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# **A Current Overview of Diabetic Neuropathy – Mechanisms, Symptoms, Diagnosis, and Treatment**

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## **1. Introduction**

Diabetic neuropathies are nerve disorders associated with diabetes, which affect approximately half of all diabetes patients [1]. The most common complication of diabetes is caused by hyperglycemia which can damage nerve fibers throughout the body [2]. Depending on the types of nerves involved, diabetic neuropathies can be categorized as peripheral, autonomic, proximal, focal neuropathies [3].

Because the pathogenesis mechanisms of diabetic neuropathy remain unknown, numerous studies try to elucidate the underlying mechanisms of this disease. Several reports have demonstrated that a variety of molecules are likely involved in the development of diabetic neuropathy, such as protein kinase C, polyol, aldose reductase, advanced glycation end-products, reactive oxygen species, cytokines [1-10]. Moreover, some risk factors including metabolite, autoimmune, inherited traits and lifestyle, may contribute to the development of diabetic neuropathy.

These multiple factors mentioned above might correlate with various symptoms of diabetic neuropathy. These symptoms vary in different organ systems, such as the extremities, digestive system, urinary tract, blood vessels, heart, and sex organs, depending on the nerves affected [9, 10]. The symptoms usually include pain, foot ulcer, dysesthesia, numbness and tingling of extremities, indigestion, nausea, vomiting, diarrhea, facial and eyelid drooping, eyesight change, dizziness, muscle weakness, dysphagia, urinary incontinence, sexual dysfunction, and speech impairment [2, 4, 9-11]

The symptoms remain minor initially and develop gradually over years. As a result, the majority of patients do not even realize they are affected until the complications become noticeable or severe. Accordingly, it is difficult to diagnose the disease in the early stages. However, doctors can diagnose diabetic neuropathy based on the patients' symptoms and

physical examinations usually including ankle reflexes, loss of sensation in the extremities, blood pressure, heart rate, muscle strength, vibration, temperature, or light touch [11-12]. In addition, nerve conduction test, electromyography and ultrasound test may help diagnose the disease [3, 4].

Due to the poorly understood mechanism, effective therapies that can cure diabetic neuropathy remain elusive. However, there exist various options to prevent or treat the disease. To date, the fundamental treatment for diabetic neuropathy is to keep blood glucose levels under control to prevent further nerve damage [4]. Additionally, drug treatment also helps relieve pain and other symptoms. The medications include tricyclic antidepressants, classic analgesics, serotonin reuptake inhibitors and antiepileptic drugs [3, 13].

Because of the side effects of drug therapy, physical treatment can help alleviate pain and some other symptoms, such as foot ulcer, muscle weakness, loss of sensation and sexual dysfunction. The physical treatment include electrical nerve stimulation, gait training, posture training, manual therapy, exercise programs, foot care, therapeutic ultrasound, hot wax, short wave diathermy, photo energy therapy [12, 14, 15]. Moreover, healthy lifestyle, quitting smoking will be beneficial to diabetic neuropathy. Recently, cell therapy has been proposed to treat diabetic neuropathy [16].

In this chapter, we will discuss the mechanisms, symptoms, diagnosis, and treatment of diabetic neuropathy.

2. Epidemiology

The incidence of diabetic neuropathy is the highest among diabetic complications, and diabetic neuropathy develops early after the onset of diabetes [1, 13, 17]. The risk factors of diabetic neuropathy are hyperglycemia and its persistence (Table 1). Hypertension, dyslipidemia, obesity, and cigarette smoking are also included in the risk factors in Western countries [1, 13, 17].

Factors	Odds ratio
Total cholesterol	1.15
Triglyceride	1.21
Body mass index	1.27
HbA1c change degree	1.36
Smoking	1.38
Duration of diabetes mellitus	1.40
HbA1c level	1.48
Hypertension	1.57

Adjusted odds ratio for associations between key risk factors and the incidence of diabetic neuropathy with logistic regression model; HbA1c: Hemoglobin A1c

Table 1. Risk factors of diabetic neuropathy [21, 22]

For the prevention of diabetic neuropathy, blood glucose control is the most important [18, 19]. In a study investigating the prevalence of diabetic neuropathy in diabetic patients and whether patients recognized the development of neuropathy, clinical diabetic neuropathy was noted in 14% on average but not recognized by most patients [20].

### 3. Pathological mechanism

The pathological mechanism of diabetic neuropathy cannot be explained with a single cause, and various hypotheses have been proposed (Table 2). These are roughly divided into metabolic [23], vascular [24], and neuroregeneration disorder hypotheses [25].

1. Activation of polyol pathway
2. Down-regulation of intracellular myoinositol
3. Dysfunction of protein kinase C
4. Down-regulation of intracellular cyclic AMP
5. Inhibition of Na <sup>+</sup> /K <sup>+</sup> /ATPase
6. Degradation of nitric oxide
7. Advance of protein glycation
8. Increase of free radical
9. Disorder of polyunsaturated fatty acid synthesis
10. Disorder of prostaglandin synthesis
11. Action attenuation of a nerve growth factor
12. Nerve blood flow degradation, nerve vascular resistance enhancement

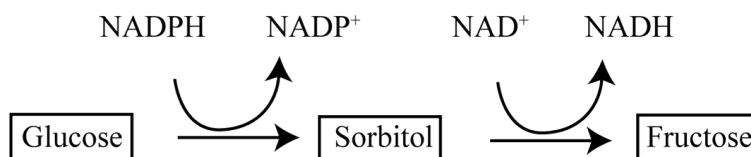
AMP: Adenosine monophosphate

**Table 2.** Potential pathogenesis of diabetic neuropathy

#### 3.1. Impairment of polyol pathway

Altered peripheral nerve polyol metabolism has been implicated as a central factor in the pathogenesis of diabetic neuropathy. Aldose reductase converts glucose to sorbitol (such as polyol) using nicotinamide adenine dinucleotide phosphate (NADPH) as a coenzyme (Figure 1). Sorbitol is further converted to fructose by sorbitol dehydrogenase using nicotinamide adenine dinucleotide (NAD<sup>+</sup>) as a coenzyme, constituting the bypass polyol pathway of glucose metabolism [26].

In hyperglycemia accompanying diabetes, the cellular glucose level rises independently from insulin, resulting in enhancement of aldose reductase activity, which elevates the intracellular sorbitol level and, subsequently, the intracellular osmotic pressure. This condition induces functional and structural abnormalities in tissue and cells.



**Figure 1. Polyol pathway.** The polyol pathway consists of two-step metabolic pathway.

An aldose reductase reduces glucose in sorbitol. This reaction oxidizes nicotinamide adenine dinucleotide phosphate (NADPH) to NADP<sup>+</sup> (the oxidized form of NADPH). Subsequently, sorbitol dehydrogenase enzymatically oxidizes sorbitol to fructose, which also produces nicotinamide adenine dinucleotide (NADH) from nicotinamide adenine dinucleotide (NAD<sup>+</sup>). The inhibition of the aldose reductase is one of key element in the prevention of diabetic complications.

In addition to osmotic pressure elevation, sorbitol accumulation decreases the intracellular myoinositol content, which inhibits phosphoinositide metabolism and reduces protein kinase C and Na<sup>+</sup>/K<sup>+</sup>/ATPase activities in peripheral nerves, being involved in the manifestation of diabetic neuropathy.

### 3.2. Activation of protein kinase C

Hyperglycemia promotes the synthesis of an endogenous protein kinase C activator, diacylglycerol [27-30]. Actually, excess activation of  $\beta$ 2-type protein kinase C in cardiovascular tissue in an animal diabetes model has been reported. Enhanced vascular protein kinase C is involved in permeability, the contractile force, and the differentiation and proliferation of cells.

Excess protein kinase C activation induces ischemia in peripheral nerves through increased vascular permeability and thickening of the basement membrane and causes neuropathy.

### 3.3. Increase in oxidative stress

Hyperglycemia enhances NADPH oxidase expression and the endothelial nitric oxide synthase (eNOS) uncoupling reaction in vascular endothelial cells, through which superoxide is excessively produced [4, 31-33]. Nitric oxide (NO) is essential for endothelial cell function.

Excess superoxide decreases NO by binding to it, and this binding reaction promotes the secondary synthesis of reactive oxygen species (ROS), such as peroxynitrite and hydroxyl radicals. ROS have strong cytotoxicity, and an increase in ROS induces neurosis.

### 3.4. Other factors

Bone marrow-derived proinsulin- and tumor necrosis factor- $\alpha$  (TNF $\alpha$ )-producing cells appear in a diabetic state [5, 34, 35]. These cells enter the dorsal root ganglions and peripheral nerves

(axon and Schwann cells) and induce cell fusion. Fused cells impair  $\text{Ca}^{2+}$ homeostasis and induce apoptosis. The appearance of these abnormal cells is resolved by insulin treatment.

It has also been clarified that the abnormality of intracellular signal transmission systems in nerve tissues including that of insulin signals is closely involved in abnormal peripheral nerve function [36]. The peripheral neuropathy developmental mechanism may be a new target of neuropathy treatment, other than blood glucose control.

## 4. Symptoms

The manifestation of subjective symptoms of diabetic neuropathy is the earliest among complications of diabetic patients, and the incidence is the highest [1, 13, 17, 37]. Its pathology starts with numbness and sensory disturbance of the four limbs, and manifests various clinical pictures, such as autonomic neuropathy and mononeuropathy (Table 3).

1. Sensory disturbance is dominant
2. A disorder of an inferior limb is dominant, and a disorder of a superior limb is mild
3. Vibratory sensation is disordered since early stage
4. A tendon reflex of an inferior limb decreases since early stage
5. Ophthalmoplegia often accompanies
6. Autonomic neuropathy often accompanies

**Table 3.** Clinical features of diabetic neuropathy

Sensory symptoms accompanying diabetic neuropathy, such as pain and numbness, distress patients, and subsequent hypoesthesia leads to the primary cause of lower limb amputation, diabetic gangrene [9, 10, 38, 39]. Diverse symptoms of autonomic neuropathy (Table 4) markedly reduce the Quality of Life (QOL) of patients [40, 41, 42].

1. Constipation, diarrhea, gastric hypokinesia (dull feeling in the stomach)
2. Dizziness (orthostatic hypotension)
3. Silent myocardial infarction: Myocardial infarction or angina without chest pain
4. Dysuria
5. Erectile dysfunction
6. Non-symptomatic hypoglycemia

**Table 4.** Diabetic autonomic neuropathy

Clinically, there are several disease types of diabetic neuropathy based on the distribution of disorders and developmental pattern (Table 5).

1. Hyperglycemic neuropathy
2. Symmetric polyneuropathy
1) Sensory / autonomic neuropathy
2) Acute painful diabetic neuropathy
3. Focal and multifocal neuropathy
1) Cranial neuropathy
2) Thoraco-abdominal neuropathy
3) Focal limb neuropathy
4) Diabetic amyotrophy
4. Mixed forms

**Table 5.** Classification of diabetic neuropathy [43]

In diabetic neuropathy, sensory neuropathy is dominant, but subjective sensory symptoms generally do not extend to the proximity from the ankle joint in many cases, and its onset is associated with numbness and pain of the toes and sole. The fingers are asymptomatic in this stage, showing “tabi (socks with the big toe separated)-type” sensory symptoms, and this pattern is frequently noted in routine medical practice.

In the late stage, “glove-socks-type” sensory abnormality manifests. Diabetic neuropathy cases with the expansion of sensory symptoms to the precordium and parietal region have been reported. This neurologic manifestation pattern is derived from the advancement pattern of axon degeneration, and it occurs because the nerves in the lower limbs are longer than those in the upper limbs.

Since diabetic neuropathy progresses slowly, the divergence between the upper and lower limb symptoms may continue for a relatively long time. Regarding sensory disturbance, in diabetic neuropathy in which positive symptoms of the feet, such as numbness and pain, develop in the early to middle stage and negative symptoms, such as hypoesthesia, develop in the terminal stage, generally, an abnormal autonomic nerve function appears from the early stage and then autonomic nerve symptoms may manifest, but the manifestation of motor neuropathy is late (Table 6).

N0	no neuropathy
N1	Asymptomatic neuropathy
N1a	Abnormal of examination without neuropathy symptom
N1b	Abnormal of examination with neurologic signs without neuropathy symptom
N2	Symptomatic neuropathy
N2a	Abnormal of examination with neurologic signs with neuropathy symptom
N2b	N2a plus weakness of ankle dorsiflexion
N3	Disabling neuropathy

**Table 6.** Severity grade of diabetic neuropathy [3]



5. Diagnosis

Diabetic neuropathy can be diagnosed when the patient has been diagnosed with diabetes and other diseases causing polyneuropathy have been ruled out. Diseases required to be differentiated are shown in Table 7.

There are no diabetic neuropathy-specific symptoms or tests, and no diagnostic criteria with international consensus have been established. Diabetic neuropathy has to be comprehensively diagnosed based on various neurologic manifestations and test results [44-46].

The symptom characteristic of diabetic neuropathy is bilateral symmetric polyneuropathy with dominance on the distal side, and it more frequently develops from the lower limbs, particularly from the feet and crura, than from the upper limbs.

1. Ongoing diabetes mellitus
2. There is no disorder to cause neurological symptom besides diabetes mellitus
3. Symmetric symptom (spontaneous pain, paresthesia, hypaesthesia, anesthesia)
4. Attenuation of reflexes in the ankle or knee
5. Pallesthesia
6. Abnormal of electrophysiological neurologic function tests
7. Symptoms of autonomic neuropathy

Table 7. Diagnosis of diabetic neuropathy

Subjective symptoms are an abnormal sensation, cold sense, and hypoaesthesia of the feet. When thick myelinated nerve fibers are mainly impaired, an increase in the pallesthesia threshold and reduction/loss of tactile sensation of the toes, movement velocity, sensory nerve conduction velocity, and the tendon reflex are observed. When thin nerve fibers and unmyelinated nerves are impaired, an increase in the thermal sensation threshold and features of autonomic neuropathy are observed. When 3 or more of these 4 items are present, the patient is diagnosed with diabetic peripheral neuropathy.

The peripheral neuropathy signs important to objectively diagnose the disease stage of diabetic neuropathy are summarized below:

5.1. Reduction/loss of Achilles tendon reflex

Since this symptom is frequently observed even in patients showing no symptoms, it is very important to identify diabetic neuropathy in the asymptomatic stage [2, 4, 9-11].

A test in a kneeling posture (Babinski position), in which loss of the reflex can be readily observed, is recommended. Many cases of diabetic neuropathy show bilateral abnormality, and apparent laterality is a sign of lumbar vertebral disease [47].



## 5.2. Pallesthesia

The impairment of vibration perception threshold is used to early diagnosis of peripheral neuropathy [48-50].

An aluminum 128-Hz tuning fork is standard for the examination of pallesthesia. Since the vibration of a tuning fork exponentially attenuates, the time required to reach the threshold is almost constant when it is hit with a force stronger than a specific level. The base of a vibrating tuning fork was placed on the hallux of the patient. The examiner asks the patients first if the vibration is perceived. Next, the patient should inform the examiner when the vibration stops. The diagnosis of diabetic neuropathy is to be suspected if the vibration duration sensation is less than 10 seconds.

## 5.3. Peripheral nerve conduction velocity test

In this test, peripheral nerves are stimulated with electricity through the skin, and the nerve conduction velocity and waveform are analyzed based on the reactions to diagnose and treat diseases. When neuropathy occurs, the nerve conduction velocity decreases [51-53].

## 5.4. Monofilament

Activity of nerves perceiving tactile and pressure sensations is investigated by attaching a monofilament to the foot. Perception decreases in diabetic neuropathy patients [54, 55].

## 5.5. Coefficient of respiratory heart rate variability

This is an autonomic nerve function test. Variation in the pulse with deep breaths compared to that on rest is investigated using electrocardiography. Normally, pulse variation increases on deep breathing, but this variation decreases when autonomic nerves are impaired [56].

# 6. Treatment

Early-stage diabetic neuropathy can be improved by blood glucose control alone, but it becomes intractable after progression to a certain stage. Aldose reductase inhibitors are being developed for treatment based on the metabolic disorder hypothesis of diabetic neuropathy, but treatment with these drugs alone may be insufficient [57].

## 6.1. Blood glucose control

In a large-scale intervention study, Diabetes Control and Complications Trial (DCCT; <http://diabetes.niddk.nih.gov/dm/pubs/control/>), 1,441 patients with insulin-dependent diabetes received intensive insulin therapy or conventional insulin treatment for 6.5 years on average [58]. In the intensive insulin therapy group, significant inhibition of the development and advancement of neuropathy was demonstrated, showing that strict blood glucose control is important for the prevention and treatment of diabetic neuropathy. However, rapid blood

glucose control exacerbates neuropathy in some patients, and this condition is termed post-treatment neuropathy. In these patients, neuropathy may have been present before the initiation of blood glucose control. Generally, pain remits within one year. Thus, it is important to relieve patients and remove their anxiety. For patients with poor blood glucose control and complications, it is safe to slowly control blood glucose.

## **6.2. Aldose reductase inhibitor**

Aldose reductase inhibitor inhibits the enhancement of polyol metabolic activity, a mechanism of diabetic neuropathy development, and it is expected to be a specific therapeutic drug for diabetic neuropathy [59-61].

Many aldose reductase inhibitors have been developed, and clinical efficacy was noted in some. However, the evidence for the efficacy of aldose reductase inhibitor for diabetic neuropathy is still insufficient. Epalrestat is a typical aldose reductase inhibitor. In a multi-center controlled clinical study with this drug, the conduction velocity of the median nerve decreased over years in the untreated group, but the drug inhibited it. The effect was marked in patients with favorable blood glucose control and a short duration of diabetic neuropathy. Thus, it is desirable to administer epalrestat in consideration of the indication. The possibility of epalrestat improving the autonomic nerve function has been reported, although it was a small-scale study [59].

## **6.3. Antioxidants**

The usefulness of antioxidants has been tested with regard to abnormal protein kinase C (PKC) activity and oxidative stress, and the improvement of neurologic manifestations and physical findings by  $\alpha$ -lipoic acid has been reported [62, 63].

## **6.4. Incretin**

Incretin (glucagon-like peptide-1: GLP-1 and glucose-dependent insulintropic polypeptide: GIP) has recently been attracting attention as a new anti-diabetes drug [64, 65].

Incretin has also been shown to act on cells or tissues other than pancreatic  $\beta$  cells, i.e., extrapancreatic actions [66]. Medical-experimentally, incretin and related drugs have various neuroprotective actions, and the possibility of incretin being effective for diabetic neuropathy has been reported [64, 65, 67].

## **6.5. Regeneration therapy**

Functional improvement of vascular and nerve cells and regeneration of degenerated tissue corresponding to the pathology of diabetic neuropathy are expected radical treatments of diabetic neuropathy [16, 68].

In studies on regenerative medicine for diabetic neuropathy, precursor and stem cells isolated and cultured from the bone marrow and fat tissue, stem cells induced to differentiate from embryonic stem (ES) and induced pluripotent stem (iPS) cells, and bone marrow mononuclear

cells containing many of these precursor and stem cells are mainly used. Further investigation aiming at clinical application is necessary.

6.6. Others

For the improvement of blood flow, prostaglandin E<sub>1</sub>, an oral prostacyclin derivative, cilostazol, and eicosapentaenoic acid (EPA) are effective in some cases.

6.7. Symptomatic treatment of pain

Pain develops in most disease types of diabetic neuropathy [69, 70].

Drug	Action
Tricyclic antidepressant	Serotonin–norepinephrine reuptake inhibitor
Carbamazepine	Na <sup>+</sup> channel block
Valproate	Central inhibition via augmentation of GABA
Topiramate	Na <sup>+</sup> channel and AMPA receptor block
Lamotrigine	Na <sup>+</sup> channel block, central inhibition
Dextromethorphan	Glutamate N-methyl-D-aspartate receptor antagonists
Tramadol	Weak $\mu$ -opioid receptor agonist, Serotonin–norepinephrine reuptake inhibitor
Mexiletine	Na <sup>+</sup> channel block
Capsaicin	Activation of transient receptor potential cation channel subfamily V member 1
Gabapentin	$\alpha 2\delta$ Ca <sup>2+</sup> channel inhibition
Pregabalin	$\alpha 2\delta$ Ca <sup>2+</sup> channel inhibition
Duloxetine	Serotonin–norepinephrine reuptake inhibitor

GABA: gamma-aminobutyric acid, AMPA:  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

**Table 8.** Drugs currently used in treatment of diabetic neuropathy and its action

Although the developmental mechanism of pain has not been fully clarified, the activation of Na<sup>+</sup> and Ca<sup>2+</sup> channels in peripheral nerves is closely involved, and mexiletine and anticonvulsants, with inhibitory actions, are effective.

The involvement of activation on the central side including the posterior horn of the spinal cord increases as the condition becomes chronic, and tricyclic antidepressants, selective serotonin reuptake inhibitor (SSRI), serotonin–norepinephrine reuptake inhibitor (SNRI), and N-methyl-D-aspartate (NMDA) receptor antagonists, have become important with regard to the site of action. The efficacy of opioids (tramadol and oxycodone) has also been reported.

On meta-analysis, tricyclic antidepressants were most effective. Among anticonvulsants, the conventional type (carbamazepine and phenytoin) has been reported to be superior to the new

type (gabapetine and pregabalin), with regard to the efficacy and adverse effects. Capsaicin and lidocaine patches are also useful to alleviate symptoms.

### **6.8. Treatment of autonomic neuropathy**

When autonomic neuropathy appears, organs innervated by autonomic nerves become functionally abnormal, and diverse symptoms develop, such as dyshidrosis, orthostatic hypotension, gastric asthenia, stool abnormality, bladder and erectile dysfunctions, and hypoglycemia unawareness. When neuropathy is mild, modification of the blood glucose control and lifestyle improves these functional disorders in many cases. When neuropathy is advanced and impairs daily living activities, symptomatic treatment with drugs corresponding to the symptoms is necessary [41, 71].

For orthostatic hypotension, firstly, drugs likely to decrease the blood pressure are withdrawn, and patients are instructed to avoid rapid postural changes while standing. Frequent ingestion of a small amount of food is effective to prevent postprandial blood pressure reduction. Compression of the lower limbs and abdominal region by wearing elastic underwear is effective for orthostatic hypotension. Salt ingestion and the administration of fludrocortisone acetate are also effective, but these are likely to cause edema and heart failure, to which attention should be paid.

For erectile dysfunction, firstly, drugs likely to cause it should be withdrawn. For patients requiring drug therapy, a phosphodiesterase inhibitor, sildenafil or vardenafil, is effective. However, these are contraindicated for patients being treated with nitroglycerin and nitrous acid medicine for ischemic heart disease because a phosphodiesterase inhibitor is very likely to cause serious blood pressure reduction.

Gastric asthenia is treated with the frequent ingestion of a small amount of food and restriction of fat and fiber ingestion. Symptoms are improved by these symptomatic treatments alone in many mild cases. When drug therapy is necessary, metoclopramide and domperidone are effective, but long-term administration may induce extrapyramidal symptoms as adverse effects, to which attention should be paid.

## **7. Conclusion**

Diabetic neuropathy is caused by dysfunction of the peripheral or central nervous system associated with abnormally high levels of blood glucose. It is often chronic and disabling. Advanced neuropathy not only reduces QOL of patients but also influences their vital prognosis, shown by the high mortality of patients with autonomic neuropathy. Therefore, to improve the vital prognosis and QOL of patients, it is important to perform periodic neurological examination from the early stage for the early diagnosis and treatment of diabetic neuropathy.

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