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# Diabetic peripheral neuropathy- advances in diagnosis and treatment

**Bigos Paula**[1] ORCID: 0009-0003-5791-8963, bigospaula@gmail.com
Jan Mikulicz-Radecki University Teaching Hospital, Borowska 213, 50-556 Wrocław
**Dendys Konrad**[1] ORCID: 0000-0002-5631-9948, konrad.dendys1@gmail.com
Jan Mikulicz-Radecki University Teaching Hospital, Borowska 213, 50-556 Wrocław
**Bieniasz Jan**[1] ORCID: 0000-0001-9139-9309, bjasiekb@interia.pl
Jan Mikulicz-Radecki University Teaching Hospital, Borowska 213, 50-556Wrocław
**Kuźnicki Wojciech**[1] ORCID: 0009-0008-8971-1410, wojciechkuznicki05@gmail.com
Lower Silesian Oncology, Pulmunology and Hematology Center (DCOPiH), Ludwika Hirszfelda Square 12, 53-413 Wrocław
**Matkowski Igor**[1] ORCID: 0009-0008-2829-9055, igor.matkowski2@gmail.com,
Jan Mikulicz-Radecki University Teaching Hospital, Borowska 213, 50-556 Wrocław
**Potyrała Piotr**[1] ORCID: 0009-0006-6304-9778, piotrekpotyrala@gmail.com,
Lower Silesian Oncology, Pulmunology and Hematology Center (DCOPiH), Ludwika Hirszfelda Square 12, 53-413 Wrocław

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## 1. Abstract

Diabetes mellitus is one of the most alarming conditions of the 21st century. The prevalence of both type 1 and 2 diabetes is constantly increasing, which also entails a growing number of patients suffering from its various complications. One of the most common chronic complications is diabetic neuropathy (DN), which is developed by at least 50% of patients

with diabetes. Diabetic peripheral neuropathy (DPN) is the most frequent type of DN. Clinically, a non-painful and a painful-DPN can be distinguished. The painful type causes a massive decrease in the quality of life and affects around 30% of individuals with DM. In recent years many instruments have been used to diagnose and treat DPN but none of them seems to be sufficient in early diagnosis and satisfactory symptoms management. To date, there is any gold standard to recognize DNP and usually it is noticed when a patient presents symptoms of neuropathy, which is too late to introduce an effective therapy. The main approaches for patients with DNP focus on improving glycaemic control, lifestyle modifications and pain therapy. Multiple medicaments are used for this purpose, among which SNRIs, TCAs and anticonvulsants are most effective. Non-pharmacologic treatment, such as acupuncture, physical therapy, nerve stimulation, also has been used, however their effectiveness remains uncertain.

## 2. Introduction

According to the latest report of International Diabetes Federation, 537 mln adults were living with diabetes in 2021, which appears as 1 in 10 persons. Moreover, this number is predicted to rise to 643 mln by 2030[1]. One of the most common complications of chronic diabetes is diabetic neuropathy, which is a heterogenous group of conditions, that affects different parts of the nervous system and presents different symptoms. Among them, the most prevalent is diabetic peripheral neuropathy, which can be defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes [2].

The pathogenesis of DPN is extremely complex due to multifactorial mechanisms. Although, the exact process remains unknown, chronic hyperglycaemia seems to be the main factor, that initiates a cascade of cellular problems resulting in damage to the peripheral nerves [3].

DPN develops gradually, firstly affecting the distal foot and toes, then approaching up to the knees [4] . The major symptom of DPN is symmetrical neuropathic pain in distal parts of lower limbs, that can manifest as spontaneous pain, numbness, burning sensation, allodynia, hyperalgesia, sensory loss, hypersensitivity, gloves and socks sensation, weakness, tingling [5], [6]. Symptoms of neuropathic pain become the most unpleasant at night, causing chronic sleep disturbances [4]. Painful diabetic neuropathy not only decreases the quality of life, but is also associated with substantial morbidity, increased mortality, anxiety and depression. Furthermore, DPN is the main cause of foot ulceration, that may lead to disability, infections and amputation. [7].

The diagnosis of DPN is currently based on clinical symptoms and signs. No single gold standard or specific biomarker exist [6], [8]. When a patient is asymptomatic or the clinical manifestation is atypical, electrophysiological examination is required, such as electroneurography and quantitative sensory testing [6], [9]. The effectiveness and need of screening are still being discussed.

Glycaemic control and lifestyle modifications not only increase the chances of successfull treatment but are also essential in the prevention of DPN. Pain relief is the main challenge in DPN treatment. Many different drugs are available for this purpose but few of them have shown a clearly positive improvement in pain in trials. The most common groups of drugs are anticonvulsants, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressant, opiate receptor agonists and topical agents [10]. Promising experimental drug therapies for DPN include vitamin D, capsaicin, melatonin [11], [12]. Nonpharmacological approach focuses on neuromodulation, exercise-based interventions and acupuncture [5], [13], [14].

## 3. Pathogenesis

The pathogenesis of chronic neuropathic pain is different from the pathogenesis of diabetic neuropathy itself, but both processes are extremely complex and multifactorial.

### 3.1.Diabetic neuropathy

DN is a neurodegenerative disease of the peripheral nervous system and targets preferentially the terminal sensory axons, especially the thin and unmyelinated small fibers. That can be observed in the characteristic “stocking and glove” pattern of syndromes [8]. Studies suggest that molecular changes which occur in the neurons perikarya in the dorsal root ganglion (DRG) are also associated with destruction of the terminal axons [4]

Long term hyperglycaemia, which is a consequence of diabetes, is the main factor in the pathogenesis of neuropathy. Together with dyslipidaemia and impaired insulin signaling, activates a cascade of biochemic processes that result in nerve and vascular damage [15]. In normal conditions glucose and lipids are metabolized trough glycolysis and beta-oxidation into acetyl-CoA that undergoes further processes to finally produce NADH and FADH2. These products are converted in the mitochondria into ATP via oxidative phosphorylation. In diabetes, due to substrate overload, acetyl-CoA is converted into toxic acylcarnitine, oxidative phosphorylation fails and leads to increased production of reactive oxygen species (ROS) rather than ATP. The excess of glucose activates the polyol and hexosamine pathways, that

also increase ROS and inflammatory cytokines production. Other by-products of excess glucose are advanced glycation end product (AGEs), that after binding with their receptors (RAGE)s leads to ROS accumulation, inflammation and decreased blood flow to peripheral nerves [16].

Moreover, hyperlipidaemia causes similar consequences with production of ROS and inflammation through the catabolization of excessive free fatty acids and macrophage activation. The consequences of the above-mentioned pathologies are mitochondrial dysfunction, DNA damage and apoptosis promotion. Acylcarnitine, increased ROS and inflammation can induce not only axonal degeneration but also Schwann cells and DRG neurons damage resulting in peripheral neuropathy.
What is more, damage of the blood vessels results in poor microvasculation and can lead to insufficient blood supply to the peripheral nerves causing their injury as well [17].

### 3.2.Neuropathic pain

The reason some patients suffer from neuropathic pain while others are asymptomatic is still unknown. As risk factors female sex, obesity, poor glycaemic control and impaired renal function are considered. The pathogenesis of neuropathic pain is mainly based on peripheral and central sensitization. [6], [17]

Peripheral sensitization is induced by increased expression of sodium channels in the nociceptors and perykaria, reduced expression of shaker-like potassium channels in myelinated axons and enhancement of calcium channel in DRG. It results in sensory neurons hyperexcitability which leads to increased stimulus responses. Another important channel in the nociceptors is TRPV- a nonselective channel that act as a sensor of harmful stimuli. Its increased activation can be caused by higher level of methyl glyoxal or inflammatory mediators, that also results in hyperexcitability and neuropathic pain. Pro-inflammatory cytokines can also directly sensitize peripheral nerves. [6], [17]

Central sensitization is an increased synaptic transmission in the spinal cord produced by strong nociceptive stimulation. In diabetic neuropathy occurs loss of GABA release inhibitory interneurons and inflammatory changes in the microglia. Changes in glial cells lead to production of brain-derived neurotrophic factor (BDNF) that plays and important role in pain-related hypersensitivity. What is more, injured neurons in the dorsal horn of the spinal cord

release ATP, that detected by purinergic receptors on the glial cells causes neuropathic pain. In patients with painful-DPN changes in higher brain centers have been also detected: reduced connectivity between cortex, thalamus and insula, cortical atrophy within the somatomotor cortex and thalamus, functional and structural changes in the ascending and descending pathways. However, it is unclear, if these changes are the consequence of peripheral nerves injury or play a significant role as a primary mechanism of central sensitization [6], [18].

## 4. Diagnosis

The diagnosis of DPN is mainly based on specific symptoms, signs and risk factors. Moreover, screening tests are available and recommended for all patients with T2DM immediately after the initial diagnosis of diabetes and then annually. For patients with T1DM screening is recommended 5 years after diagnosis and then annually as well [19].

### 4.1. Risk factors, signs and symptoms

The first step to make a relevant diagnosis is to considerate the risk factors, that include: obesity, older age (<70), poor glycaemic control, dyslipidaemia, hypertension, tall stature, metabolic syndrome and recent falls [16].

The symptoms of DPN also can lead to a proper diagnosis. Usually, neuropathic pain begins in the toes and expand proximally creating a characteristic pattern of “stocking and gloves” [16] . As neuropathic pain tingling, burning, lancinating, hyperalgesia and allodynia are considered. The symptoms of large-fiber injury such as numbness, weakness of the limbs and loss of balance may be confusing because of their prevalence in other diseases. For better detection of the symptoms several questionnaires are available. The most commonly used are the Neurological Symptom Score (NSS), the McGill Pain Questionnaire, the Diabetic Neuropathy Symptoms (DNS), the Neuropathy Symptoms Profile (NSP) and other. Each questionnaire consists of a unique scoring system, that defines the probability of DNP and sometimes also classifies the severity of it [20].

Although up to half of DPN patients may be asymptomatic they can present complications such as foot ulceration even earlier then symptomatic patients. When presenting mentioned above risk factors, they should be closely physically examined to discover eventual neurological defects [16] . Bedside tests are the most common methods of physical examination. Small-fiber associated signs are reduced or absent pinprick and temperature sensation, while large-fiber associated signs include reduced or absent vibration and light-touch sensation, as well as reduced ankle reflexes. These signs may be evaluated using non-

invasive tests that require only simple tools. The pinprick sensation is examined mostly using a sharp pin, temperature sensation a cold tuning fork, vibration sensation a 128-Hz tuning fork, light touch a 10g monofilament, and ankle reflexes require a neurological hammer [16], [17]. These tests are most used in clinical practice, however, with thirty other items they create the Neuropathy disability score (NDS), that evaluates more precisely other signs such as cranial nerve damage, muscle strength, sensation loss and other [20].
Although bedside tests are widely available and easy to perform, they are based on patient's subjective feelings and sensations. What is more, they detect the signs mostly when DNP is well established, and the changes are unreversible. That is why reliable screening and diagnostic methods, that detect early changes in nerve fibers are needed.

For higher diagnostic accuracy, a reliance on both sign and symptoms should be performed. That is provided by Composite Scoring Systems. One of the most popular is the Toronto Clinical Neuropathy Score (TCNS), which includes symptoms, reflex test and sensory test scores. It is useful not only in diagnosis and screening but also in staging DNP [21]. Another widely used composite system is the Michigan Neuropathy Screening Instrument (MNSI), which consists of a questionnaire and simple foot examination [20]. These tests are validated, reliable, easy and quick to perform and interpret, what makes them a reasonable method of screening [17], [20].

### 4.2. Objective confirmatory tests and screening

The vast majority of patients does not require additional testing for confirm the diagnosis of DPN. However, in cases when patients present atypical symptoms and signs or when clinicists have doubts about the diagnosis, objective confirmatory tests are available. For large-fiber testing the current "gold standard" is Nerve Conduction Studies (NCS). It is an electrophysiological examination that tests motor and sensory nerve fibers in the upper and lower limbs. It records responses to surface stimulation, which can appear as changes in amplitude, conduction velocity or prolonged responses [16], [17]. NCS is a valid diagnostic method but cannot be used as a screening tool for DPN because it requires higher costs, a specialist operator, it's time consuming and uncomfortable for the patients [20].

A potential alternative method to NCS is DPNCheck, a novel point-of-care nerve conduction device [22]. It tests the sural nerve conduction velocity and amplitude in a quicker and easier way than NCS. Although it has been validated in both T1DM and T2DM, research have been

on small number of patients, especially suffering from T1DM. Another limitation is the need of sural nerve being present, although it can be anatomically absent in up to 9% of world's population [20] .

A "gold standard" in detecting small fiber damage, which in most cases appears earlier than large fiber neuropathy, is measurement of intra-epidermal nerve fiber density (IENFD) by punch skin biopsy [16], [17], [20] . Biopsy samples are viewed under an epifluorescence microscope using the techniques of indirect immunofluorescence (IF) and bright-field immunohistochemistry (BFI). It shows the density of terminal branches of peripheral nerves in the epidermidis [20]. However, it is mostly used for research purposes due to its invasive character [17].

Neuropad is a unique, 10-minutes long, innovative screening test for small fiber DNP that uses sweat as a biomarker of early neuropathy. Sweat production requires undamaged small autonomic c-fibers, that can be injured due to diabetic neuropathy. Neuropad is an adhesive pad containing cobalt compounds, that are applied on the feet and change color from blue to pink when the sweat production is normal. It is reported that an abnormal response of Neuropad is highly associated with DPN, and its sensitivity for early DPN detection is good to excellent [20]. Neuropad is easy to use and interpret, which makes it a suitable screening method that can be self-administered by patients at home. However, standardization of time before result analysis, the cut-off value, and the right position on the foot is still needed. Currently, a software app is being work on that may answer some of these requirements [20], [23].

Sudoscan is another promising screening test that measures electrochemical skin conductance (ESC) of sweat in the hand and feet, with feet giving more valuable results. However, ESC measurements may also be associated with patients' gender, age, weight, skin color, that should be taken into consideration when analyzing the results. The validation studies of Sudoscan gives promising result, but also highlights the need for standardization of the classification criteria [20], [24].

A diagnostic test that evaluates both small and large nerve fibers is Quantitative Sensory Testing (QST). It consists of different tests, that can use thermal thresholds (both warm and cold), thermal pain measurements and vibration threshold. It has been validated to be an

objective confirmatory diagnostic method but due to its long time requirement it is used mostly for research purposes rather than in clinical practice. Like every method QST also presents some limitations. The results are affected by various factors such as skin temperature, duration of intervals between tests, location and number of stimuli, stimulus characteristic etc. The methodology of assessment is not enough standardized to avoid these interactions [16], [20].

Corneal Confocal Microscopy (CCM) is a rapid, non-invasive test that visualizes nerve fibers in the cornea. It is innervated by a large number of unmyelinated sensory and autonomic fibers. There are many parameters possible to analyze in CCM, out of which the corneal nerve fiber length (CNFL) is currently the most reliable and frequently used for detecting early DNP. Inferior whorl length (IWL), nerve fiber width and nerve fiber area are recently investigated parameters that have shown significant differences between neuropathic and non-neuropathic patients with DM in studies. However, more research is needed to confirm their usefulness in the diagnosis of DPN. Langerhans cells, that are normally located in the peripheral cornea, in response to pathological conditions, such as diabetes, mature and migrate to the central cornea. This process can also be observed using CCM. The high-quality imaging of the corneal C-fibers shows great potential in early detecting small fiber neuropathy. Furthermore, it is easy to perform that makes it a promising large-scale screening method for DPN [20], [25].

## 5. Treatment

Although many methods of treatment of DPN are available, none of them is sufficiently effective and the management of this complex disease remains a challenge. Currently there are three main approaches in the therapy of DPN: improved glycaemic control and lifestyle modification, targeting the pathogenesis of DPN and symptoms management [6], [17].

### 5.1.Glycaemic control

Intensive glycaemic control plays a significant role in preventing DPN and in slowing its progression in patients suffering from T1DM and prediabetes. Sustaining optimal glyceamic levels form early stage of diabetes reduces the risk of DPN up to 60% [7]. However, studies show little to no positive effect of aggressive glycaemic control for patients with T2DM. Moreover, in this case, it increases the risk of life-threatening hypoglycaemic episodes [7], [16], [17].

### 5.2. Lifestyle modification and physical exercises

Lifestyle modification is most effective for patients with T2DM. Personalized exercises and diet, along with optimal blood pressure and lipidaemia control is an optimal approach to minimalize the risk of DPN and reduce neuropathic symptoms, including pain [17]. Exercise-based interventions increase general physical fitness, enhance body composition and improve neuromuscular strength [3].

Various exercise protocols are available, including aerobic and resistance training as the most popular, mobility and functional movement-based exercise training, balance and proprioception-based exercise training and whole-body vibration exercise training [3], [6], [26].

Aerobic exercise engages large muscle groups to work over a prolonged period. The examples of aerobic are swimming, jogging, cycling and walking. It increases cardiorespiratory fitness, that is associated with a reduction in mortality, and helps to treat metabolic symptoms of T2DM, such as hyperlipidaemia and obesity. Several studies have shown reduction of neuropathic pain and its interference in patients with DPN, along with psychological positive effects and overall improvement in quality of life. What is more, studies demonstrated positive changes in electrophysiological examinations [3], [6]

Resistance training aims to increase muscular endurance, strength and power. The exercises engage mostly lower parts of the body or full body in general. It shows positive effects in microvascular perfusion, glycemic control and neural drive. It seems to reduce the advancement of walking and balance disorders in patients with DPN. However, it demonstrates better effectiveness combined with aerobic exercise rather than as a sole intervention [3], [26].

Mobility and functional movement-based training is beneficial for patients with DPN when performed at least for 4 weeks. It includes weight-bearing exercises, that should start using “light” intensities and then increasing it over time for safety reasons. This training brings positive effects on posture and balance, enhances gait function and most important- decreases neuropathic pain [3].

Balance and proprioception-based training includes such activities as stretching, yoga and tai-chi. It strengthens deep muscles, improves the postural control and balance and reduces fall

risk. What is more, tai-chi showed improvements in glucose control and neuropathic total syndrome score. Balance and proprioception-based exercises are especially recommended for patients that are less physically fit, older or suffer from more severe cases of DPN [3], [27].

Whole-body vibration exercise training is an alternative method of strength training. It uses a vibrating platform that stimulates repetitive, reflexive contractions of the muscles, giving positive effects on muscle function, flexibility, body composition and blood pressure [3].

It should be noted that studies differ among each other in intensity, frequency and duration of training. For optimal clinical result exercises should be selected in a personalized way for each patient. Furthermore, more research is needed to standardize the exercises, evaluate the effectiveness and safety of above-mentioned trainings specifically in patients with DPN [3], [6].

### 5.3.Pathophysiological approach

Simultaneously with the deeper understanding of the pathogenesis of DPN, new therapeutic options have appeared, targeting pathophysiological processes that lead to peripheral nerves damage.

Aldose-reductase is an enzyme that catalyzes the transformation of glucose into sorbitol in the polyol pathway. Inhibitors of aldose-reductase aim to prevent the activation of polyol pathway and its consequences. There are several drugs of this group that have reached phase III of clinical trials, but most of them turned out to be ineffective or no more effective than placebo [12], [28] . One meta-analysis concluded that aldose-reductase inhibitors could ameliorate cardiovascular autonomic neuropathy in mild or asymptomatic patients [28]. In United States none of the drugs of this group is marketed, however epalrestat is available in Japan for the treatment of diabetic neuropathy [17].

Alpha-lipoic acid (ALA) is an antioxidant that decreases lipid peroxidation, what reduces the production of ROS and minimalize oxidative stress. It may also improve blood flow, increase the speed of nerve conduction and has anti-inflammatory impact [6], [12], [29] . Studies show that daily intravenous infusions of ALA in dose 600 mg ameliorate neuropathic symptoms and signs after 3 weeks. What is more, oral treatment for 5 weeks in the same dose decreases pain, paresthesia and numbness [6] . Moreover, it appears to be safe and well tolerated. It is

suggested that a combined intervention with other current treatment of DPN would give optimal therapeutic effects [29].

Thiamine (vitamin B1) is an essential cofactor of transketolase, that takes part in carbohydrate metabolism. Thiamine levels are frequently low in both types of diabetes, while its clearance is low. What increases its intracellular level is benfotiamine administration. Benfotiamine is a synthetic prodrug of thiamine, that not only activates transketolase, but also inhibits the hexosamine pathway and reduces the formation of AGEs. Studies have shown, that using a 300 mg dose twice a day over the first 6 weeks significantly ameliorates neuropathic symptoms and signs. Furthermore, a combination of benfotiamine, pyridoxine and cyanocobalamine improves nerve conduction velocity [12], [15], [16].

### 5.4.Symptomatic treatment

Management of symptoms of DPN, especially neuropathic pain remains a challenge of current medicine. Both pharmacological and non-pharmacological approaches are available. The recommendations by most guidelines consist of three-line pharmacological therapy.

#### 5.4.1. Pharmacological methods

For first-line therapy tricyclic antidepressants (TCA), serotonin-norepinephrine reuptake inhibitors (SNRIs) and calcium channel alpha-2-delta ligands (anticonvulsants) are considered. Second-line recommendations are tramadol (weak opioid) and topical analgesic medications, and third-line therapy includes strong opioids [15], [18].

TCAs inhibit the reuptake of serotonin and noradrenaline, that provide their analgesic effect. Among TCAs amitriptyline is the most frequently used drug. It showed efficacy in neuropathic pain in patients with DPN in several studies [7], [17]. However, TCAs present a few adverse effects, such as urinary retention, mouth dryness, constipation and orthostatic hypertension. What is more, they require up titration to effective doses over a period of about 6-8 weeks (maximum to 150 mg daily). Desipramine and nortriptyline are better tolerated than amitriptyline and seem to be safer in older adults [7], [17].

The most studied SNRI is duloxetine, which became the first agent approved by FDA (U.S. Food and Drug Administration) for treating PDN. It showed mean pain relief and improvement of QOL in placebo-treated control trials. The most frequent side-effects are nausea, somnolence, hyperhidrosis and loss of appetite. The recommended dose for

duloxetine is 60 mg a day. Another agent of this group-venlafaxine also has shown evidence of efficacy for DPN and could be used as an alternative to duloxetine but is not formally approved [7], [17], [30].

Leading agents of anticonvulsants are pregabalin and gabapentin that inhibit alpha2-delta calcium channels in the dorsal horn. Pregabalin is another drug approved by FDS for treating painful-DPN. Its efficacy in neuropathic pain improvement has been shown across many clinical studies. The recommended dosage of pregabalin is 150 mg daily up to 300 mg if needed. Its most common side effects are dizziness, somnolence, blurred vision and weight gain [30] . Gabapentin has also been reported to relieve pain and is suggested to use for treatment of painful-DPN if pregabalin is ineffective. What is more, it showed improvement in sleep, mood and QOL [7], [16].

Tramadol, as a weak opioid, is a μ-receptor agonist and an inhibitor of noradrenaline and serotonin reuptake. Clinical trials have confirmed its efficacy in relieving neuropathic pain. Moreover, this effect might be long-lasting. The recommended dosage is 200 mg/d, that can be increased to maximum 400 mg/d when required [6], [17] . Common adverse effects are constipation, nausea, somnolence and dizziness [7].

The main advantages of topical analgesic treatment have fewer side effects and drug interaction. Capsaicin is an alkaloid derived from red chili peepers. It is a selective agonist of transient receptor potential vanilooid-1. 8% capsaicin dermal patch has been approved by FDA and it may provide up to 12 weeks of pain relief [16] . Lower concentrated cream (0,075%) also showed significant pain improvement [7]. It should not be used on active skin lesions and sensory loss areas [15]. Local adverse effects of capsaicin are stinging, burning and erythema [16]. Lidocaine patches 5% and clonidine gel 0,1% are also available. Topical lidocaine shows best effects in combination with other analgesic drugs [7]. Clonidine gel is associated with only mild local reaction [15].

The strongest opioids used for DPN treatment are oxycodone, morphine and methadone.
They are recommended to use only in severe pain with great caution because of a high risk of addiction and increased mortality. The risk-to-benefit ratio of strong opioids therapy in DPN needs to be evaluated in more studies [7], [17].

### 5.4.2. Non-pharmacological methods

Most common non-pharmacological approaches to painful-DPN include acupuncture, spinal cord stimulation (SCS) and transcutaneous electrical nerve stimulation (TENS).

The mechanism of acupuncture against diabetic neuropathy is not fully understood. Most studies report that acupuncture significantly relieves neuropathic pain. The side effects of this therapy are swelling, numbness and pain. Studies suggest that acupuncture administered on the wrist or ankle could be more affective then in other areas of the body. However, the current research on acupuncture and its effect on DPN is insufficient to make a specific, reliable conclusion and well-designed clinical trials are needed [14].

TENS is a non-invasive form of neuromodulation performed with adhesive electrodes that conduct electrical stimuli of various frequencies. The mechanism of analgesic effect is unknown. Some trials showed significant improvements in symptoms of DPN, especially when TENS was administered as an adjunctive to amitriptyline. However, all trials have been small and short in duration, that makes their results uncertain [16], [30].

SCS is an invasive form of neuromodulation, where the electrodes are surgically implanted in the epidural space. The best results in treating neuropathic pain present the high frequency (10 kHz) SCS. According to studies, it produces a durable paresthesia-free pain relief. The most promising results come from a Randomized Clinical Trial, where 6 months after the beginning of the therapy 76% of patients reported mean pain relief and over 60% of subjects show neurological improvement. SCS seems to be effective and safe in treating DPN, however evidence-based treatment guidelines are still required [13].

## 5.5. Experimental therapies

Despite of many therapeutic methods for DPN treatment being available the average efficacy in pain relieve does not overcome 50%. Hence the need for experimental therapies being introduced and evaluated.

One of the most promising approaches is innovative drug delivery systems which use nanoparticles (liposomes, nanoemulsions, si-RNA, exosomes etc.) to transport analgesic (baclofen, bupivacaine or morphine) directly to the dorsal root ganglion. In association with nanoparticles conventional analgesic might significantly enhance their action by directly targeting the source of pain [4].

According to studies, therapeutic vitamin D supplementation could be another reliable method treating and preventing DNP and diabetic foot ulcers. It might be administered as an adjuvant therapy to other treatment options. Studies also suggest that, in an optimal dose, it can slowdown the progress of neuronal damage [31].

The most recent finding is a patented Nerve Support Formula NeuropAWAY ® that contains: methylcobalamine, L-citrulline, beta alanine, R-alpha-lipoic acid, L-arginine, acetyl-L-carnitine and taurine. To evaluate its action a randomized, double-blind, placebo-controlled trial has been performed. The results have shown a highly significant decrease in NRS scores, that suggest that the formula is effective in reducing neuropathic pain [32].

Another promising method of treatment of DPN is stem cell therapy. It has been proven well in both animals and human subjects' studies. Stem cells and growth factors are injected into damaged area to differentiate into cells that can repair injured peripheral nerves and blood vessels. Cell-based therapy uses bone-marrow derived cells, embryonic stem cells, pluripotent stem cells, endothelial progenitor cells, mesenchymal stem cells and dental pulp stem cells [10].

Melatonin, thank to its neuroprotective, anti-inflammatory and inhibitory actions on the excitability of neurons, is considered another potential treatment method of DPN. However, the studies vary in key aspects of treatment, such as dosage and time of administration, making it difficult to develop a unified view on their results (Oliveira-Abreu et al., 2021).

Beneficial effects on neuroprotection and hyperalgesia has also metformin, a drug used as a first-line treatment for T2DM patients. However, it causes vitamin B12 deficiency, that could be associated with increased risk of neuropathy in diabetic patients. Further clinical trials are needed to investigate exact effects of metformin on DPN [33].

## 6. Conclusions

Managing diabetes neuropathy remains a challenge in current medicine. The importance of early detection of DPN is undisputable. Resisting mainly on signs and symptoms delays the diagnosis of DPN to the point, where many changes are irreversible, making the treatment extremely difficult. Considering that a perfect screening test should be fast, easily accessible

and non-invasive, corneal confocal microscopy is a promising candidate to become a large-scale screening method.

Although many methods of treatment of DPN are available, only in 50% of patients the therapy is effective. It can be concluded that better understanding of the pathogenesis of DPN creates opportunities to explore new methods, that would target directly the pathophysiological processes. However, the best therapeutic results are achieved with therapy combining different approaches: lifestyle modification, including glycemic control and physical exercises, analgesic drugs and neuromodulation. Most promising effects among all treatment methods gives spinal cord stimulation. Many experimental therapies are being researched, which offers a positive perspective for the future.

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The contributions of author's can be presented as follows:

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