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General approach to diabetic neuropathy

Diyabetik Nöropatiye Genel Yaklaşım

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ABSTRACT

Diabetic neuropathy is the most common complication of diabetes mellitus. It causes microvascular and macrovascular damage and diagnosis can easily be overlooked by most physicians. Generally, the diagnosis of DN can be omitted by physicians dealing with diabetes treatment since it starts with non-specific findings, shows slow progression and can be confused with complaints in many diseases. It is estimated that there will be 578 million people diagnosed with DM in the world in 2030. Chronic hyperglycemia, microvascular insufficiency, oxidative and nitrosative stress, impaired neurotropism and autoimmunity are some of the factors that cause nerve destruction. Paresthesias such as tingling, burning, electrical shock-like sensations, numbness, throbbing, compression, pinpricks to the skin, complaints are the most common symptoms. There is no treatment for pathogenetic mechanisms in diabetic neuropathy that eliminates neuronal damage. The purposes of treatment are slowing down the progression of the disease, controlling the pain, preventing complications, quick and adequate treatment of occurred complications, maintaining the functional capacity of the patient. In this review, we aimed to comprehensively address the general approach to diabetic neuropathy, diagnosis and treatment.

Keywords: diabetes mellitus, neuropathic pain, neuropathy, diagnosis, treatment

ÖZ

Diyabetik nöropati (DN), diabetes mellitusun en yaygın komplikasyonudur. Mikro ve makrovasküler hasara neden olur ve çoğu hekim tanıyı kolaylıkla gözden kaçırabilir. Genel olarak; DN tanısı, spesifik olmayan bulgularla başladığı, yavaş ilerleme gösterdiği ve birçok hastalığa ait şikayetlerle karışabileceği için diyabet tedavisi ile uğraşan hekimler tarafından ihmal edilebilir. 2030 yılında dünyada 578 milyon kişinin DM tanısı alacağı tahmin edilmektedir. Kronik hiperglisemi, mikrovasküler yetmezlik, oksidatif ve nitrozatif stres, bozulmuş nörotropizm ve otoimmünite sinir harabiyetine neden olan faktörlerden bazılarıdır. Karıncalanma, yanma, elektrik çarpması benzeri hisler, uyuşma, zonklama, bası, deriye iğne batması gibi parestezik yakınmalar en sık görülen semptomlardır. Diyabetik nöropatide nöronal hasarı tamamen ortadan kaldıran patogenetik mekanizmaların tedavisi yoktur. Tedavinin amacı hastalığın ilerlemesini yavaşlatmak, ağrıyı kontrol altına almak, komplikasyonları önlemek, oluşan komplikasyonların hızlı ve yeterli tedavisi ve hastanın fonksiyonel kapasitesini korumaktır. Bu derlemede, diyabetik nöropati, tanı ve tedaviye genel yaklaşımı kapsamlı bir şekilde ele almayı amaçladık.

Anahtar Kelimeler: Diabetes mellitus, tanı, tedavi, nöropati, nöropatik ağrı

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Introduction

Diabetic neuropathy (DN) is the most common complication of diabetes mellitus (DM) [1]. In developed countries, it is the most common cause of neuropathy, leading to more hospitalizations than any other diabetes complication. It is also the major cause of non-traumatic amputations [2]. Generally, neuropathic pain is the first symptom that makes the patient consult a physician in type 2 diabetes, which is asymptomatic for many years. Diagnosis of DN can be omitted by physicians dealing with diabetes treatment since it starts with non-specific findings, shows slow progression and can be confused with complaints in many diseases [3]. While 50% of pathological findings were detected in simple diagnostic tests (vibration detection threshold (VDT) test, pinprick test), in 90% of the same patients, positive findings (for changes in autonomic function and peripheral sensitization), were found to support positive DN by complex tests [4]. The major cause of morbidity associated with diabetic neuropathy is foot ulcers induced by somatic neuropathy and extremity losses due to gangrene. Foot ulcer prevalence varies from 3% to 30% among patients with diabetes, and amputation risk increases 8 to 23-fold if there is a preexisting ulcer in the extremities [5]. In autonomic nervous system involvement due to diabetes, mortality is observed in 25-50% of the patients within 5-10 years.

Since DN was first identified, several classifications have been made. Commonly used simple classification defines patients as symmetric polyneuropathy (e.g., sensorimotor polyneuropathy), focal/multiple neuropathies (e.g., diabetic amyotrophy). Sensorimotor polyneuropathy is the most common form of the polyneuropathy of DM. Polyneuropathy is seen in approximately 25% of diabetic patients in the general population [6]. Diabetic polyneuropathy (DP) is generally one of the late complications of diabetes. It has been shown that long-term high blood glucose values associated with the duration of the disease contribute to metabolic and vascular changes and accelerate the risk and course of symmetrical sensorimotor polyneuropathy. At first, there is a decrease in the awareness of pain and heat due to the involvement of small nerve fibers and in the following process, the sensation of touch and vibration decreases with the involvement of large nerve fibers. Positive symptoms such as paresthesia and pain may be observed by the involvement of sensory nerve fibers. However, 50% of cases are asymptomatic. In DP, cardiovascular autonomic system involvement increases mortality risk with a 5-year mortality rate of 16%–50% [7]. In light of recent data, diabetic autonomic neuropathy or autonomic imbalance in the sympathetic-parasympathetic nervous system might be an important cardiovascular risk.

Epidemiology

It is estimated that there will be 578 million people diagnosed with DM in the world in 2030 [8]. It has been shown that the prevalence of diabetes in Turkey is 7.2% and the prevalence of impaired glucose tolerance is 6.7% [9]. The data on the frequency of DN varies according to the characteristics of the selected methods for diagnosis. Symptoms, examination findings, quantitative sensory tests and electrophysiological tests are the methods used for diagnosis. In epidemiological studies based on different diagnostic criteria, the prevalence of chronic sensorimotor neuropathy was found to be 4-64%. In Turkey, in the most recent study performed by Erbas T. et al., 14% of patients with DM had painful neuropathy, while 40% of patients had clinical diabetic peripheral polyneuropathy findings. Poor glycemic control, retinopathy, microalbuminuria, hyperlipidemia, diabetic foot and foot amputations, have been commonly observed in patients diagnosed with diabetic peripheral neuropathy [10].

Diabetic Neuropathy Classification

Although there are many neuropathy classifications prepared considering anatomical and clinical features, most of these classifications are similar to each other. The classification summarized in Table 1 is one of the most commonly used [11].

Etiopathogenesis

Chronic hyperglycemia, microvascular insufficiency, oxidative and nitrosative stress, impaired neurotropism and autoimmunity are some of the factors that cause nerve destruction. DN progress with a wide variety of clinical symptoms and consists of clinical pictures with

these symptoms having different pathological mechanisms. The elucidation of pathogenesis is important for the development of causative treatments (see Figure 1).

Table 1. Classification of Diabetic Neuropathy

1. Quickly reversible
a. Hyperglycemic neuropathy
2. Generalized symmetrical polyneuropathies
a. Sensorimotor (chronic)
b. Acute sensorial
c. Autonomous
3. Focal and multifocal neuropathies
a. Cranial neuropathies
b. Thoracolumbar radiculoneuropathies
c. Focal extremity neuropathies
d. Proximal motor neuropathies (Amyotrophy)
4. Chronic inflammatory demyelinating polyneuropathy

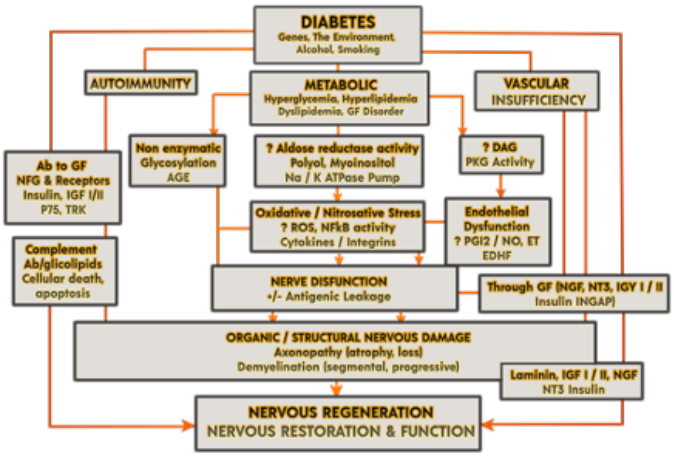

Figure 1. The pathogenesis of diabetic neuropathy. (Ab, antibody; AGE, advanced glycation end products; ATPase, adenosine triphosphatase; C, complement; DAG, diacylglycerol; EDHF, endothelial derived hyperpolarizing factor; ET, en-dothelin; GF, growth factor; IGF, insulin-like growth factor; NFkb, nuclear factor kappa b; NGF, nerve growth factor; NO, nitric oxide; NT3, neurotrophin3; PGI2, prostaglandin I2; PKC, protein kinase c; ROS, reactive oxygen species; TRK, tyrosine kinase (12).)

Symptoms and Clinical Features

DN clinic shows a rich variety. Diabetes has widespread involvement from the somatic peripheral nerves to the autonomic nervous system. There are very different clinical manifestations depending on the affected nerve segment: from cardiovascular symptoms to erectile dysfunction, neuropathic pain to foot ulcers, it may present with various clinical findings. Half of the DP patients present with neuropathy related symptoms and the other half are asymptomatic. A good neurological examination is very important for the detection of asymptomatic patients. Long axons are more sensitive to nerve damage and complaints usually begin distally to the lower limbs and more rarely from the distal upper limbs. Involvement of myelin-free C, thin myelin A delta, thick myelin Aα and A_β type neurons are typical. Although it little known, there is a great deal of evidence showing that thin fibers are involved earlier and neuropathic pain begins earlier than sensory loss and decreased nerve conduction velocity [12]. In the skin biopsies taken at the initial stage of DP, all findings showing thin fiber damage, especially decrease in the density of intraepidermal nerve fibers, were detected, however nerve conduction velocity, quantitative sensory tests and neuropathic disability scores indicating thick never fibers were found to be completely normal [13].

The most prominent feature of DN is that sensory symptoms begin much earlier than the symptoms of motor involvement. Sensory symptoms may be positive or negative: positive findings are symptoms of neural hyperactivity that are felt as stimuli without stimulation. Paresthesias such as tingling, burning, electrical shock-like sensations, numbness, throbbing, compression, pinpricks to the skin, complaints such as dysesthesia, hyperpathy, hyperalgesia or allodynia are the most commonly described pain-positive symptoms. It may present non-painful positive symptoms such as felting, drowsiness, feeling like wood and a feeling of walking on pebbles. The pain is usually localized distally to the lower extremity and exacerbates at night. Sleep disorders, anxiety, depressive symptoms, decreased appetite, weight loss, sexual dysfunction and difficulty in concentration, are often correlated by the severity of pain. The most common symptom of negative symptoms is the loss of sensation. Motor losses in DP are milder than sensory losses and are limited to the distal lower extremity. Depending on the severity of the involvement, atrophy and reflex losses may occur in the foot muscles; due to loss of pain sensation and deformities in the feet, prominent metatarsal head, claw-foot, hammertoe deformities are frequently observed. These deformations also increase the risk of callus

formation, ulcers and amputation. Neuropathic pain is the most important symptom that leads the patient to the physician in diabetic neuropathy cases with delayed diagnosis. Figure 2 and Table 2 describe different forms of diabetic neuropathy: different forms of DN, usually in the same patient (e.g., distal polyneuropathy and carpal tunnel syndrome), are important to be noted as that they may present together [14].

Diagnosis

A series of conferences have been organized aiming to redefine the minimum criteria for diagnosis, in order to overcome the existing problems arising from the differences in the methods used in the identification and diagnosis of neuropathy. The tests found in Table 3 and Table 4 are suitable for assessing each nerve fiber type and function. From distal symmetrical diabetic polyneuropathy, we can divide DP into 5 groups according to the Toronto classification [15].

1- Possible DP: Symptoms such as numbness, tingling, burning or symmetrical distal sensory loss against touch and vibration during the examination, one of the symptoms or signs such as pin prick and thermal sensory loss and/or allodynia/hyperalgesia, decreased or lost Achilles reflex.

2- Possible DP: Two or more neuropathic symptoms and examination findings (such as decreased sensory sensation, decreased or absent uneven Achilles reflex)

3- Proven DP: Abnormal neurophysiologic/ morphometric results accompanied by any symptom or finding

4- Subclinical DP: Abnormal neurophysiological/morphometric test results detected in the absence of signs or symptoms

5- Small fiber neuropathy (SFN): There is no commonly agreed definition yet. SFN is divided into 3:

a. Possible SFN: Presence of length-dependent symptoms and / or clinical signs of small fiber nerve injury

b. Possible SFN: Presence of length-dependent symptoms, clinical signs of small fiber damage and normal sural nerve conduction

c. Proven SFN: Presence of length-dependent symptoms, clinical signs of small fiber damage, normal sural nerve conduction, abnormal intraepidermal nerve fiber (IENF) density measurement and / or abnormal thermal cut-off measurements in ankle sural biopsy.

In diabetic polyneuropathy, the diagnosis should be made according to clinical and neurological examination findings. Neurological examination findings such as sensory loss, allodynia, hyperalgesia, motor weakness and absence of reflexes should be detected with positive and negative sensory and motor symptoms. Symptoms alone have low predictive value in the diagnosis of polyneuropathy. For polyneuropathy diagnosis, positive findings on examination are a better predictor than the patient's symptoms.

Differential Diagnosis

Non-diabetic factor should be considered in the etiology of neuropathy in 10% of diabetic cases. The non-diabetes causes of neuropathic pain should be questioned in the patients with asymmetric neurological deficits, predominant motor deficits, mononeuropathies, cranial nerve involvement, rapid and progressive neurological insufficiency, progressive neuropathy despite optimal glycemic control, those with onset of symptoms on upper limbs, familial history of non-diabetic neuropathy, in those with whom DN cannot be detected.

Types of Diabetic Neuropathy Associated with Pain

Table 5 lists the types of painful diabetic neuropathy. In this section, the clinical features of these painful neuropathy types in diabetes will be discussed in more detail.

I. Focal and multifocal neuropathies

Focal neuropathies consist of focal extremity neuropathies and cranial neuropathies. Focal extremity neuropathies are usually caused by entrapment neuropathies. Mononeuropathies are usually observed in the elderly population, are acute onset and tend to self-limit within 6-8 weeks. The involvement of the median nerve

Table2. Characteristic Differences Between Mononeuropathy, Trap Neuropathy, Distal Symmetrical Polineuropathy

Features	Mononeuropathy	Trap Neuropathy	Polyneuropathy
Starting	Fast	Progressive	Progressive
Pattern	Single nerve involvement sometimes multiple involvement	Single nerve exposure to trauma	Distal Symmetric Polyneuropathy
Nerve involvement	3, 4 and 7. cranial nerves, ulnar median, peroneal	Median, ulnar, peroneal median and lateral plantar	Mixt, motor, sensory autonomic
The natural course	Spontaneous remission	Progressive	Progressive
Distribution of sensory loss	Along the innervation pattern of the affected nerve	Area distal to the affected nerve that is trapped	Distal and symmetrical glove sock style scatter pattern

Table3. Sensory tests that can be performed at the bedside

Sensory Modality	Nerve Fiber	Instrument	Associated Sensory Receptors
Vibration	Aβ	128 Hz diapason	Ruffini mechanoreceptors
Pain (pinprick)	C	Free nerve endings termination	Heat and pain receptors
Pressure	AβAα	1 g and 10 g monofilament	Pacini receptors
Light touch	AβAα	Cotton touch	Meissner bodies
Cold	Aα	Skin contact with cold	Cold thermoreceptor

Table 4. Advanced objective tests for the diagnosis of diabetic neuropathy

Neurological Test	Types of neuropathy	Measurement	Advantages
Quantitative sensory tests	Thin and thick fiber neuropathy	Assessment of sensory loss	A measurable semiquantitative test
Skin biopsy and intraepidermal nerve fiber density (IENF)	Small fiber neuropathy	Somatic non-myelinated nerves, dermal myelinated nerve fibers, automatic nerve fibers consisting of small sensory fibers	Quantitative measurement of epidermal thin fibers by various antibody staining methods
Corneal confocal microscopy	Small fiber neuropathy	Detects small nerve fiber loss in cornea.	Non-invasive technique that correlates with the severity of neuropathy
Potential evoked by heat contact	Small fiber neuropathy	Heat-induced potentials are recorded with electroencephalography.	In the absence of other tests, it shows damage to thin fibers.
Evaluation of sudomotor functions	Distal small fiber neuropathy	A test for measuring electrochemical conduction between chlorine ions in hand and foot sweat	Early detection of neurophysiological abnormalities in peripheral autonomic functions
Nerve conduction studies	Thin and thick fiber neuropathy	Evaluation of conductivity of ner ve fibers by electrical stimulus	Objective, universally measurable and recordable method.

Table 5. Types of Painful Diabetic Neuropathy

I. Focal and multifocal neuropathies
a. Cranial
b. Focal extremity (Trap neuropathies)
c. Amyotrophy (Proximal motor neuropathy)
d. Truncal (Thoracolumbar) radiculoneuropathy
II. Generalized symmetrical polyneuropathies
Acute sensorial

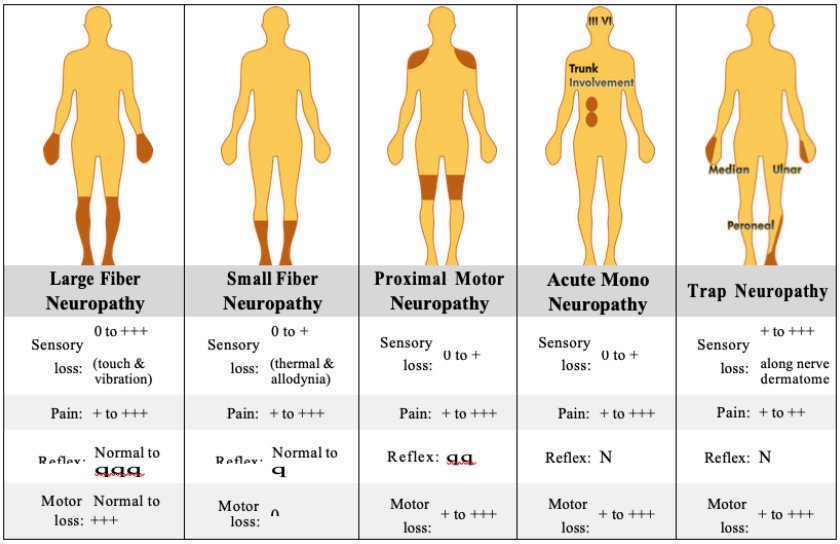

Figure 2. Clinical presentation of large fiber and small fiber neuropathy in diabetic polyneuropathy. N, normal. (16)

(5.8%), ulnar nerve (2.1%), radial nerve (0.6%) and common peroneal nerves are observed in mononeuropathies, respectively [14].

A. Cranial Neuropathies

1. Ocular Neuropathy

Ocular neuropathies are the most frequent microvascular complication of diabetes [16]. Ocular neuropathy usually occurs in older age and long-term diabetes, and most commonly 3, 4 and 6th cranial nerves are involved and symptoms specific to the involved nerve are observed. 3rd nerve involvement causes ptosis, diplopia and ipsilateral headache. Clinical findings usually improve within 3 months but may be recurrent.

2. Others

Involvement of facial nerve, optic and olfactory nerves, corneal myelinated and non-myelinated small fibers is more common in diabetic patients. Recurrent laryngeal nerve pathologies with trigeminal and vagal neuropathy are rare but can be seen.

B. Focal Extremity Mononeuropathies

1. Carpal tunnel syndrome

The prevalence of carpal tunnel syndrome (CTS) in diabetes is 3 times higher than in the normal population (20). In a recent study, it was reported that 65% (76) of the 117 diabetic patients had hand problems. 64 of these patients had CTS [17]. Neuropathy is characterized by symptoms of the median nerve trapped under the transverse carpal ligament. Resting splint, anti-inflammatory agents, cortisone injection under the ligament and decompression surgery in unresponsive cases,

are recommended for treatment.

2. Ulnar nerve neuropathies

Ulnar neuropathy at the elbow, known as cubital tunnel syndrome, is the second most common entrapment neuropathy. The most affected ones are the intrinsic muscles of the hand, and weakness and atrophy occur in the progressive stage. In the treatment of symptoms, conservative treatment is performed for unresponsive cases.

C. Proximal Motor Neuropathy

Proximal motor neuropathy of the lower extremity is often called diabetic amyotrophy. It is more common in Type 2 diabetic patients between the ages of 50-60. It is thought that vascular, metabolic and immune factors are involved in the etiology. Electrodiagnostic examinations show that the lesion is located in nerve roots and plexus. Pain is often an initial complaint and is worse at night, weakness becomes apparent a few weeks after the onset of pain and atrophy of quadriceps, iliopsoas, or the adductor muscles occur. Generally, recovery is completed over a period of 12-24 months and the prognosis is good. The first approach to treatment is strict pain control. It is important to ensure good glycemic control for the etiology. In addition, the benefits of high-dose corticosteroid use and IV immunoglobulin administration have been reported in selected cases [18, 19].

D. Truncal Radiculoneuropathy

Thoracoabdominal or truncal neuropathy or radiculopathy, occurs most commonly in diabetic patients over the age of 50 years. The onset is usually acute, it mainly involves T3-T12 and is generally unilateral. This condition may often be confused with myocardial infarction, an intraspinal pathological event, abdominal disease or malignancy, and differential diagnosis should be made. Sensory loss and allodynia may be present in the painful area. Symptoms tend to gradually improve within a few months. In addition, IV immunoglobulin and high dose corticosteroid administration may be beneficial.

II. Generalized Symmetrical Polyneuropathies

A. Acute Sensorial Neuropathy

It is a neuropathy that occurs following a period of high glucose levels or diabetic ketoacidosis in newly diagnosed diabetics. According to some authors, it is a characteristic variant of distal symmetrical polyneuropathy. The syndrome is characterized by severe pain, cachexia, weight loss, depression and erectile dysfunction in men. It is mostly seen in male patients. A physician should exclude such factors as Fabry disease, amyloidosis, HIV infection, heavy metal poisoning and excessive alcohol consumption. Rapidly normalizing blood glucose by insulin or even by oral anti-diabetic therapy in poor glycemic controlled cases, may trigger this condition. Although the exact mechanism is not known, blood glucose level alterations are thought to cause perineural ischemia [20]. Another group of researchers linked the disease to lumbosacral radiculoplexus neuropathy, and suggested that there are immune-mediated mechanisms in the pathogenesis of the disease. Symptoms usually regress spontaneously within weeks following glucose control.

B. Chronic Sensorimotor Neuropathy or Distal Symmetric Polyneuropathy

The most common type of DN is chronic sensorimotor neuropathy [21]. Although it is similar in type I and II diabetes, chronic sensorimotor neuropathy may accompany the condition even at the time of diagnosis of type II diabetes. A progressive decrease in peripheral nerve fibers has been demonstrated in skin and skin biopsies taken from patients diagnosed with diabetes or in the prediabetic phase [22]. Sensory symptoms in patients are more pronounced than motor symptoms and usually involve lower extremities.

Treatment approaches for pathogenesis in diabetic neuropathy

There is no treatment for pathogenetic mechanisms in diabetic neuropathy that completely eliminates neuronal damage. The purposes of treatment can be listed as follows:

1. Slow down the progression of the disease

2. Pain control

3. Preventing complications

4. Rapid treatment of occurred complications

5. Maintain the functional capacity of the patient

Importance of Glycemic Control

The most effective approach for the prevention of all microvascular complications of diabetes and neuropathic pain is undoubtedly to achieve good glycemic control. According to the data of the Diabetes Control and Complications Trial Research Group (DCCT) studies, a 60-69% risk reduction of neuropathy development was found in Type I diabetic patients who were followed up with intensive insulin therapy for nearly 8 years and were targeted to keep HbA1c close to normal [22]. This Epidemiology of Diabetes Intervention and Complications study, the continuation of the DCCT study, showed that this positive effect continued even 13-14 years after the end of the treatment. As a result, good blood sugar metabolic control achieved in the first 10 years of diabetes diagnosis may prevent neuropathy and this positive effect persists even after HbA1c increases [23]. The results of studies on the relationship between strict blood glucose control and neuropathy risk in patients with Type 2 diabetes are not as clear as in patients with Type 1 diabetes. In the ADVANCE study, which included 11,140 patients with type 2 diabetes, patients were divided into 2 groups. The first group consisted of patients receiving standard glucose therapy and the second group consisted of patients with strict sugar control. During the five-year observation period, new-onset neuropathy and neuropathic symptoms worsening in these patients were observed in similar rates [24]. Multiple daily insulin injections reduces neuropathy risk by 10-25% [25]. Although clinical course and treatment modalities are different in both Type 1 and Type 2 diabetes, metabolic targets are common. High blood glucose values are the triggering factor in the development of microvascular complications in both diabetes types. Near-normal glucose control is a prerequisite for the prevention and treatment of neuropathy. An individual with a blood glucose levels above ≥126 mg/dl for fasting, ≥200 mg/dl for postprandial (two hours after eating) is being diagnosed as diabetes [26]. In Type 2 diabetic patients with multiple risk factors and comorbidities, strict glycemic control alone is partially effective in preventing distal symmetric polyneuropathy. It causes a slight slowdown in the progression of neuropathy without preventing neuronal loss. Targets to change lifestyle should be set to prevent distal symmetric polyneuropathy in patients with prediabetic, metabolic syndrome or Type 2 diabetes.

Aldose Reductase Inhibitors

The major enzyme of the accelerated polyol pathway due to hyperglycemia is aldose reductase. They act by inhibiting the activity of this enzyme and reducing neural sorbitol levels. Epalrestat is the only aldolase reductase inhibitor currently licensed in Japan. In a randomized, placebo-controlled study for 3 years, it was reported that median motor nerve conduction rate and minimum F wave delay were prevented by administering 150 mg of epalrestat daily to 594 diabetic neuropathy patients. It has been shown that it significantly reduces symptoms such as numbness, sensory abnormalities, and cramping (30).

Antioxidants

Data suggest that oxidative and nitrosative stress is important in the pathogenesis of neuropathy and that antioxidants may be used in the treatment. Prolonged oral alpha-lipoic acid administration has been shown to cause clinical improvement and a slight delay in the progression of neuropathic deficits in patients with mild distal symmetric polyneuropathy. Due to its controversial results, its place in the pain treatment of diabetic neuropathy is not clear [27-30].

Growth Factors

Low levels of NGF induce peripheral nerve lesions in diabetic patients [31]. Increased neovascularization in nerve cells has been shown in diabetic neuropathic mice with IGF-1 supplementation [32]. Positive effects of VEGF on nerve functions have been shown in diabetic animal model studies [33]. VEGF gene therapy studies on humans are ongoing.

Immune treatment

The diabetes-related monosialoganglioside antibodies (anti-GM1 autoantibody) are

Table 6. 6 Drugs Used in the Treatment of Symptomatic Pain in Patients with Diabetic Polyneuropathy

Pharmaceutical group	Medication	Dose	Drug side effects
Tricyclic's	Amitriptyline, Nortriptyline, Imipramine, Desipramine	50-150mg, 50-150mg, 25-150mg, 25-150mg	Drowsiness, dizziness, dry mouth, tachycardia, orthostatic, hypotension, urinary retention, constipation, sweating, blurred vision
SSRI's	Paroxetine, Citalopram	40mg, 40mg	Drowsiness, dizziness, sweating, nausea, anorexia, diarrhea, impotence, tremor
SNRI's	Duloxetine	60-120mg	Nausea, dizziness, anorexia
Anticonvulsants	Gabapentin, Pregabalin, Carbamazepine, oxcarbazepine, Topiramate	900-3600mg, 150-600mg, 200-1200mg, 600-1800mg, 400mg	Drowsiness, dizziness, confusion, ataxia, drowsiness, confusion, edema, weight gain, drowsiness, dizziness, nausea, leukopenia, hyponatremia, drowsiness, ataxia, loss of appetite, tremor
Opioids	Tramadol, Oksikodon	200-400mg, 20-80mg	Nausea, constipation, drowsiness, nausea, constipation, addiction
Topical	Capsaicin, Lidocaine	0,0075 %-8 %, 0,04 %-5 %	Local irritation, Local irritation
Injection	Botilinum toxin	Max 200IU	None

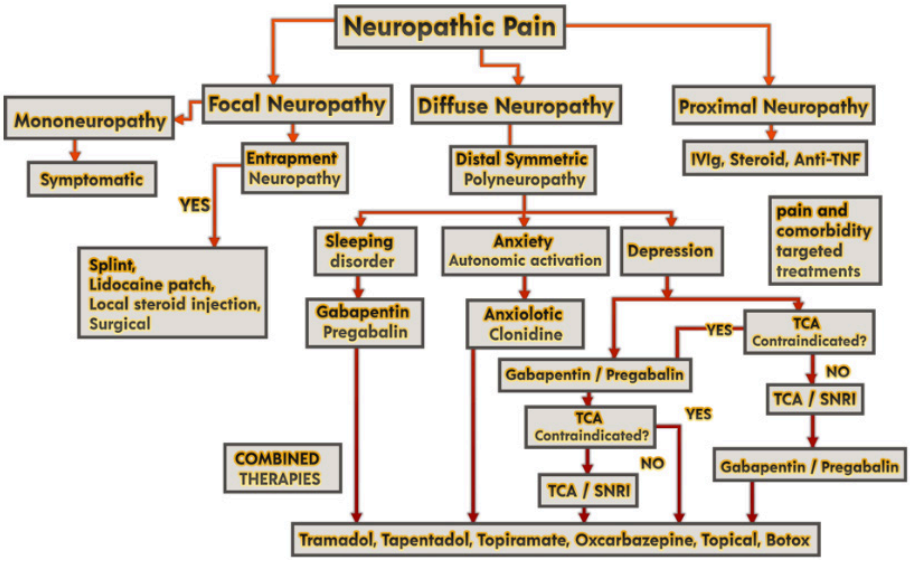

Figure 3. Diabetic neuropathy treatment scheme. (TCA, tricyclic antidepressants; SNRI, selective serotonin and noradrenaline reuptake inhibitors (36,37).)

detected in 12% of patients with proximal motor neuropathy. The relationship between autoimmunity and neuropathy is evident in patients with proximal motor neuropathy, chronic inflammatory demyelinating polyneuropathy, vasculitis, monoclonal gammopathy. Recent data has shown that even though autoantibodies against neuronal cells are not neurotoxic, they are not so innocent and have prognostic value in the development of neuropathy [34]. The use of high-dose corticosteroids and iv immunoglobulin in the treatment of these cases have been reported.

Pain Therapy

Drugs used in the treatment of diabetic neuropathy are used in painful diabetic neuropathy to reduce neuropathic pain, to control autonomic neuropathy symptoms and to improve quality of life. Figure 3 summarizes the treatment algorithm for neuropathy pain.

Tricyclic and Tetracyclic Antidepressants

Serotonin (5-HT) and norepinephrine (NE) reuptake inhibition is used for the treatment of neuropathic pain with mechanisms of action such as blocking of the Na and Ca channels. Imipramine, amitriptyline, clomipramine 5-HT and NE are reuptake inhibitors, desipramine is a relative NE reuptake inhibitor. In a Cochrane review it is reported that there is no unbiased evidence for a beneficial effect and there seems an overestimation of the treatment [35]. Antidepressant switch should be considered after a failure with one [35]. Side effects are summarized in Table 6.

Selective Serotonin-Noradrenaline Reuptake Inhibitors

This group includes venlafaxine, duloxetine and milnacipran. This group of drugs causes balanced inhibition of 5-HT and NA. SNRIs do not interact with adrenergic, muscarinic, histaminergic receptors, such as tricyclics. Therefore, they do not cause side effects such as drowsiness, weight gain, constipation and cardiotoxicity. SNRIs, like tricyclic antidepressants, act on neuropathic pain by creating inhibitory effects on interneurons in the spinal cord via pathways descending with balanced inhibition of 5-HT and NA. Duloxetine as an antidepressant, can be prescribed for neuropathic pain. In Turkey, diabetic neuropathic pain is indicated up to 120 mg/day. Duloxetine 60 and 120 mg showed significant pain relief for the first month but not continued [36]. Another advantage is that it does not cause weight gain like other antidepressants [37]. In a Cochrane review it is reported that there is no evidence to revise the guidelines to recommend the use of venlafaxine in neuropathic pain and placebo effects were notably strong in several studies [38].

Anticonvulsants

Antiepileptic drugs are effective drugs that have been used for the treatment of neuropathic pain for a long time. The most important known mechanisms of action of antiepileptics are blocking of sodium channels, inhibiting calcium conduction, activating the GABA system and reducing the effectiveness of glutamate. With a better understanding of the pathophysiology of diabetic polyneuropathy and the mechanisms of action of drugs used in treatment, a realistic choice of polytherapies emerges and a synergistic effect can be achieved by the combination of drugs with different mechanisms of action.

Ca Channel Modulators (Pregabalin, Gabapentin, Mirogabalin)

Five types of calcium channels were identified. Of these, N and L-type channels are involved in the modulation of sensory neurons of the spinal cord. Gabapentin and pregabalin (gabapentinoids) show the effects of voltage-dependent calcium channels by binding to α2 delta subunits. Unlike conventional calcium channel antagonists, it does not block calcium channels and modulates their activity. The mechanism of action of this drug group in neuromodulation has not yet been clearly elucidated.

Gabapentin

Gabapentin is a GABA receptor agonist. In a randomized, double-blind, placebo-controlled trial of 165 patients (67% in patients receiving 3600 mg/day gabapentin), 60% of patients had moderate pain relief, while the pain reduction in the placebo group remained at 30%. It shows effects on both central and peripheral nerve system. Gabapentin is the first line agent of diabetic neuropathic pain in the United Kingdom [39]. Chou et al. showed similar effects of gabapentin when compared with tricyclic antidepressants for pain relief of diabetic neuropathy [40]. Gabapentin also shows positive effects on sleep disorders that accompany pain [41].

Pregabalin

Pregabalin has a stronger efficacy with α2 delta affinity, which is six times higher than gabapentin. The analgesic efficacy of the drug increases in a dose-dependent manner and the analgesic effect starts faster than gabapentin. At a daily dose of 600 mg, the NNT score is 4 and 300mg is 5.9 [42-45]. Like gabapentin, pregabalin also has positive effects on symptoms associated with pain, sleep disturbance, mood changes and anxiety. Gabapentinoids are almost ideal drugs that are well tolerated due to their pharmacokinetic properties. Concomitant use of clozapine, opioids, and sedative drugs may increase side effects. In addition, they show little drug interaction. They do not metabolize and bind to proteins. The most

common side effects are dizziness, drowsiness, peripheral edema, headache and weight gain.

Although the research is promising, there has been increasing concern as the latest data address the abuse of and dependence on gabapentinoids. There are studies suggesting that euphoric effect might be abused by patients who previously had substance addiction. As in other potentially addictive gabamimetics (benzodiazepines, propofol, etc.), rapid tolerance to the euphoric effect develops. Gabapentinoids has potential of drug abuse [46]. For these reasons, gabapentinoids should not be considered as the first choice in patients with a history of multiple drug use (especially opioid) and substance use disorder. Gabapentin may be preferred in this group of patients, because gabapentin is relatively less likely to cause addiction than pregabalin. In patients without a history of substance use disorder, it is not necessary to take additional measures different from other drugs prescribed for the use of gabapentinoids [47].

Mirogabalin

Mirogabalin firstly developed by Daiichi Sankyo for the treatment of Fibromyalgia. When primary end point was not met (additionally pregabalin found to be more effective) trial was discontinued. Mirogabalin has a high affinity for the a2delta-1 subunit of voltage-gated calcium (Ca2+) channels (VGCCs) on the dorsal root ganglion. In 2019, oral mirogabalin (Tarlige®; 2.5, 5, 10 and 15mg) were approved in Japan for the treatment of peripheral neuropathic pain (PNP) on the basis of trials conducted in patients with diabetic peripheral neuropathic pain (DPNP). Half-life of Mirogabalin is about 2–3 h after a single dose and 2–5 h after sequential doses. Average daily pain score reduction was significantly greater with mirogabalin 30 mg/day. Adverse Events occurred in 31.3% in patients with DPNP which were reported as somnolence (12.5 and 19.9%), dizziness (9.0 and 11.8%) and weight gain (3.2 and 6.7%) [48].

Na Channel Blockers

Voltage-dependent sodium channels are crucial determinants of neuronal excitability and signaling. After nerve injury, hyper excitability and ectopic discharges occur at the site of injury and the body of

the dorsal root ganglion cell. Carbamazepine, oxcarbazepine, are the most effective blockers of sodium channels for pains in the form of lightning flashes produced by such ectopic discharges. Although carbamazepine is widely used in the treatment of neuropathic pain, it is not recommended for the treatment of painful diabetic neuropathy due to its limited data [49]. In a Cochrane review It is concluded that Lacosamide (200–600 mg/day) has limited efficacy in the treatment of peripheral diabetic neuropathy [50].

Opioid Agents

In a randomized controlled trial of tramadol use in the treatment of patients with diabetic polyneuropathy, it was found to be more effective than a placebo, and this effect lasted for at least six months. Although the side effect profile is similar to other opioid analgesics, the development of dependence and tolerance in long-term tramadol treatment is rare and the possibility of abuse is low [51]. The recommended maximum daily dose is 400-600 mg. In liver diseases or renal insufficiency, it is recommended to decrease the tramadol dose or to increase the dose range. It should be kept in mind that serotoninergic syndrome (myoclonus, rigidity, hyperreflexia, tremor, confusion, agitation, restlessness, coma) may occur if tramadol is used together with other serotoninergic drugs (especially SSRI). Oxycodone, one of the strongest opioids, may be used in severe patients resistant to other analgesic treatments. Although there is limited information about combination therapies, oxycodone may be considered as a combination therapy in patients who cannot achieve adequate pain palliation with monotherapy. When oxycodone treatment and placebo were compared in patients with diabetic polyneuropathy who could not achieve pain palliation with antidepressant and antiepileptic drugs, at the end of the 4-week observation, it was shown that pain was relieved and quality of life improved significantly [52]. Recent recommendations emphasize the importance of a physician's risk assessment (in terms of dependence and abuse) and clinical skills for the management of existing medicines before

the opioid is prescribed for the safe and effective use of opioids [53]. In a Cochrane review, it is reported that the studies provide very limited, very low-quality evidence of the efficacy and safety of methadone for chronic neuropathic pain. No conclusions can be made regarding the current status [54].

Tapentadol

Tapentadol is a novel, centrally acting analgesic molecule. It has two action mechanisms: one is inhibiting NE reuptake and the other one is activating μ-opioid receptors [55]. Tapentadol ER (100- 250 mg bid) was effective and well tolerated for the management of moderate to severe chronic pain associated with DPN [56]. It has been approved by the FDA for the treatment of painful diabetic polyneuropathy. Unfortunately, the drug is still not available in Turkey [4].

Cannabinoids

Cannabinoids should have a potential neuropathic pain treatment. With good toleration, flexible-dose of nabilone 1-4 mg/day should be effective for DPN symptom relief, improving sleep disturbances and a better quality of life [57].

Topical Capsaicin

The reduction of substance P on the axon ends of C fibers helps to relieve pain. By prolonged administration of capsaicin, substance P and other possible neurotransmitters released from the sensory nerve endings are depleted. Thus, the transmission of the painful stimulus from the peripheral nerve endings is reduced or completely eliminated. Capsaicin appears to have the potential to be the choice of neuropathic pain management [58].

Lidocaine

The use of topical lidocaine in painful neuropathy is associated with post-herpetic neuralgia. While 5% lidocaine was given to one group treated for 2 weeks, the other group was given pregabalin for 4 weeks and lidocaine was shown to be as effective as pregabalin in reducing pain without side effects. This treatment may be continued with oral mexiletine and superficial pain caused by overstimulation is targeted with oral mexiletine treatment [59].

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