We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

6,600
Open access books available

177,000
International authors and editors

195M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
A Current Overview of Diabetic Neuropathy –
Mechanisms, Symptoms, Diagnosis, and Treatment

Takashi Kawano

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/58308

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].

Table 2. Potential pathogenesis of diabetic neuropathy

| 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⁺/K⁺/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

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⁺) 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.
An aldose reductase reduces glucose in sorbitol. This reaction oxidizes nicotinamide adenine dinucleotide phosphate (NADPH) to NADP⁺ (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⁺). 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⁺/K⁺/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 β2-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-α (TNFα)-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 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 hypoesthesia 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 folk is standard for the examination of pallesthesia. Since the vibration of a tuning folk 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 multicenter 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 α-lipoic acid has been reported [62, 63].

6.4. Incretin

Incretin (glucagon-like peptide-1: GLP-1 and glucose-dependent insulinotropic 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 β 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\textsubscript{1}, 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\textsuperscript{+} channel block                                    |
| Valproate                   | Central inhibition via augmentation of GABA                            |
| Topiramate                  | Na\textsuperscript{+} channel and AMPA receptor block                  |
| Lamotrigine                 | Na\textsuperscript{+} channel block, central inhibition               |
| Dextromethorphan            | Glutamate N-methyl-D-aspartate receptor antagonists                    |
| Tramadol                    | Weak µ-opioid receptor agonist, Serotonin–norepinephrine reuptake inhibitor |
| Mexiletine                  | Na\textsuperscript{+} channel block                                   |
| Capsaicin                   | Activation of transient receptor potential cation channel subfamily V member 1 |
| Gabapentin                  | α\textsubscript{2}δ Ca\textsuperscript{2+} channel inhibition          |
| Pregabalin                  | α\textsubscript{2}δ Ca\textsuperscript{2+} channel inhibition          |
| Duloxetine                  | Serotonin–norepinephrine reuptake inhibitor                            |

GABA: gamma-aminobutyric acid, AMPA: α-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\textsuperscript{+} and Ca\textsuperscript{2+} 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 (MNDA) 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.
Author details

Takashi Kawano∗
Department of Anesthesiology and Intensive Care Medicine, Kochi Medical School, Japan

References

[1] Hinder, LM., Vincent, AM., Burant, CF., Pennathur, S. & Feldman, EL. Bioenergetics in diabetic neuropathy: what we need to know. J Peripher Nerv Syst 2012; 17(Suppl. 2) 10-4.

[2] Yagihashi S, Mizukami H, Sugimoto K. Mechanism of diabetic neuropathy: Where are we now and where to go? Journal of Diabetes Investigation 2011; 2(1) 18–32.

[3] Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, Lauria G, Malik RA, Spallone V, Vinik A, Bernardi L, Valensi P: Toronto Diabetic Neuropathy Expert Group. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 2010; 33(10) 2285-93.

[4] Vincent AM, Russell JW, Low P, Feldman EL. Oxidative stress in the pathogenesis of diabetic neuropathy. Endocr Rev 2004; 25(4) 612-28.

[5] Chan L, Terashima T, Urabe H, Lin F, Kojima H. Pathogenesis of diabetic neuropathy: bad to the bone. Ann N Y Acad Sci 2011; 1240 70-6.

[6] Jack M, Wright D. Role of advanced glycation endproducts and glyoxalase I in diabetic peripheral sensory neuropathy. Transl Res 2012; 159(5) 355-65.

[7] Lorenzi M. The polyol pathway as a mechanism for diabetic retinopathy: attractive, elusive, and resilient. Exp Diabetes Res 2007; No.61038.

[8] Xia P, Kramer RM, King GL. Identification of the mechanism for the inhibition of Na+, K+-adenosine triphosphatase by hyperglycemia involving activation of protein kinase C and cytosolic phospholipase A2. J Clin Invest 1995; 96(2) 733-40.

[9] Dinh T, Tecilazich F, Kafanas A, Doupis J, Gnardellis C, Leal E, Tellechea A, Pradhan L, Lyons TE, Giurini JM, Veves A. Mechanisms involved in the development and healing of diabetic foot ulceration. Diabetes 2012; 61(11) 2937-47.

[10] Bagyánszki M, Bódi N. Diabetes-related alterations in the enteric nervous system and its microenvironment. World J Diabetes 2012; 3(5) 80-93.

[11] Al-Geffari M. Comparison of different screening tests for diagnosis of diabetic peripheral neuropathy in Primary Health Care setting. Int J Health Sci (Qassim) 2012; 6(2) 127-34.
[12] Balbinot LF, Canani LH, Robinson CC, Achaval M, Zaro MA. Plantar thermography is useful in the early diagnosis of diabetic neuropathy. Clinics (Sao Paulo) 2012; 67(12) 1419-25.

[13] Boulton AJ, Malik RA, Areizzo JC, Sosenko JM. Diabetic somatic neuropathies. Diabetes Care 2004; 27(6) 1458-86.

[14] Höke A. Animal models of peripheral neuropathies. Neurotherapeutics. 2012; 9(2) 262-9.

[15] Pieber K, Herceg M, Paternostro-Sluga T. Electrotherapy for the treatment of painful diabetic peripheral neuropathy: a review. J Rehabil Med 2010; 42(4) 289-95.

[16] Han JW, Sin MY, Yoon YS. Cell therapy for diabetic neuropathy using adult stem or progenitor cells. Diabetes Metab J 2013; 37(2) 91-105.

[17] Said G. Diabetic neuropathy—a review. Nat Clin Pract Neurol 2007; 3(6) (June), pp. 331-40.

[18] Dyck PJ, Davies JL, Clark VM, Litchy WJ, Dyck PJ, Klein CJ, Rizza RA, Pach JM, Klein R, Larson TS, Melton LJ 3rd, O'Brien PC. Modeling chronic glycemic exposure variables as correlates and predictors of microvascular complications of diabetes. Diabetes Care 2006; 29(10) 2282-8.

[19] Martin CL, Albers J, Herman WH, Cleary P, Waberski B, Greene DA, Stevens MJ, Feldman EL: DCCT/EDIC Research Group. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. Diabetes Care 2006; 29(2) 340-4.

[20] Bongaerts BW, Rathmann W, Heier M, Kowall B, Herder C, Stöckl D, Meisinger C, Ziegler D. Older subjects with diabetes and prediabetes are frequently unaware of having distal sensorimotor polyneuropathy: the KORA F4 study. Diabetes Care 2013; 36(5) 1141-6.

[21] Tesfaye S, Chaturvedi N, Eaton SE, Ward JD, Manes C, Ionescu-Tirgoviste C, Witte DR, Fuller JH; EURODIAB Prospective Complications Study Group. Vascular risk factors and diabetic neuropathy. N Engl J Med 2005; 352(4) 341-50.

[22] Forsblom CM, Sane T, Groop PH, Tötterman KJ, Kallio M, Saloranta C, Laasonen L, Summanen P, Lepäntalo M, Laatikainen L, Matikainen E, Teppo AM, Koskimies S, Groop, L. Risk factors for mortality in Type II (non-insulin-dependent) diabetes: evidence of a role for neuropathy and a protective effect of HLA-DR4. Diabetologia 1998; 41(11) 1253-62.

[23] Zochodne DW. Diabetic polyneuropathy: an update. Curr Opin Neurol 2008; 21(5) 527-33.

[24] Dyck PJ. Hypoxic neuropathy: does hypoxia play a role in diabetic neuropathy? The 1988 Robert Wartenberg lecture. Neurology 1989; 39(1) 111-8.
[25] Yasuda H, Terada M, Maeda K, Kogawa S, Sanada M, Haneda M, Kashiwagi A, Kikkawa R. Diabetic neuropathy and nerve regeneration. Prog Neurobiol 2003; 69(4) 229-85.

[26] Yabe-Nishimura C. Aldose reductase in glucose toxicity: a potential target for the prevention of diabetic complications. Pharmacol Rev 1998; 50(1) 21-33.

[27] Borghini I, Ania-Lahuerta A, Regazzi R, Ferrari G, Gjinovc A, Wollheim CB, Pralong WF. Alpha, beta I, beta II, delta, and epsilon protein kinase C isoforms and compound activity in the sciatic nerve of normal and diabetic rats. J Neurochem 1994; 62(2) 686-96.

[28] Hempol A, Maasch C, Heintze U, Lindschau C, Dietz R, Luft FC, Haller H. High glucose concentrations increase endothelial cell permeability via activation of protein kinase C alpha. Circ Res 1997; 81(3) 363-71.

[29] Roberts RE, McLean WG. Protein kinase C isozyme expression in sciatic nerves and spinal cords of experimentally diabetic rats. Brain Res 1997; 754(1-2) 147-56.

[30] Geraldes P, King GL. Activation of protein kinase C isoforms and its impact on diabetic complications. Circ Res 2010; 106(8) 1319-31.

[31] Yorek MA. The role of oxidative stress in diabetic vascular and neural disease. Free Radic Res 2003; 37(5) 471-80.

[32] Pop-Busui R, Sima A, Stevens M. Diabetic neuropathy and oxidative stress. Diabetes Metab Res Rev 2006; 22(4) 257-73.

[33] Figueroa-Romero C, Sadidi M, Feldman EL. Mechanisms of disease: the oxidative stress theory of diabetic neuropathy. Rev Endocr Metab Disord 2008; 9(4) 301-14.

[34] Terashima T, Kojima H, Fujimiya M, Matsumura K, Oi J, Hara M, Kashiwagi A, Kimura H, Yasuda H, Chan L. The fusion of bone-marrow-derived proinsulin-expressing cells with nerve cells underlies diabetic neuropathy. Proc Natl Acad Sci U S A 2005; 102(35) 12525-30.

[35] Terashima T, Kojima H, Chan L. Bone marrow expression of poly(ADP-ribose) polymerase underlies diabetic neuropathy via hematopoietic-neuronal cell fusion. FASEB J 2012; 26(1) 295-308.

[36] Brussee V, Cunningham FA, Zochodne DW. Direct insulin signaling of neurons reverses diabetic neuropathy. Diabetes 2004; 53(7) 1824-30.

[37] Rutkove SB. A 52-year-old woman with disabling peripheral neuropathy: review of diabetic polyneuropathy. JAMA 2009; 302(13) 1451-8.

[38] Cappellari A, Airaghi L, Capra R, Ciammola A, Branchi A, Levi Minzi G, Bresolin N. Early peripheral nerve abnormalities in impaired glucose tolerance. Electromyogr Clin Neurophysiol 2005; 45(4) 241-4.
[39] Isak B, Oflazoglu B, Tanridag T, Yitmen I, Us O. Evaluation of peripheral and autonomic neuropathy among patients with newly diagnosed impaired glucose tolerance. Diabetes Metab Res Rev 2008; 24(7) 563-9.

[40] Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care 2003; 26(5) 1553-79.

[41] Low PA, Benrud-Larson LM, Sletten DM, Opfer-Gehrking TL, Weigand SD, O’Brien PC, Suarez GA, Dyck PJ. Autonomic symptoms and diabetic neuropathy: a population-based study. Diabetes Care 2004; 27(12) 2942-7.

[42] Zilliox L, Peltier AC, Wren PA, Anderson A, Smith AG, Singleton JR, Feldman EL, Alexander NB, Russell JW. Assessing autonomic dysfunction in early diabetic neuropathy: the Survey of Autonomic Symptoms. Neurology 2011; 76(12) 1099-105.

[43] Thomas PK. Classification, differential diagnosis, and staging of diabetic peripheral neuropathy. Diabetes 1997; 46(2) S54-7.

[44] Rathur HM, Boulton AJ. Recent advances in the diagnosis and management of diabetic neuropathy. J Bone Joint Surg Br 2005; 87(12) 1605-10.

[45] Onde ME, Ozge A, Senol MG, Togrol E, Ozdag F, Saracoğlu M, Misirli H. The sensitivity of clinical diagnostic methods in the diagnosis of diabetic neuropathy. J Int Med Res 2008; 36(1) 63-70.

[46] Freeman R. Not all neuropathy in diabetes is of diabetic etiology: differential diagnosis of diabetic neuropathy. Curr Diab Rep 9(6) 423-31.

[47] Shehab DK, Al-Jarallah KF, Abraham M, Mojiminiyi OA, Al-Mohamedy H, Abdella NA. Back to basics: ankle reflex in the evaluation of peripheral neuropathy in type 2 diabetes mellitus. QJM 2012; 105(4) 315-20.

[48] van der Naalt J, Fidler V, Oosterhuis HJ. Vibration perception threshold, complaints and sensory examination in diabetic patients. Acta Neurol Scand 1991; 83(5) 297-300.

[49] van Deursen RW, Sanchez MM, Derr JA, Becker MB, Ulbrecht JS, Cavanagh PR. Vibration perception threshold testing in patients with diabetic neuropathy: ceiling effects and reliability. Diabet Med 2001; 18(6) 469-75.

[50] Manivannan M, Periyasamy R, Narayananmurthy VB. Vibration perception threshold and the law of mobility in diabetic mellitus patients. Prim Care Diabetes 2009; 3(1) 17-21.

[51] Baba M, Ozaki I. Electrophysiological changes in diabetic neuropathy: from subclinical alterations to disabling abnormalities. Arch Physiol Biochem 2001; 109(3) 234-40.

[52] Vinik AI, Kong X, Megerian JT, Gozani SN. Diabetic nerve conduction abnormalities in the primary care setting. Diabetes Technol Ther 2006; 8(6) 654-62.
[53] Kong X, Lesser EA, Potts FA, Gozani SN. Utilization of nerve conduction studies for the diagnosis of polyneuropathy in patients with diabetes: a retrospective analysis of a large patient series. J Diabetes Sci Technol 2008; 2(2) 268-74.

[54] Bourcier ME, Ullal J, Parson HK, Dublin CB, Witherspoon CA, Ward SA, Vinik AI. Diabetic peripheral neuropathy: how reliable is a homemade 1-g monofilament for screening? J Fam Pract 2006; 55(6) 505-8.

[55] Perkins BA, Orszag A, Ngo M, Ng E, New P, Bril V. Prediction of incident diabetic neuropathy using the monofilament examination: a 4-year prospective study. Diabetes Care 2010; 33(7) 1549-54.

[56] Astrup AS, Tarnow L, Rossing P, Hansen BV, Hilsted J, Parving HH. Cardiac autonomic neuropathy predicts cardiovascular morbidity and mortality in type 1 diabetic patients with diabetic nephropathy. Diabetes Care 2006; 29(2) 334-9.

[57] Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol 2012; 11(6) 521-34.

[58] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329(14) (September), pp. 977-86.

[59] Hotta N, Akanuma Y, Kawamori R, Matsuoka K, Oka Y, Shichiri M, Toyota T, Nakashima M, Yoshimura I, Sakamoto N, Shigeta Y. Long-term clinical effects of epalrestat, an aldose reductase inhibitor, on diabetic peripheral neuropathy: the 3-year, multicenter, comparative Aldose Reductase Inhibitor-Diabetes Complications Trial. Diabetes Care 2006; 29(7) 1538-44.

[60] Matsuoka K, Sakamoto N, Akanuma Y, Hotta N, Shichiri M, Toyota T, Oka Y, Kawamori R, Shigeta Y; ADCT Study Group. A long-term effect of epalrestat on motor conduction velocity of diabetic patients: ARI-Diabetes Complications Trial (ADCT). Diabetes Res Clin Pract 2007; 77(1) S263-8.

[61] Ramirez MA, Borja NL. Epalrestat: an aldose reductase inhibitor for the treatment of diabetic neuropathy. Pharmacotherapy 2008; 28(5) 646-55.

[62] Ziegler D, Nowak H, Kempler P, Vargha P, Low PA. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis. Diabet Med 2004; 21(2) 114-21.

[63] Papanas N, Maltezos E. α-Lipoic acid, diabetic neuropathy, and Nathan’s prophecy. Angiology 2012; 63(2) 81-3.

[64] Kazakos KA, Sarafidis PA, Yovos JG. The impact of diabetic autonomic neuropathy on the incretin effect. Med Sci Monit 2008; 14(4) 213-20.
[65] Panchapakesan U, Mather A, Pollock C. Role of GLP-1 and DPP-4 in diabetic nephropathy and cardiovascular disease. Clin Sci (Lond) 2013; 124(1) 17-26.

[66] Drucker DJ, Sherman SI, Bergenstal RM, Buse, JB. The safety of incretin-based therapies—review of the scientific evidence. J Clin Endocrinol Metab 2011; 96(7) 2027-31.

[67] Hölscher C. Potential role of glucagon-like peptide-1 (GLP-1) in neuroprotection. CNS Drugs 2012; 26(10) 871-82.

[68] Isner JM, Ropper A, Hirst K. VEGF gene transfer for diabetic neuropathy. Hum Gene Ther 2001; 12(12) 1593-4.

[69] Hovaguimian A, Gibbons CH. Clinical Approach to the Treatment of Painful Diabetic Neuropathy. Ther Adv Endocrinol Metab 2011; 2(1) 27-38.

[70] Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, Feldman E, Iversen DJ, Perkins B, Russell JW, Zochodne D; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. (2011) Neurology 2011; 76(20) 1758-65.

[71] Vinik AI, Erbas T. Recognizing and treating diabetic autonomic neuropathy. Cleve Clin J Med 2001; 68(11) 928-30, 932, 934-44.
