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Chapter 13

# Diabetic Neuropathy and Treatment Strategy – New Challenges and Applications

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Additional information is available at the end of the chapter

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**Abstract**

Smart drug delivery systems are very popular drug delivery systems for treatment to common disease such as gene therapy, heart disease, cancer therapy, and neuropathy. Neuropathy is the most common chronic complication of diabetes that is associated with especially loss of peripheral nerve fibers. Hyperglycemia, insulin deficiency and dyslipidemia largely affect the development and progression of diabetic neuropathy. Several metabolic disruptions including altered protein kinase C, elevated polyol pathway activity, oxidative stress, the formation of advanced glycation and lipoxidation end products, and various pro-inflammatory changes directly affect neural tissue and cause neurodegenerative changes in diabetes. The therapeutic interventions of these metabolic pathways have a limited success to relieve the symptoms of diabetic neuropathy. This review emphasizes on the pathogenesis of neurovascular changes, presently available therapeutic approaches future directions for the management of diabetic neuropathy and related new drug delivery systems.

**Keywords:** Diabet, Diabetic neuropathy, Treatment

## 1. Introduction

Diabetes mellitus (DM) is the most common disease, causing neuropathy worldwide. In the last century, although we have more information about clinical forms of diabetic neuropathy, sufficient knowledge about the pathophysiology of neuropathy could not be reached.

Diabetic neuropathy is defined as a peripheral neuropathy that may occur in clinical and subclinical levels and develops in the DM ground in the absence of other peripheral neuropathy factors.

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While neuropathy is present at the time of diagnosis in 10% of diabetic patients, this rate reaches to 50% at the end of 20 years. There are studies, which demonstrate that neuropathy starts within 9 years after the diagnosis of Type 2 diabetes. It may include manifestations associated with somatic and/or autonomic parts of peripheral nervous system.

The relationship between DM and neuropathy is known for over 100 years. The classification was first suggested by Leyden in 1893 with hyperesthetic (painful), paralytic (motor), and ataxic forms. Large sensory, small sensory, autonomic, and motor fibers may be affected by neuropathy. The findings may be symmetrical or asymmetrical. The most common form of neuropathy is distal sensorimotor polyneuropathy. The most common mononeuropathy is carpal tunnel syndrome (CTS). However, the recognition of some rare types such as diabetic lumbosacral radiculoplexus neuropathy that may cause pain and weakness is important for the reduction of morbidity.

The annual incidence of neuropathy is closely associated with the known duration of diabetes. Height, maximum body mass index, smoking, systolic and diastolic blood pressures, estradiol level, and cholesterol level were not found different in those with neuropathy and without neuropathy.

Given that diabetes is estimated to affect about 246 million people worldwide, it may be calculated that there are 20–30 million people suffering from symptomatic diabetic neuropathy. This number is thought to double by 2030 [1].

The contribution of neuropathy to mortality is very low. Disability was reported to be in 44% of the patients with Type 1 DM and definite neuropathy, and partial restriction was reported to be in activity in 74% of those with Type 2 DM and sensory neuropathy [2,3]. Hypertension, independent of duration of diabetes, has been shown to be the most important factor in the development of neuropathy in a study of Pittsburg Epidemiology of Diabetes Complications (EDC) about the effects of hypertension, height, and smoking on the incidence of distal symmetric polyneuropathy in long-lasting and poorly controlled diabetic patients [4].

Diabetic cardiac autonomic neuropathy is a serious complication seen in one fourth of Types 1 and 2 diabetic patients. It results in high mortality and silent myocardial ischemia. Autonomic dysfunction has been shown as the reason for having the risk of cardiovascular disease and sudden death in patients with Type 2 diabetes. The activation of cytokines is the indicator of the inflammation in patients with diabetes. These changes have been associated with the sympathetic–vagal balance disorders. Patients have complaints of orthostatic hypotension, exercise intolerance, lack of enhanced stability during surgery, silent myocardial infarction, and ischemia. The use of heart rate change (HRV) and Valsalva maneuver has been reported in the diagnosis of cardiac autonomic neuropathy [5]. An over activation of the sympathetic system and the activation of inflammatory cascade were observed with hyperleptinemia and lack of adiponectin in case of sleep apnea that is common in diabetes and metabolic syndrome. Ultimately, negative effects seen in the autonomic nervous system as a result of cardiovascular function impairment give rise to higher morbidity and mortality in diabetic patients [6].

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## 2. Pathogenesis of diabetic neuropathy

Diabetic neuropathy develops as a result of involvement of different nerves in varying degrees in different individuals. The actual lesions were observed to be in peripheral nerve axons in histopathological studies conducted in patients with diabetic neuropathy. *Schwann* cells, perineural cells, and endoneurial vascular structures are also affected by neuropathies. *Wallerian* degeneration, segmental and paranodal demyelination, and endoneurial connective tissue proliferation occurred with the loss and damage of thick and thin myelinated nerve fibers. Severe axonal atrophy, widespread fiber loss, and nodal and paranodal changes develop in Type 1 diabetes. Structural changes in Type 2 diabetes are milder. Mild axonal atrophy, localized fiber loss, segmental demyelination, and *Wallerian* degeneration are observed. Primary axonal changes are more evident in Type 1 diabetes, and primer *Schwann* cell pathology is more evident in Type 2 diabetes.

There is a close relationship between the degree and duration of hyperglycemia and the development of diabetic neuropathy. Development of neuropathy can be delayed or prevented through good metabolic control. The development of clinical diabetic neuropathy was observed to be decreased by 69% in the primary prevention group and 57% in the secondary intervention group after 5 years of intensive diabetes treatment in those with Type 1 diabetes in a study. Six separate factors associated with each other are thought to have an important role in the pathogenesis of DM.

Several mechanisms have been suggested in the pathogenesis of diabetic neuropathy. These are metabolic processes which involve direct nerve damage, endoneurial microvascular damage, autoimmune inflammation, and reduced neurotrophic support.

Epidemiological studies showed that the duration and severity of hyperglycemia are major risks in the development of neuropathy in patients with Types 1 and 2 DM [7]. Common opinion on the development of DSP (diabetic symmetric polyneuropathy) is that starting of the early nerve damage from the short, thin, myelinated A-delta fibers and unmyelinated C type of nerve fibers. The gold standard to assess the morphological changes in the short nerve fibers is a skin biopsy. However, not providing information about the nerve function, cost, and superficiality and being of no use in all patients with Type 1 diabetes limit this technique. The presence of a valid clinical practice, which identifies early short fiber disorder by using imaging techniques, was reported recently [8].

### 2.1. Metabolic factors

#### *2.1.1. Increased glycosylation end products*

The glycosylation of the plasma and tissue proteins plays a major role in diabetic microvascular complications by causing the formation of advanced glycation end products (AGEs). Excess glucose combines with amino acids on circulating and tissue proteins in the presence of chronic hyperglycemia. This non-enzymatic process initially leads to the formation of reversible early glycosylation end products and, later, to irreversible advanced glycosylation end products.

Advanced glycosylation products change their function by modifying intracellular proteins and extracellular matrix proteins that interact with extracellular integrins. AGE precursors modify plasma proteins by binding IGU receptors RAGE (receptor of advanced glycation end products) in mesangial endothelial cells, microglia, and macrophages. Thus, they initiate the production of reactive oxygen species (ROS). The activation of NF-κB initiates proinflammatory gene expression. Cytokines and growth factors are expressed by macrophages and mesangial cells [9]. Significantly increased serum concentrations of AGEs have been reported to lead to the development of diabetic complications by their proinflammatory effect in diabetic patients. The other effects of AGEs are increasing in vascular permeability, procoagulant activity, adhesion molecule expression, and monocyte invasion [10].

*Sorbitol:* Glucose, which enters into the cell, is metabolized to sorbitol by the enzyme aldose reductase. Glucose is converted to sorbitol and fructose by the enzyme aldose reductase due to excessive activation of this pathway owing to hyperglycemia. The accumulation of sorbitol in the cell results in the reduction of myoinositol and taurine, and this leads to decrease in Na–K adenosine triphosphatase (ATPase) activity and reduction of nerve conduction velocity. As a result of the accumulation of sorbitol in the cell, nicotinamide adenine dinucleotide phosphate (NADPH) associates with reduced cell metabolism, increased cell osmolarity, and decreased intracellular myoinositol, and the cell has a tendency to oxidative stress. Hyperglycemia may cause an increase in glucose in some intracellular tissues (such as nerves, lenses, kidneys, and blood vessels) that do not require insulin for glucose transport. Sorbitol and fructose that increase in these tissues cause two undesirable effects. First, accumulated sorbitol and fructose lead to an influx of water and eventually to osmotic cell injury by increasing intracellular osmolarity. Second, sorbitol accumulation results in reduction in the myoinositol content and impairment of Na–K ATPase. This mechanism may be responsible for the damage in Schwann cells and retinal capillary pericytes and causes peripheral neuropathy and microaneurysms. Although the relationship between oxidative stress and diabetic retinopathy, nephropathy, and neuropathy is well known, the therapeutic efficacy of many antioxidants (including aldose reductase inhibitors, vitamins C and E) tested in clinical trials has not yet been established.

*Hexosamine:* Uridine diphosphate-*N*-acetyl glucosamine (UDPGlcNAc), which regulates transcription factors needed for normal cell functions, is produced in hexosamine pathway. Excess glucose is replaced with glycolytic mediators in hexosamine pathway, and thus, glucose flux to hexosamine pathway results in cell injury and increased oxidative stress. The effects of aldose reductase inhibitors in animal models were found to be more effective than clinical trials. One of the reasons is being lower dose used in clinical trials compared with dose used in animal studies.

*Protein kinase C*: Excess glucose is converted to diacylglycerol that activates protein kinase C. The activation of protein kinase C increases in contractility, permeability, and vascular cell proliferation and enhances the production of extracellular matrix and cytokines. Thus, vasoconstriction and nerve ischemia occur. These neurovascular changes also contribute to diabetic neuropathy. Diacylglycerol-protein kinase C activation was also shown to be associated with many vascular abnormalities in retinal, renal, and cardiovascular tissues in diabetes

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and insulin resistance period. High glucose enhances ROS formation by causing NF-κB activation in endothelial cells. This condition may be prevented by PKC (protein kinase C) inhibitors [9].

*Poly (ADP-ribose) polymerase:* Nuclear enzyme poly (ADP-ribose) polymerase (PARP) becomes activated in response to high glucose. This enzyme helps to repair DNA by separating nicotinamide adenine dinucleotide (NAD+) into the remains of nicotinamide and adenine ribose. Over activation of PARP results in increased free radical formation, harmful changes in gene transcription, protein kinase C activation, and increased AGEs.

### 2.2. Oxidative stress

As mentioned above, hyperglycemia causes accumulation of ROS and oxidative stress eventually by interacting with many different ways. The free radical is a chemical species usually having very reactive unpaired electron in the molecular or atomic orbit. Although free radical reactions are necessary for defense mechanisms of immune system cells including neutrophils and macrophage, the overproduction of free radicals results in tissue injury and cell death. Free radicals affect all essential components of cells such as lipids, proteins, DNA, and carbohydrates and lead to the deterioration of their structure. The formation and elimination rates of free radicals are in balance in the organism, which are known as oxidative balance. The organism is not affected by free radicals as long as oxidative stability is provided. Studies in which the relationship between diabetes and diabetes complications and the ROS are shown, it is highlighted that tissue injury due to non-enzymatic glycation, metabolic stress caused by changes in energy metabolism, sorbitol path activity, hypoxia, and ischemia–reperfusion, increases the production of free radical and alters the antioxidant defense system. There are studies, which support that the formation of free radical is a direct result of hyperglycemia, as well as experimental trials that show that the formation of free radical starts when the endothelial and smooth muscle cells were incubated in the medium containing high concentrations of glucose. Hyperglycemia-mediated ROS production occurs via three mechanisms. The first mechanism is the auto-oxidation of glucose and superoxide production. Glucose is converted to reactive keto aldehydes and superoxide anion in the presence of a transition element. The chain of reactions results in the transformation of superoxide radical into extremely reactive hydroxyl radical via hydrogen peroxide. The intracellular glucose oxidation leads to the release of NADH. NADH is used for providing needed energy for ATP production by the oxidative phosphorylation way in the respiratory chain. Superoxide radical is released during this reaction in the respiratory chain. The production of superoxide radicals increases in this way in the presence of high glucose concentration. Mitochondrial respiratory chain is the main intracellular source of ROS production. It is considered that superoxide radical occurs continuously during normal respiration chain of events. Recent studies showed that much pathology in diabetes was associated with increased mitochondrial ROS production. The second mechanism in the hyperglycemia-mediated ROS production is the glycation of proteins and the formation of AGE products. When the proteins exposed to high glucose concentrations, glucose leads to uncontrolled glycation reactions by binding to protein without requiring the mediation of an enzyme. The glycated protein causes the formation of ROS by

donating an electron to molecular oxygen. AGE products are formed after this non-enzymatic reaction. Advanced glycosylation products lead to endothelial damage by increasing vasoconstriction via endothelin-1 and have the capacity to generate free radicals through complex biochemical mechanisms. Toxic effects of AGEs also include being able to change the structure and function of proteins and to induce oxidative stress with its receptors. The third mechanism of ROS production is polyol pathway. High glucose concentration causes the sorbitol production by polyol pathway. As NADH is used for the activity of enzyme aldose reductase in this pathway, intracellular NADH is consumed. NADH is required for converting oxidized glutathione to reduced form and nitric oxide (NO) synthesis. Therefore, being active of the sorbitol way and the absence of NADPH ultimately mean a limitation of cell's antioxidant capacity. The decrease in reduced glutathione and NO synthesis that has a function in vasodilatation leads to the reduction of endoneurial blood flow, consequently endoneurial hypoxia or ischemia. Due to this event, the damage occurs in neuronal cells, Schwann cells.

### 2.3. Vascular hypotheses

Swellings of the capillary vascular endothelial cells, thickening of the blood vessel wall, and undergoing aggregation or fibrin and occlusion with platelets of capillary lumen were shown in various studies. The sudden onset of clinical signs of focal neuropathies in diabetes supports the vascular cause. Decrease in NO production, abnormalities in eicosanoid production, and an increase in oxidative pathway lead to vasoconstriction in endoneurial microvascularization and nerve hypoxia.

### 2.4. Immunological mechanisms

Autoantibodies against the sympathetic ganglia develop in patients with insulin-dependent diabetes. Endoneurial or epineural lymphocytic infiltration has been displayed in the sural nerve biopsy of diabetic patients. Coexistence of diabetic neuropathy and chronic inflammatory demyelinating polyneuropathy is also a suggestive finding of immune or cytotoxic factors [11].

### 2.5. Neurotrophic factors

Neurotrophins are proteins that ensure the growth, permanence, survival, and differentiation into different specific populations of the neurons. There are studies, which show that impaired neurotrophic support is involved in the pathogenesis of diabetic polyneuropathy. Since nerve growth factor (NGF), a typical growth factor for the nerve, is needed for the survival and the continuity of sympathetic and thin sensory nerve fibers, it was examined particularly well. NGF also regulates the expression of the neuropeptides including calcium gene-related peptide and substance P in sympathetic nerves and sensory neurons of dorsal root ganglion. Retrograde axonal transport from target tissue to neuronal cell body is impaired in diabetes. There is evidence, which shows that NGF expression is decreased in the skin, submandibular glands, and the sympathetic ganglia in experimental diabetic neuropathy. NGF, when administered to rats with streptozotocin-induced diabetes, prevented the protection of the response to thermal painful stimuli (tail flick threshold) and the decrease in levels of neuro-

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peptides including calcitonin gene-related peptide and substance P measured in the cervical dorsal root ganglia. In diabetic autonomic neuropathy model, dystrophic changes in sympathetic ganglia following the administration of NGF indicate that there may be a different dosing effect. Neurotrophin-3 (NT-3) supports the differentiation and survival of sensory neurons. Decreased messenger RNA (mRNA) was shown in the leg muscle of NT-3 diabetic mice. Due to their neurotrophic effect in the treatment of diabetic neuropathy in recent years, glucagon-like peptide-1 (GLP-1) analogues (exendin-4) and peptides such as ghrelin were also found to give successful results in animal models [12].

## 3. Diagnosis

Symptoms and physical examination findings should be evaluated together for an accurate diagnosis of diabetic peripheral neuropathy (DPN). Standardization and easy application of diagnostic methods are of great importance in terms of widespread availability. There is no gold standard in the detection of presence of diabetic neuropathy. The San Antonio consensus panel recommends performing at least one measurement in five different diagnostic categories. These are symptom scoring, physical examination scoring, QST, cAFT, and EDS. The neurological examinations of the patients often reveal gloves socks style sensory deficit, hyporeflexia or areflexia, increase in vibration sense perception threshold, and moderate atrophy and weakness particularly in intrinsic foot muscles.

Neuropathic pain is one of the most common symptoms that are ignored by both the patient and the physician. Of the patients, 12.5% with painful DPN stated that they had never mentioned the pain to the physicians before and 40% expressed that they had received no treatment for pain. There are several questioning methods to query pain due to diabetic polyneuropathy, but none of these methods have been accepted as the gold standard.

Visual Analog Scale (VAS) is an easy method applied by grading the pain on a scale of 1–10 by the patient. Another method of pain assessment is "The Leeds Assessment of Neuropathic Symptoms and Signs" (LANSS) pain inquiry. Having a LANSS score of 12 or more is diagnostic for neuropathic pain. The Michigan Neuropathy Screening Instrument is one of the other commonly used interrogation methods, which is used in the diagnosis of neuropathic pain. Neuropathy Disability Score (NDS), which was first developed by Dick for the standardization of examination findings and correct interpretation of the findings and was simplified and modified in the following years, is regarded as a reliable and easy method that does not require experience in neurology. NDS = 0 is considered normal, NDS = 10 indicates maximum deficits, and NDS = 6 or more indicates the risk of developing diabetic foot ulcers. Touch pressure, vibration, hot–cold sensation, thermal pain, cold pain, and mechanical pain detection thresholds are tested in quantitative sensory testing.

The tests related to the vasomotor control, baroreceptor reflex, sudomotor function, pupil, bladder, and bowel innervation are used in autonomic function tests. Electrodiagnostic studies are one of the most common and objective methods used in the diagnosis of DPN. Weakness of electrodiagnostic studies is not showing the early stages of thin fiber damage. Unmyelinated

C fiber injury, the most common cause of painful DPN, does not provide any electrophysiological findings, but thick myelinated Aα and Aβ fiber involvements have EDS findings.

Staining of a 3-mm skin sample using protein gene product-9.5 allows the assessment of intraepidermal thin fibers and early diagnosis of neuropathic damage. Although its sensitivity is high, its use is limited because it is an invasive procedure [13].

## 4. Treatment in diabetic neuropathy

The prevention of occurrence of diabetic polyneuropathy or its definitive treatment is impossible.However, some measures that slow down the development of neuropathy, reduce the severity of symptoms, and prevent the complications of neuropathy may be taken. Normal or nearly normal blood glucose control of the patients should be provided. Keeping HGBA1C below 7, cholesterol control, smoking cessation, alcohol reduction, avoiding obesity, and having foot care delay the progression of neuropathy. When the structural link between membrane ion channel dysfunction and axonal loss is assessed, neuropathy can be diagnosed at an early stage with the detection of clinical biomarkers (biomarkers) that may identify the presence of early changes in ion channel. Therefore, the opportunity arises to start treatment without irreversible nerve damage [14].

### 4.1. Metabolic control

The most important treatment for the prevention of diabetic PNP (peripheral neuropathy) is to control blood glucose. According to Diabetes Control and Complications Center (DCTT) data, the reduction of neuropathy by 57% has been shown in Type 1 DM after 5 years of tight blood glucose control.

### 4.2. Myoinositol

The addition of myoinositol to the diet was shown to improve nerve Na–K ATPase activity and nerve conduction values in laboratory studies; however, no improvement was found in electrophysiological parameters in humans. Their potential benefits are being able to inhibit nerve damage. Thus, its administration is recommended at an early stage.

### 4.3. Vitamin addition

Vitamin treatment is often a non-specific therapy in neuropathy. Controlled studies show that receiving thiamine, vitamin B12, pyridoxine, or pantothenic acid in diabetic neuropathy is of no use [2,15].

### 4.4. ROS inhibitors

*Alpha lipoic acid:* High doses of alpha-lipoic acid were shown to have therapeutic efficacy in the treatment of diabetic polyneuropathy and insulin resistance in experimental and clinical

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trials [2,9]. The patients (with symptomatic diabetic neuropathy) were given randomized IV ALA 5 days a week (600 mg) or placebo in Sydney trials. After this treatment, a significant improvement was noted in TSS of the patients treated with ALA compared to those given placebo (5.7 vs. 1.8 points $p \leq 0.001$) [16].

*Nicotinamide:* It inhibits oxidative stress–PARP activation cascade.

*Resveratrol:* It regulates NCV, diabetic neuropathic pain and inhibits NF-κB.

*Routine:* It prevents protein glycosylation.

*Taurine:* It reduces oxidative and nitrosative stress in Schwann cells. It reverses neurovascular insufficiency and reduces increased pain sensitivity [9,17,18].

*NO agonist:* NO is one of the factors that play a role in the pathogenesis of DPN and l-arginine, a NO agonist, was shown to increase Na–K ATPase activity [9].

*Aldose reductase inhibitors:* Many aldose reductase inhibitor drugs that are effective through the polyol pathway were reported in the DPN treatment. Sorbinil, an aldose reductase inhibitor, prevents sorbitol accumulation by inhibiting the enzyme aldose reductase in those with diabetes and corrects neuronal dysfunction due to the change in the myoinositol content. It leads to increase in NCV. Tolrestat is the other aldose reductase inhibitors and repairs impaired NCV. Ponalrestat is effective in the delayed treatment of DPN. It normalizes NCV and prevents the impaired neural induction of ornithine decarboxylase. Fidarestat induces the maturation of the nerve fibers, stimulates the repair of nerve fibers, and stops the destruction of nerve fibers. Epalrestat prevents the progression of MNCV, regulates the polyol pathway, and suppresses the production of IGU [9].

*PKC inhibitors*: Ruboxistaurin, a PKC-β inhibitor, was found to be successful in treating neuropathic sensory symptoms. It improves nerve fiber functions and microvascular blood flow and increases life quality in those with DPN [9,19,20].

*Immunosuppressive therapy:* Inflammatory vasculopathy is thought to be important in the pathogenesis of cases in which proximal diabetic neuropathy or amyotrophy was detected. The treatment that is appropriate to the natural progress of diabetic amyotrophy and whose validity was accepted is the treatment with immunomodulatory agents including IVIG or corticosteroid. Better response is achieved with corticosteroid therapy and its cost of treatment is less compared to IVIG. However, blood glucose regulation may be difficult with corticosteroid. Starting with the dose of 0.75 mg/kg/day 3–4 times a week and discontinuing gradually are recommended [21].

*Pain treatment in diabetic neuropathy:* Antidepressants, particularly tricyclic drugs, are the most frequently used. Amitriptyline, imipramine, and nortriptyline may be used. Anticonvulsants such as carbamazepine, gabapentin, pregabalin, and lamotrigine are among the treatment options. Antiarrhythmics, mexiletine, and lidocaine are other pharmacological agents that are used in case of unresponsiveness to other drugs. Capsaicin derived from paprika may be preferred to as a topical agent for treating pain [21].

*Tricyclic antidepressants:* A great percentage of patients were given at an average dose of 105 mg of amitriptyline or at an average dose of 111 mg desipramine in a double-blind, randomized, placebo-controlled trial of the patients with painful diabetic peripheral neuropathy (PDPN). Decrease in pain by 74%, 61%, and 41% was observed in patients who received amitriptyline, desipramine, and placebo, respectively. Number needed to treat (NNT) is 2.1 (1.9–2.6) and number needed to harm (NNH) value is 2.8 for minor adverse events and 19 for major adverse events. TCAs may promote orthostatic hypotension and may prolong QT (**Q wave** and **T wave**) interval. An increase in the risk of sudden death has been reported with TCAs by taking more than 100 mg amitriptyline or its equivalent [22].

*Selective serotonin reuptake inhibitors (SSRIs)***:** Alternatively, the patients are treated with SSRIs because of many side effects of TCAs. These agents inhibit the presynaptic serotonin reuptake selectively [9]. Unlike the tricyclics, SSRIs lack the postsynaptic receptor-blocking effect. NNT to achieve 50% pain relief is 6.8 (3.4–441), and NNH is not known. While the benefit was observed with paroxetine and citalopram, no benefit was obtained with fluoxetine [22].

*Serotonin-norepinephrine reuptake inhibitors (SNRIs):* The direction of the treatment of DPN was shifted toward SNRIs because SSRIs are less effective in the treatment than TCAs and SNRIs inhibit both serotonin and norepinephrine reuptake. Duloxetine and venlafaxine are examples of SNRIs. Venlafaxine was argued to decrease the pain, and the effect on norepinephrine is presumed to be more specific in a study in which high dose of venlafaxine was used. Duloxetine is more effective in terms of the affinity in noradrenergic and serotonergic reuptake inhibition. Many people were given duloxetine in the randomized, placebo-controlled studies and 60 mg and 120 mg daily doses were reported to be effective in DPN [9,23,24].

*Anticonvulsants:* Antiepileptic drugs act by blocking sodium channels (felbamate, lamotrigine, oxcarbazepine, topiramate, and zonisamide), potentiating the activity of GABA (tiagabine and topiramate), blocking calcium channel (felbamate, lamotrigine, topiramate, and zonisamide), antagonizing glutamate at *N*-methyl-d-aspartate (NMDA) $\alpha$-receptors (felbamate), and behaving as the antagonist of AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazole) receptors (felbamate and topiramate). Rational polytherapy by which we can obtain a synergistic effect comes to the fore through understanding the mechanisms of these drugs. For example, lamotrigine can be given for sodium channel blocking and felbamate may be added to antagonize glutamate receptors or different mechanisms can be targeted with a single medication, for instance, topiramate, and chance of success may be increased. It was reported that a patient who was unresponsive to one of the antiepileptic drugs will respond to another drug or combination treatment consisted of two or more drugs [25,26].

*Topical capsaicin (capsaicin = 8-methyl-*N*-vanillyl-trans-6-nonenamide):* C fibers use neuropeptide P as a neurotransmitter, the reduction of axonal substance P causes pain relief. Storage of substance P, which is released from sensory nerve terminals, finishes with the application of capsaicin. Thus, the transmission of painful stimulus from peripheral nerve terminals is reduced or completely eliminated. A significant improvement was observed in patients with painful neuropathy treated with Capsaicin cream (0.075%) for 8 weeks. The treatment with capsaicin should be limited to 8 weeks, because it is noted that adverse event may be observed in sensory nerves at the end of this period. Eight percent capsaicin patch may be used in

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postherpetic neuralgia; however, it is contraindicated in diabetic neuropathy, because it desensitizes the nociceptive sensory nerve endings, so it is reported that the risk of development of diabetic foot ulcers may be increased [25,27].

*Topical lidocaine:* Use of topical lidocaine in painful neuropathy is associated with postherpetic neuralgia [16]. Lidocaine has been shown to be as effective as pregabalin in reducing pain without causing the side effects in a multicenter, randomized, open-label, parallel group study conducted by treating a group ($n$ = 99) with 5% lidocaine for 2 weeks and treating another group ($n$ = 94) with pregabalin for 4 weeks. This therapy may be continued with oral mexiletine in order to succeed. Relief of superficial pain caused by overstimulation is targeted with oral mexiletine [25].

*Acetyl-l-carnitine:* It was reported that the pain and the slowed nerve conduction velocity were improved, and nerve regeneration was increased with acetyl-l-carnitine in rats with streptozotocin-induced diabetic neuropathy. It was reported that the pain disappeared with acetyl-l-carnitine, and the pain was resolved by prophylactic treatment in paclitaxel-treated rats [28].

## 5. Current therapeutic strategies in diabetic neuropathy

DPN is one of the most common symptoms of chronic neuropathic pain in clinical practice. Various treatment methods are tried in patients with diabetic neuropathy. Tramadol, an opioid, is a weak opioid analgesic used for reducing severe pain. It was reported that randomized controlled trials for a period of 6 weeks were better than the placebo and symptomatic relief continued for at least 6 months. The likelihood of side effects, as other opioid-like drugs, is common. However, the development of drug tolerance and the development of addiction with long-term therapy with tramadol are not common. NMDA receptors play a key role in the sensitization of the neuropathic pain, but the use of these drugs is not widespread because of their dose-limiting side effects [25]. NMDA receptor antagonists are used for modulation of excitatory transmission in the primary afferent spinothalamic neuron synapses in recent years. The pain ceases with the blockade of excitatory glutamatergic NMDA receptors in the spinal cord. Dextromethorphan is one example of such painkiller medications. NMDA receptor antagonists have been shown to be as effective as opioid analgesics for chronic pain conditions. The diagnosis of diabetic neuropathy was made by a clinical evaluation (medical history, motor, sensory, and reflex examination) and electrophysiological tests for 24 patients with Type 2 diabetes and diabetic neuropathy. Pain complaints of the patients were assessed with a VAS before and after the treatment. While a significant improvement in VAS scores was observed in both treatment groups compared to the control group, the difference between treatment groups was found to be significant. In conclusion, Memantine (NMDA receptor antagonist) treatment provides an improvement in the treatment of neuropathic pain in diabetic polyneuropathy [29].

Flavonoids, which many positive effects on human health were determined, have antioxidant, anti-inflammatory, cholesterol lowering, antibacterial, antihyperglycemic, and antiallergic features. It may be called P factor or P vitamin considering its capillary circulation regulating

blood pressure lowering effects. The main one of these flavonoids is proantocianidin found in grape seeds. The grape seed extract was given at the dose of 25 mg/kg and 50 mg/kg by oral gavage for 6 weeks in a study in which diabetes was induced in BALB/C mice. The pain threshold was measured using the Hot Plate Test, a thermal pain model, in these animals at the end of second and sixth weeks. When the sciatic nerve and abdominal aorta tissue from animals were examined histologically at the end of the study, hot plate measurements of the groups received grape seed extract and the measurements between other groups were considered significant. UCE (was seen to decrease damage in diabetes-induced micro and macrovascular complications in histological evaluations [30].

### 5.1. DPP-4 inhibitors

Dipeptidyl peptidase-4 incretin hormones are secreted from intestinal endocrine cells. It plays a key role in regulating blood glucose levels by stimulating glucose-dependent insulin secretion, decreasing glucagon secretion, and slowing gastric emptying. DPP-4 inactivates GLP-1 and glucose-dependent insulin tropical polypeptides (GIP) in vivo by destroying them. These peptides are short lived in the circulation because they are destroyed by DPP-4. Alogliptin is a DPP-4 inhibitor. The effects of this medication on vascular and neural complications were evaluated in male Sprague–Dawley rats with STZ-induced diabetes. Alogliptin was observed to regulate MNCV and thermal response latency after a 12-week treatment. No improvement in the decrease in intraepidermal nerve fiber density was detected while SNCVs of the mice were regulating. PKF 275-055, new analog of Vildagliptin, was given to STZ-induced diabetic rats in the study of Bianchi et al., and it was found that it displays an anabolic effect by preventing changes in nociceptive threshold, Na–K ATPase, and NCP. DPP-4 inhibitors were stated to prevent some neural and vascular complications associated with diabetes in the studies conducted [9,31,32,33].

### 5.2. Cannabinoid CB1 receptor antagonists

Nabilone is a CB1 predominant receptor agonist. It was used in neuropathic pain based on the anecdotal evidence and uncontrolled case series [34]. Pain reduction has been reported to occur in 30% of the patients in a single center, randomized, double-blind, placebo-controlled, flexible 5-week study conducted by administering a dose ranges from 1 to 4 mg per day or placebo. DPN symptoms disappeared, and their impaired sleep and standard of living were improved in those received flexible dose. Nabilone is a well tolerated and successful adjuvant in patients with DPN. Rimonabant is a CB1 receptor antagonist; it accelerates skin blood flow and decreases TNF-$\alpha$ level in diabetic rats. It was stated that Rimonabant may be beneficial in the treatment of DPN due to its micro and macro blood vessel protection and inflammatory effects [9,34,35].

### 5.3. Natural products

*Metanx:* It is a product, used for the endothelial function disorder, containing l-methyl folate, pyridoxal 5′ phosphate and methylcobalamin. It prevents endothelial NO synthesis, oxidative stress in endothelium, and peripheral nerves. A significant improvement was noted in numbness, tingling, pain, burning, sharp pain, and allodynia by giving Metanx to placebo-

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controlled diabetic neuropathy patients for 24 weeks. An increased emotional, social functions, and vitality components of mental health were also detected. Side effects at less than 2% were seen along this response. Generally, the side effects were rash and gastrointestinal disorders and were no greater than the side effects seen with placebo [25].

*Botulinum toxin:* It was tried in trigeminal neuralgia and was reported that it has a long-term antinociceptive effect in CTS without having electrophysiological repair [25].

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