropathies have been reported in diabetes mellitus. As a result of DN being a group of heterogeneous states, the clinical classification of various syndromes has proven difficult. Most classifications of DNs are oversimplified due to the inability to explain the variability and duplication of etiologies, clinical manifestations, natural histories, and prognoses. The clinical manifestations and somatic neuropathy measurements were the subject of a recent technical review with an in-depth discussion and relevant references to the literature. Table 3.1 shows the recent recommended comprehensive classification scheme for DN [2].

Table 3.1 Type of neuropathies in diabetes mellitus

Focal
Mononeuritis
Compressive
Upper extremity: Carpal and cubital tunnel syndrome
Lower extremity: Fibular and tarsal tunnel syndrome
Autonomic
Gastroparesis
Cardiac
Vascular
Cranial nerve: VI palsy, III palsy
Amotropy
Mononeuritis multiplex
Diffuse
Large or mixed fiber
Small fiber

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J. P. Hong, H. Suh (eds.), *Diabetic Foot Reconstruction*,
https://doi.org/10.1007/978-981-16-9816-3_3

3.3 Clinical Progress

DN progresses slowly and is overlooked in about 50% with no abnormal initial symptoms or symptoms. Symptoms are often worse in the early stages. Numbness of the foot can increase the risk of developing diabetic foot ulcers. Symptoms and signs of neuropathy include pathophysiologically thick nerve fiber symptoms (muscle weakness, muscle atrophy, etc.) and thin nerve fiber symptoms (loss of sweat, pain and decreased temperature sensation, dry skin, decreased blood flow). On the other hand, it can be classified into benign sensory symptoms (paresthesias: prickling, tingling, "pins and needles," burning, crawling, itching, abnormal sensation to temperature, pain) and negative paresthesias (numbness, insensitivity). Pain is the most common complaint. Symmetrical symptoms on the toes gradually rise to the feet over time, causing symptoms on the fingers and hands (in the form of stocking and glove). Benign symptoms are predominantly more common at night, and some patients may complain of pain just by receiving a duvet or clothing (allodynia). In some patients, the symptoms may progress and the typical sensory ataxia form of gait may be seen due to proprioceptive sensory nerve injury in the sole of the foot. The earliest clinical aspect of motor nerve lesions in DN patients is weakening of the anterior renal muscles of the toes. As a result, local overpressure is applied to the metatarsal head and toe sites when a typical nail toe deformation occurs, and ulcers are likely to occur [3].

In diabetic patients, DN is usually easily diagnosed, but in the case of severe motor neuropathy, polyneuropathy caused by other causes, especially chronic inflammatory demyelinating polyneuropathy (CIDP) or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes), etc., and peripheral neuropathy caused by hypothyroidism or vitamin B12 deficiency. In addition, care should be taken not to be diagnosed as pseudopolyneuropathy even if it is not polyneuropathy by classifying other accompanying neurological diseases (e.g., spinal diseases).

3.4 Diagnosis

For diagnosis of DN during outpatient treatment, neurological examination for touch, pain, temperature, pressure, and vibration angles, along with clinical symptoms, and examination and examination for muscle weakness and muscle atrophy should be performed. Vibration sensory testing can be performed using a 128 Hz tuning fork. Among several tests, the pressure test using 5.07 Semmes Weinstein monofilament, which can apply a pressure of 10 g, is known as the most straightforward, cheapest, and most reliable method, so it is being performed as a guideline for the prediction of the high-risk group for ulceration. However, the results of previous studies on the sensitivity and specificity of the test are so diverse that some suggest that there is a problem in diagnosing DPN with this test alone. Quantitative sensory test (QST), which objectively evaluates vibration sensation, pressure sensation, and temperature sensory threshold, is considered as a useful tool for DPN diagnosis in both clinical and research fields, as it can detect nerve fiber problems that cannot be confirmed by neuroelectromyography. In particular, the vibration sensory threshold test is the most commonly used alone in clinical practice. However, there is a recent report that QST is not a completely objective test and is influenced by several subjective factors such as age and concentration [4].

Neuroelectromyography is an objective standard guideline for diagnosing DN, determining the current level, type, and worsening, and distinguishing it from other diseases. A decrease in the amplitude of a sensory nerve evoked potential (below 6 μV) due to a decrease in the gastrocnemius axon is considered the earliest reliable change. The decrease in gastro-gastric nerve conduction velocity and peroneal motor nerve conduction velocity due to changes in demyelination is also recognized as a significant initial variable [5].

The American Association of Neurology (AAN) suggested five diagnostic criteria for DN. This refers to the symptoms, neurophysical examination, neuroelectromyography, QST, and autonomic function test areas.

3.5 Treatment

3.5.1 Medical Treatment

3.5.1.1 General Principle

Depending on the patient, DN can range from asymptomatic to severe, with pain and foot ulcers that interfere with daily activities. Treatment of diabetic peripheral neuropathy, including painful neuropathy, is arguably essential to clinicians and is one of the most challenging problems. Consultation with various clinical departments is necessary, and patient education is considered critical. The primary purpose of treatment for diabetic peripheral neuropathy is to prevent nerve regression, support regeneration, improve the quality of life, prevent serious complications, and reduce the burden of medical costs. The treatment of diabetic peripheral neuropathy can be broadly divided into three types: first, treatments that control glycemic control and risk factors that correspond to the underlying causes of DN; second, treatments based on etiologic studies of the development of DN; and third, treatment of symptoms related to pain caused by diabetic peripheral neuropathy [6].

3.5.1.2 Glycemic Control

Glycemic control can have a primary preventive effect on DN, relieve symptoms, and prevent progression. Hyperglycemia and glucose fluctuations are known to affect the exacerbation of symptoms. According to a large epidemiological study (EURODIAB IDDM Complications Study) conducted in Europe, the pathogenesis of DN is smoking, a history of cardiovascular disease, vascularity hypertension, and hyperlipidemia. This shows that the risk factors are closely related to the pathogenesis. When treating diabetic peripheral neuropathy, it is essential to actively regulate the blood glucose level, as it is the leading cause of neuropathy. Prospective and retrospective studies have shown that hyperglycemia and the severity of diabetic peripheral neuropathy are closely correlated and that active regulation of blood glucose is therefore an essential therapeutic factor [7].

3.5.1.3 Symptomatic Treatment

Pain in DN and damaged peripheral nerves causes altered nociception transmission to the central nervous system which can result in functional and structural changes that exacerbate the experience of pain. Painful DN is observed in 10–20% of all diabetic patients and in 40–50% of DN patients. Neuropathic pain requires early treatment, as it can lead to severe symptoms such as sleep disturbance, depression, anxiety, and loss of appetite, resulting in a decreased quality of life for diabetic patients.

Tricyclic antidepressants (TCAs) alone or in combination with phenothiazine fluphenazine (amitriptyline and nortriptyline, etc.), with initial small doses of 10–25 mg at night, can improve symptoms. The dosage can be increased while observing the potential side effects, such as deep vein thrombosis, urinary congestion, and glaucoma.

Antiepileptic drugs such as carbamazepine are widely used, with the initial dosage starting at 100 mg twice daily. The dose is then gradually increased after observing the reported effects and side effects. Leukopenia may occur within 3 months of use, and frequent blood cell testing should therefore be performed.

Gabapentin is another antiepileptic drug that has recently been used to relieve acute mild neuropathic pain. The initial dosage of 300 mg daily can be gradually increased while observing its effectiveness and side effects, with a maximum daily dosage of 2400 mg.

The use of topical capsaicin ointment (0.075%) has been reported in a case of typical c-fiber neuropathy with dysesthesia, such as explosive passage dysfunction and ovulation. It can be applied four times a day. The pain was reported to be worsened initially, but relieved after several days.

A local anesthetic ointment, lidocaine, is best used when there is no response to other pain treatments and for the spontaneous recovery of diseases. Its analgesic effects last for 3–21 days. If the reported therapeutic effect is good, orally administered mexiletine can be administered in combination. The drug has also been effective in

clinical studies, with initial daily doses starting at 150 mg and increasing to 600–900 mg [8].

3.6 Surgical Treatment

The traditional medical approach to the treatment of DN is an attempt to achieve a euglycemic state and obtain regular care of the feet. Regular care includes daily foot inspection for the presence of erythema, yearly sensory testing to detect neuropathy, and provision of special protective footwear. If there is a painful neuropathy component, burning, or dysesthetic feet, then the traditional medical approach includes both non-narcotic and narcotic medications, which are often ineffective in relieving pain. Since there is no known cure for DN, the disease inevitably progresses with time. Sensory loss in neuropathy increases the risk for infection, ulceration, and amputation.

Due to the nature of the neurological disease and the ambiguity of the symptoms, surgeons may also miss the opportunity for surgical intervention. Surgical decompression of peripheral nerves is not recommended in all patients with DN but can be performed to reduce pain and prevent complications when local compression of peripheral nerves is considered critical. The most common chronic compression site in the lower extremities of diabetic patients is the tibial nerve in the tarsal tunnel and the common peroneal nerve near the fibular head. DN and chronic compression symptoms are similar to those of carpal tunnel and tarsal tunnel syndromes.

Thus, if a DN patient has local symptoms of nerve compression, symptomatic treatment focused on reducing local edema, inflammation, and pressure with physical therapy and shoe calibration is preferred to surgery. Injecting a mixture of corticosteroids and lidocaine under ultrasound guidance can also be used for both diagnosis and treatment. It is essential to consider and provide alternative treatment options and the clinician can assist in the planning and provision of these options. Finally, if there is a strong suspicion of capture neuropathy due to local nerve compression showing abnormalities, such as Tinel's sign, then decompression surgery should be performed. Therefore, the drug treatment must be maintained [9].

3.6.1 Surgical Approach to Peroneal and Tibial Nerve

3.6.1.1 Common Peroneal Nerve Entrapment

The surgical approach regarding the common peroneal nerve is common, as this nerve can be injured concomitantly with knee and ankle joint injuries. A comparison study of 29 bilateral cadaver dissections and 65 unilateral clinical decompressions was undertaken to identify the anatomic variations of the common peroneal nerve at the fibular neck. This study demonstrated that while the fibrous band deep to the peroneus longus muscle was present in only 30% of cadavers, it was present in 78.5% of cadavers with clinical symptoms of nerve compression that would require neurolysis of the common peroneal nerve. Additional findings were that the lateral gastrocnemius muscle might have a thick fascial origin deep to the common peroneal nerve that requires division. The common peroneal nerve entrance into the anterior and lateral compartments of the leg may be tight because of the proximal origin of the soleus muscle (Fig. 3.1). Therefore, these observations require a surgical approach for neurolysis of this nerve to search for each of these variations [10].

3.6.1.2 Superficial Peroneal Nerve Entrapment

The superficial peroneal nerve (SPN) is located in the lateral compartment of the lower leg, although in 25% of people it can also be found in the anterior compartment and can sometimes be found in both compartments. The SPN exits the fascia of the lateral compartment, on average, approximately 10–12 cm proximal to the lateral malleolus. The incision for neurolysis of the SPN is made anterior to and in parallel with the fibula to permit access to both the anterior and lateral compartments. The incision may be more proximal or distal depending on the

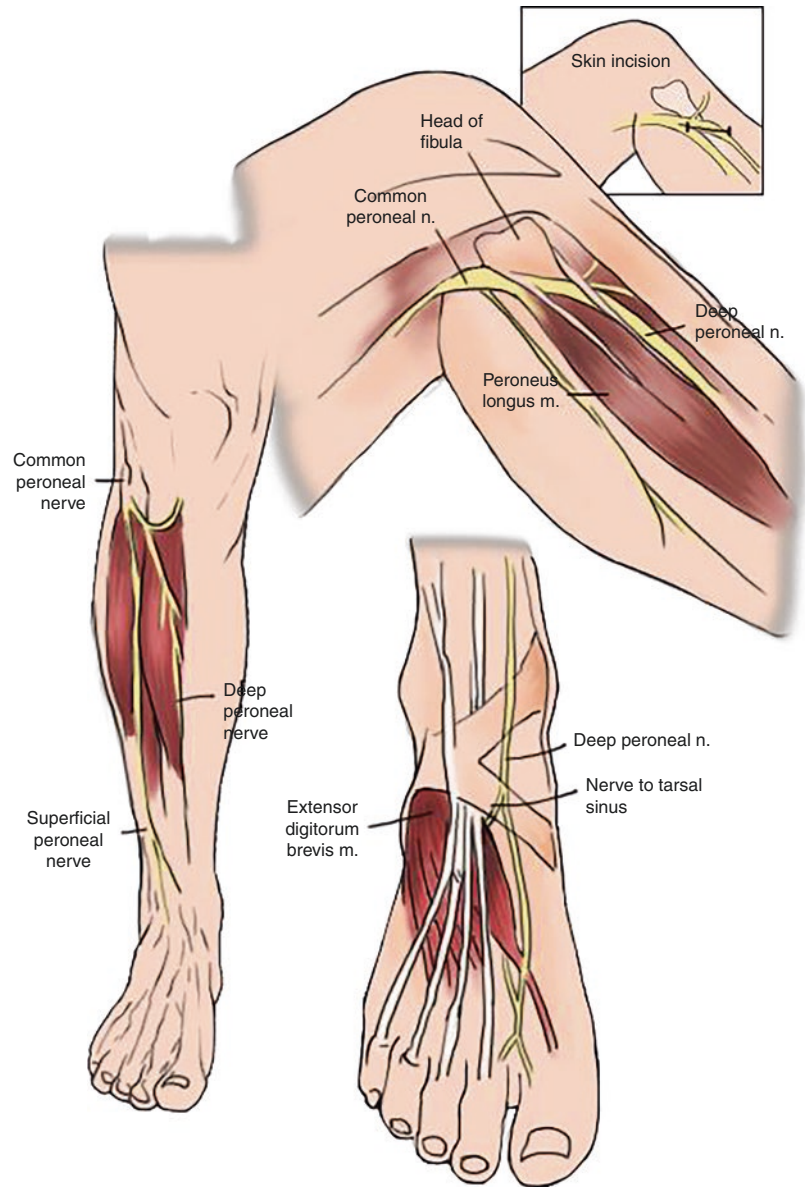

Fig. 3.1 Peroneal innervation of the lower leg

patient's height and the location of the positive Tinel's sign. The incision should be made with caution to the subcutaneous space, to avoid damage to the SPN, which is sometimes found in this space. A slight elevation in the fascia, accompanied by a small blood vessel and some fat, often marks the location of nerve entrapment as the SPN travels from deep toward the superficial fascia to enter the subcutaneous space. An incision of approximately 15 cm is made to ensure the SPN is free from constriction and to avoid a new small muscle herniation through a small fascial window [11].

Both the anterior and lateral compartments should be evaluated, even if the SPN is found in the first compartment entered. If the SPN cannot be found in either, it would lie within the septum itself. The septum should be opened carefully to avoid injury to the SPN or one of its branches. The incised fascial edges is then cauterized, as the fascia is well-vascularized and can cause a postoperative hematoma or seroma. The skin is

then sutured with an interrupted intradermal 4–0 monocryl and continuous interrupted 5–0 nylon sutures.

3.6.1.3 Deep Peroneal Nerve Entrapment

The entrapment of the deep peroneal nerve (DPN) in the anterior tarsal tunnel, which is a broad and deep space beneath the extensor retinaculum, has been described as a site of compression. Compression in this region is only possible with trauma and therefore cannot be the site of compression in patients with neuropathy. In patients with neuropathy, the DPN is entrapped between the extensor hallucis brevis tendon and the underlying bones at the juncture of the first and second metatarsals and the cuneiform. This is the site at which the Tinel's sign radiates pain distally [12].

To release this entrapment, the incision is made obliquely across this region. Blunt dissection should be used in the subcutaneous tissue to identify and retract the superficial peroneal branches and prevent damage. The extensor hallucis brevis tendon is then unambiguously identified, and a 2-cm section is resected to identify whether the DPN sits medially or laterally to the dorsalis pedis artery.

3.6.1.4 Tibial Nerve Entrapment

There are four tunnels to decompress in the ankle joint:

1. The tibial nerve in the tarsal tunnel
2. The medial plantar nerve in the medial plantar tunnel
3. The lateral plantar nerve in the lateral plantar tunnel
4. The calcaneal nerve in one or more calcaneal tunnels

The tibial nerve in the tarsal tunnel is approached through an incision that is posterior to the medial malleolus and midway to the Achilles tendon. The tunnel begins immediately proximal to the medial malleolus. The flexor retinaculum is opened and its edges are cauterized to prevent them from re-attaching postoperatively. The tarsal tunnel is usually not a site of chronic compression. This exposure permits the rest of the decompressions to proceed safely and if present permits decompression of intraneural pressure within the tibial nerve. The tarsal tunnel ends when the flexor retinaculum divides to encompass the abductor hallucis brevis (AHB) muscle. To approach the medial and lateral plantar nerves, an incision is made toward the plantar aspect of the foot at the site of the lateral plantar tunnel. This incision is brought proximally to join the tarsal tunnel release incision. The superficial fascia of the AHB muscle is then incised and spread gently. Care must be taken not to injure the small (<1 mm) nerve that goes from the medial plantar nerve superficially to the vessels. This nerve then enters the fascia and emerges to innervate the medial ankle skin at the site where the typical incision is made for a plantar fascia release (Fig. 3.2).

The medial calcaneal tunnel(s) can be identified in one of two ways. First, the calcaneal nerves arise from the tibial nerve within the tarsal tunnel [13]. These are identified in the posterior fat below the tibial nerve and are followed distally to enter the tunnel. Second, from the fibrous roof of the lateral plantar tunnel, the fascia is traced proximally and is found to form the roof of the calcaneal branches that arise from the lateral plantar nerve before it enters the lateral plantar tunnel. Each of these tunnels is spread gently, and the roof is then carefully divided to avoid injury to one of the small branches of the calcaneal nerve [14].

3.7 Postoperative Management

Postoperatively, the patient will be allowed full weight-bearing immediately and will use a walking frame for 3 weeks. The goal of walking with a walking frame is to permit nerve gliding while minimizing the ankle range of motion so that the sutures do not pull out. The dressing is removed after the seventh day, and the sutures can get wet. Betadine must be applied to the incisions twice a

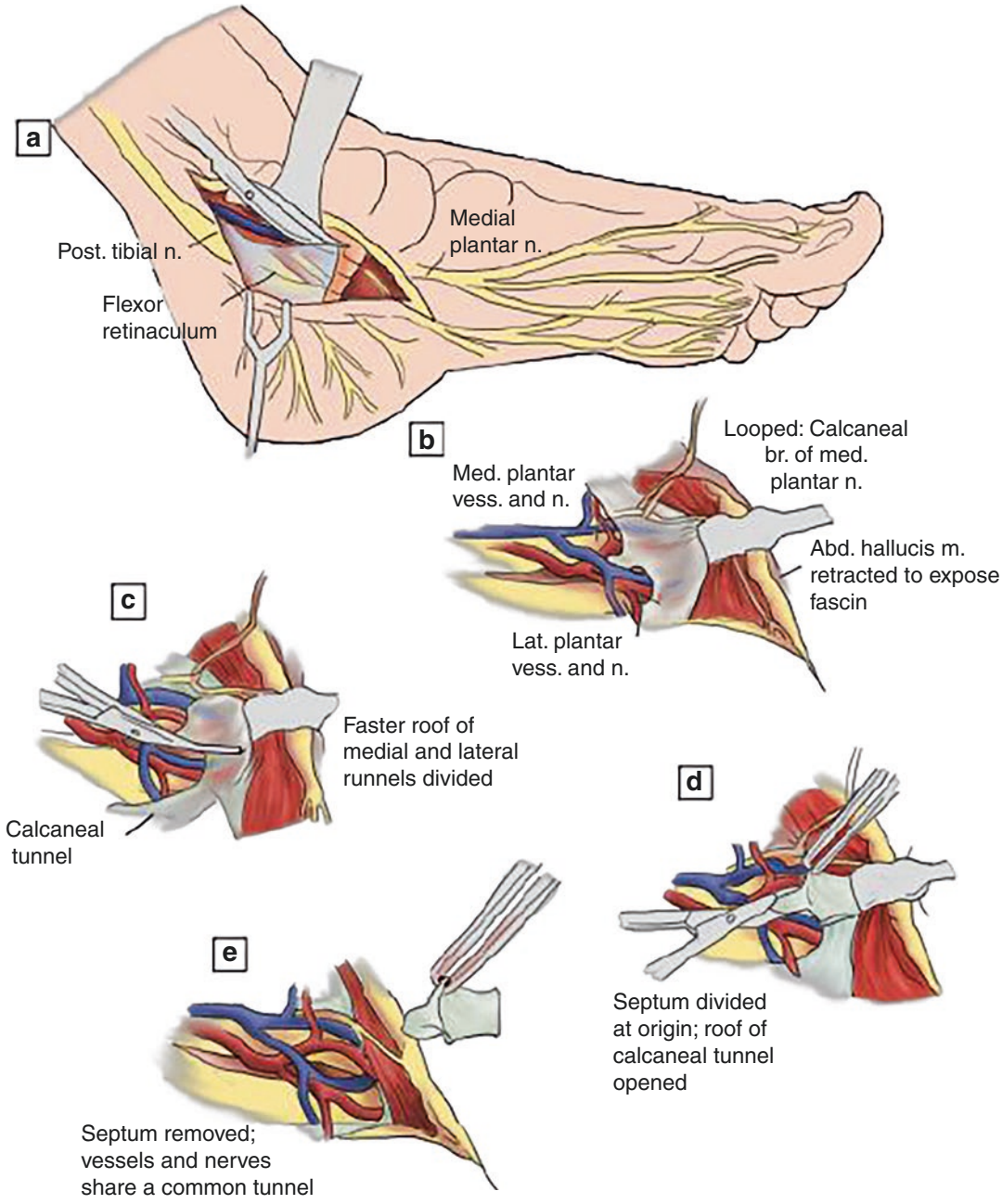

Fig. 3.2 Tibial nerve decompression. (**a**) Incision through flexor retinaculum. (**b**) Identification of calcaneal br. of med. plantar n. (**c**) Division of fascia roof of med. and lat. Tunnels. (**d**) Septum removal. (**e**) Roof of calcaneal tunnel open

day. After removing the sutures, the patient should begin mobilizing in a heated pool as a form of physical therapy. This therapy is preferred three times a week, with twice a week being the minimum. No other therapies are usually necessary. The patient will then progress through increasing degrees of ambulation and activity, as tolerated [15].

Analgesia should be reduced as the pain decreases. In patients who did not complain of

pain preoperatively and who experience pain postoperatively due to nerve regeneration, a regimen of neuropathic pain medication can be started, with opioids continued as needed.

Repeat neurosensory testing should be performed at 6–12 weeks postoperatively to document sensory recovery. It may be done sooner if the patient is experiencing significant pain, as the neurosensory testing will document a reassuring nerve regeneration pattern to the patient and the physician [16].

The contralateral side may be operated on as early as 6 weeks postoperatively if sufficient pain relief or sensory recovery is observed. Typically, patients wait approximately 3 months to undergo surgery on the contralateral side. The longest time interval between surgeries was 1 year.

3.8 Conclusion

Although various drug treatments for diabetic neuropathy can relieve pain, symptoms caused by the degeneration of the nerve itself, including sensory abnormalities, do not improve. If it is accompanied by local nerve compression, surgical treatment can improve the symptoms, so a careful diagnosis is required. Efforts by patients and medical staff to maintain normal blood sugar levels are essential, and attention should be paid to preventing foot ulcers and infections.

Disclosure Statement The authors have nothing to disclose.

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