Original Article

Possible Pharmacological and Nonpharmacological Treatments for Diabetic Polyneuropathy

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Abstract

Objective: Diabetic neuropathy (DN) is a microvascular complication of diabetes that arises due to damage to nerves. It arises due to hyperglycemia and the pathways that it follows are most commonly initiated by reactive oxygen species-induced oxidative stress. **Methodology:** There are various growth factors and receptors involved in the process, and the usual understanding of its origin is rather unclear. Until now, no absolute cure exists for the treatment of DN; however, there are a lot of pharmacological and nonpharmacological treatment options that are recommended and can help to ease the pain associated with DN. This paper reviews these options that are divided into broad categories of pharmacological and nonpharmacological treatment options. **Results:** The pharmacological treatment options include the use of natural plants with antioxidant and anti-inflammatory potential, thymosin, Pregabalin, duloxetine, anticonvulsants, and antinociceptive agents. **Conclusions:** Whereas, the nonpharmacological treatments suggest the surgery, supplements, acupuncture, exercises such as yoga, and transcutaneous electrical nerve stimulation therapy. Both of these can help patients, especially if consider collectively.

Keywords: Diabetic neuropathy, duloxetine, Gua Sha, surgical treatments

Introduction

Of the various types of micro- and macrocomplications associated with diabetes, the most common and serious complication is the nerve damage characterized by numbness in hands and feet, effecting the proper functioning of organs such as kidney and heart to complete paralysis of body.[1] These series of neurological conditions are referred to as diabetic neuropathy (DN). There are four most common types of DN, namely peripheral neuropathy (PN) also known as distal neuropathy, autonomous neuropathy (AN), proximal neuropathy also called as diabetic amyotrophy or radiculoplexus neuropathy, and mononeuropathy (MN) also called as focal neuropathy. There are other types of DN, which are less common, such as chronic sensorimotor Distal Polyneuropathy (DPN) and amyotrophic neuropathy.[2]

The most commonly recognized is the PN, with effecting over 50% of patients suffering with diabetes including Type I and II. PN is defined as peripheral nerve dysfunction in type 2 diabetic patients. PN is most commonly characterized by localizing where nerve is damaged. The neuropathy depends on length and is diffused that type of PN is then called as distal symmetric polyneuropathy.[3] The symmetrical neuropathies include acute sensory neuropathy, DPN, and autonomic neuropathy. The most common is DPN.[4] Diabetes and DN are related and are grouped into two categories, i.e., the focal or diffuse neuropathy, which is caused due to damage by diabetes. It is characterized by damage to three of nerve fibers, i.e., peripheral somatic or autonomic nerve fibers. The focal neuropathy refers to damage caused either to single nerve or mononeuropathy and multiple peripheral nerves or mononeuropathy multiplex, cranial nerves, regions of the brachial or lumbosacral plexuses (plexopathy), or the nerve roots (radiculopathy). The diabetic nerves also have increased susceptibility to compression. The most common cranial neuropathy affects the third nerve, producing unilateral headache, diplopia, and ptosis with papillary sparing (diabetic ophthalmoplegia).

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The risk of developing the DN increases with progressive age and for the period of time the patient is suffering from diabetes. The diabetic neuropathic pain starts usually during early diagnosis or prediabetes.[5] Furthermore, an elevated blood pressure, an increased level of cholesterol poor oral health,[6] sleep deprivation, mental health,[7] depression,[8] and likely the hereditary factors can also be categorized as risk factors for developing DPN.[9] Although the neuropathy increases the duration of diabetes, PN is not always associated with diabetes. The Rochester DN Study reported that one-tenth of patients with DM had neurologic deficits unrelated to the disease.[10] The unhealthy nutrition and adopting inactive style aids in dysbiosis and chronic systemic inflammation, and there is adequate research suggesting it to be the contributing factor in the development of prediabetes, diabetes, and metabolic syndrome-associated neuropathies.[11] Bladder function is common in patients with DN.[12] Alcohol intake can alter the intake and absorption of various minerals, nutrients, and especially vitamins such as lack of riboflavin (Vitamin B2), niacin (Vitamin B3), pyridoxine (Vitamin B6), folate (Vitamin B9), cobalamin (Vitamin B12) found to be associated with neuropathy.[13] High dose of thiamine (Vitamin B1) can decrease the oxidative stress-induced hyperglycemia in rats by inhibiting hepatic ADP ribosylation.[14]

The blood sugar level needs to be well controlled or else constant elevated sugar level can lead to various severe complications such as permanent blindness, kidney failure, lower limb amputation, and other long-established harmful effects that disturb the well-being of an individual. In chronic condition, the kidneys can be effected by diabetes causing diabetic kidney disease. According to one report, 44% of all new cases of kidney failure requiring renal replacement therapy were caused by diabetes mellitus.[15] This nephropathy is due to the fact that diabetes activates renin-angiotensin-aldosterone system (RAAS) directly, which increases the pressure state inside glomerulus. This results in mesangial expansion resulting in cell damage that responds by producing cytokines that produce inflammation, the generation of Reactive Oxygen Species (ROS) that results in endothelial dysfunction. The expansion of mesangial cells affects the process of leg podocytes expanding which has 2 effects. The first is a decrease in surface area for filtration and the second is to cause the filtration system to leak causing larger protein molecules to be filtered out of the blood. When the patients have severe DM, it can cause decline of excitatory cholinergic fibers and neuronal density.[16] Neuropathy, nephropathy, and retinopathy all of these are considered as microvascular complications of diabetes.[4] Furthermore, diabetes and neurodegeneration are strongly related. Hippocampus of the brain is effected by diabetes and the research indicates that it is damaged by glucose. This gives rise to beta-amyloid, an end product of glycosylation. This is further altered by glucose to increase inflammatory predisposition in the brain, making it a major concern in diseases such as Alzheimer's diseases. Diabetic patients are also at risk of getting a stroke or prone to other neurodegenerative diseases. Seeking professional help from health-care professionals could relieve the pain and it's associated and related.[17,18]

This review is an effort to follow the works that are already documented[19,20] and exploring it further with recent literature. There are some reviews which focused particularly on drugs such duloxetine,[21] pregabalin, or tricyclic antidepressants (TCAs)[22,23] and their effect in the management of pain.[24] Griebeler *et al*. proved the analgesic as an effective measure using systematic meta-analysis of a number of reviews.[25] Quattrini and Tesfaye analyzed the different types of instruments that are used for the assessment of neuropathic pain.[26] Some researchers on the other hand discussed pathophysiology and epidemiology of DN pain.[27] Robust meta-analysis of all the pharmacological and nonpharmacological treatment options is not found in abundance.[28,29] The use of nanoparticle for pharmacological treatment is also abundantly utilized.[30,31] This review is an attempt to summarize all these methodologies in one place.

Pathophysiology of Diabetic Neuropathy

The origin of DPN is not widely understood but is believed to influence multiple pathways and activate ROS species, causing oxidative stress.[32] This causes the release of cytokinesis which in turn results in inflammation and elicits a sensation of pain.

The pathways involved in pathophysiological diabetic neuropathic pain are all related to metabolic conditions and / or cell redox.[33,34] This metabolic pathway is a polyol pathway with a model that explains the possible developments performed by the final model of glycosylation products and oxidative stress theory. One of these pathways is the sorbitol-aldose reductase (AR) pathway, also known as the polyol pathway. This is a two-step process where glucose is first converted to sorbitol by AR and then to fructose sorbitol dehydrogenase.[35,36] Targeting this pathway by inhibiting metabolic reflux is likely to be beneficial in treating DPN.[37] The way polyol pathway works is that it results in the increase of sugar alcohol compound such as sorbitol. This increase causes a decline in the activity of Na^+/K^+-ATPase also known as the Na^+/K^+ pump. This is followed by building up of axonal sodium. These processes eventually will cause structural damage and damage to axoplasmic transport. Due to the fatal increase in glucose levels, the product is produced from the process of glycosylation and glycation of free amino groups occurs on proteins, lipids, and nucleic acids. Basement membrane endothelial cells lose its functionality upon glycosylation, declining vasodilation and elevating macrophages and inflammatory cytokines. ROS is produced when the level of nitric oxide is reduced due to structural damage caused by glycosylation. These can cause cell death and damage, which subsequently disturbs the vasodilation of microvascular perfusion, resulting in severe deficiency of blood supply to the damaged region.[38]

Other pathways that are involved are the hexosamine pathways.[39] The protein kinase C pathway, which refers to a group of

12 isoenzymes that bind diacylglycerol. Elevated level of diacylglycerol is associated with increased glucose level. DN arises from activation of this pathway by the synthesis of diacylglycerol from glycolytic intermediates.[40] Inhibitor of this pathway can improve Na^+, K^+, and ATPase activity as well as improve the nerve conduction velocity and neuronal blood flow, thus beneficial in treating DN.[41] The final pathway of advanced glycation products results in an increase in the amount of glycation and its accumulation in plasma proteins alters cellular signaling and enzyme activity that gives rise to diabetic complications such as DN.[42] These advanced glycated end products are found in peripheral nerves of patients with diabetes, and targeting generation and degeneration is found to be effective in controlling DN.[43,44] Polymerase pathways (ADP - ribose) (PARP), pathways followed by increased ROS species that cause oxidative stress and apoptosis -induced along with inflammation are also some of the common pathways recommended for DN.[45] This pathway individually is not very dangerous but when working collectively will develop a state of imbalance in the cell powerhouse and this alters the redox state of the cell resulting in the production of ROS species. An elevated level of ROS causes activation of the PARP pathway, which regulates the expression of genes involved in promoting inflammatory reactions and neuronal dysfunction. Decreased nutrients to the neuronal brain or neuronal ischemia and decreased blood flow due to a narrowing known as neurovascular flow are both of these conditions caused by high glucose levels in the blood and are responsible for DN.

Brain-derived neurotropic factor (BDNF) binds to TrkB receptors in the neuron to form a complex, which causes the tyrosine residue formation and the phosphorylation of TrkB. BDNF is believed to be involved in changing the plasticity of spinal neural pathway and is the center for pathological pain. The downstream regulatory element antagonist modulator (DREAM) protein is involved in the pain process, which inhibits the expression of prodynorphin gene. A group of researchers proved that mice that are deficient in this DREAM protein show reduce analgesia in several thermal, mechanical, chemical, or visceral pain. It also shows an increase in spinal prodynorphin mRNA, which is thought to be responsible for this reduced thermal behavior of mice. The involvement of DREAM protein in the DNP is yet to be researched further to understand it more properly. Some evidence suggest the involvement of linked microglia and other nonneuronal cells in the development of DNP. Activation of these microglia releases neuromodulators and cytokinesis to develop DNP. An experiment was performed in which a microglial activation inhibitor, minocycline was given to diabetic rats with DPN. Rats that are hyperglycemic showed increased tactile allodynia and nociceptive behavior. These were complemented by increased expression of spinal OX-42, BDNF, and DREAM protein levels. Administration of minocycline decreased tactile allodynia and nociceptive behavior. It also inhibited the diabetic-induced increase in spinal expressions of OX-42, BDNF, and DREAM proteins. Thus, minocycline could decrease DNP by controlling spinal BDNF and DREAM protein expressions.[46]

Nociceptors are those receptors located at the free nerve endings of unmyelinated C fibers and lightly myelinated Ad fibers that are associated with neuropathic pain;[47] these are activated by different stimuli such as mechanical, thermal, or chemical. One of the forms of these receptors known a mechanosensitive nociceptor is activated by mechanical pressure and stress. Neuropathic pain is also associated with lipid metabolites release like lysophosphatidic acid (LPA), which occurs when the tissue is damaged. These lysophosphatidylcholine acts by coupling its receptors with G protein. Release of proinflammatory cytokines and inflammatory mediators promotes the hyperalgesia and allodynia along changing intracellular signaling, which is observed in neuropathic pain. The pain experience is promoted by secondary messengers and nitric oxide signaling pathways.[48] It is believed that LPA1 and LPA3 are specifically involved in the pain promotion due to DN.[49]

Diabetic Peripheral Neuropathy Treatments

They are classified under two major categories that include the most commonly prescribed pharmacological pathway using drugs and the use of nonpharmacological treatment options such as exercise, therapies, and ancient Chinese therapies such as acupuncture.

Pharmacological treatments

There are a variety of the most recommended and commonly used medications for DNP including the use of Hydroxychloroquine [50,51] or intravenous infusion of lidocaine. [52,53] and phenytoin[54] were highly preferred treatments in the past, with the emergence of seizures as a popular treatment option two decades ago.[55] Currently, the use of antagonists and analgesics explored using target receptors[56.57]] such as metamizole[58] is more common.

Phytotherapy

Natural secondary metabolites such as flavonoids,[59] terpenoids, and alkaloids have diverse biological applications including in the management of neuropathic pain by acting as an antioxidant agent.[60] These modify the activity of protein kinase C, by modulating the central nervous system (CNS) neurotransmitter systems, which helps in the modulation of neuropathic pain. The proposed therapies for the neuropathic management are inadequate and have shown less effectiveness with more severe side effects, making it as debating and well researched topic among scientists. Natural products (NPs) or their secondary metabolites pose less side effects and more effectiveness while reliving neuropathic pain.[48,61] Oral herbal medications are suggested as a possible treatment options to lower blood glucose level and relieve diabetes associated complication.[62-64]

The major complication that diabetic patients with hyperglycemia face is the microvascular complication. This

complication arises from the increase in ROS species is experience with hyperglycemia. An experiment was performed on albino diabetic rats in which methanolic extracts of two plants Allium cepa and Allium sativum by acting as prescribed antioxidant agents were given to rats in a dose -dependent manner to determine its effect on DN, after hyperalgesia and oxidative stress marker trials were evaluated and shown that diabetic -induced rats reduced thermal hyperalgesia with weight maintained and decreased plasma glucose levels were shown. Thus, the extract of outer scales of onion because of the greater phenolic component showed significant improvement and can be used as a treatment option.[65] *Rosmarinus officinalis* commonly known as rosemary is a medicinal herb that is high in antioxidants and shows various biological activities. Antinociceptive and neuroprotective effects of leaf extract were evaluated in the model of DU pain. The study was performed on animal models where diabetes was induced in rats by administered of single intraperitoneal injection of streptozotocin (STZ). The leaves were shade dried, powdered, extracted, and concentrated to dryness, which was then freeze dried. The plant contains phytochemical constituents such as carnosol, rosmanol, carnosic acid, methyl carnosate, caffeic acid, and rosmarinic acid. HPLC of the extract was performed which determined 4.5% rosmarinic acid as the main phenolic compound of the extract. Control group received citrate buffer injection. Serum glucose concentrations using glucose oxidase–peroxidase assay confirmed the diabetes in rats. ≥250 mg/dl glucose level indicated diabetic rats. The diabetic rats were given the RE or saline once every day through oral gavage for 3 weeks. CO_2 anesthesia was used to kill the rats at the end of 4 weeks past the STZ injection. The result indicated that the reduction of level of biochemical markers of apoptosis, caspase-3, and Bax:Bcl-2 ratio, which was activated during diabetes. The suppression of these markers results in decreased cell toxicity of hyperglycemia. Decrease of Bax expression reduced hyperglycemia, whereas caspase-3 inhibition reduces neuropathic pain. Other side effects of high glucose levels include motor deficit and neuropathic pain, inflammation is also reduced by the extract. Diabetes is associated with oxidative stress that causes apoptosis, rosmarinic acid into flavonoids have antioxidant potential to reduce this stress.[66] Another plant *Salvia libanotica* is a traditional antidiabetic plant rich in phenolic compounds.[67] The root extract was used on diabetic mice with induced DNP and its effect to thermal latency was measured with common tail flick and hotplate method. Treatment of mice with the extract showed significant improvement with hyperalgesic response in thermal tests, the hot plate latency was also improved by 8 week from 29.3%–36.6% for all doses of extract, and this latency was further improved to 61.6% after 8 weeks. Thus, it is demonstrated that dose-dependent SLF extract enhances peripheral nerve function as well as catalase activity and hyperglycemia in diabetic rats demonstrating its effectiveness. It alleviates hyperalgesia in pain conditions and can provide clinicians promising drugs for the management of the symptoms of DN.[68]

Deguelin is a natural rotenoid s suggested to possess antidiabetic properties by acting as a natural antioxidant agent. DN was induced nu the use pf streptozotocin, and the mice were treated with deguelin for 14 days. After the end of experiment, it was proved that it majorly inhibited mechanical and thermal hyperalgesia, as well as cold allodynia. It also improved the nerve conduction velocity in the DN rats, which is beneficial in controlling neuropathic pain. The expression level of caspase-3 was decreased, and an elevated sodium, potassium, and ATPase activity was observed in sciatic nerves. Hyperglycemia is managed with a decrease in increased glucose levels achieved with the use of deguelin. This in turn reduces oxidative stress and neuritis, and increases levels of H2S, nuclear respiratory factor 2 and heme oxygenase - 1. Thus, deguelin can be effective against the DN; however, further clinical studies need to be conducted to be sure.[69]

Curcuma caesia extract, locally known as black turmeric, is an herb belonged to the family Zingiberaceae. The *in vitro* assay of the methanolic extract of *Curcuma caesia* was also found to be effective against type 2 diabetes against yeast cell.[70] It has a smooth muscle relaxant property and anti-inflammatory activity with an ability to reduce oxidative stress and acts as potential chemoprotective and DN agent.[71]

Painful diabetic peripheral neuropathy (DPN) may be associated with low Vitamin D levels.[72] DN is associated with subclinical inflammation. Hyperglycemia activates cytokines, DPN shows increased levels of cytokine proinflammatory mediators.[73]

Death of neuron and cognitive decline that is most commonly present with diabetes is reduced with apigenin by decreasing the level of ROS and nitric oxide synthase. It is a phenol-rich compound present in plants such as celery thyme and parsley. It shows antioxidant activity by suppressing ROS level. A study was performed to determine its effect on peripheral nerve degeneration. It was shown that has a neuroprotective effect against peripheral nerve degeneration according to four key phenotypes: axonal degradation, myelin fragmentation, transdedifferentiation, and proliferation of Schwann cells via Krox20- and extracellular signal-regulated kinase-independent processes. This allows the scientists to suggest it as a treatment option for peripheral neurodegenerative diseases.[74]

Curcumin has also been reported to reduces blood glucose and glycosylated hemoglobin levels and prevented weight loss with its effective against DN.[75] The alkaloid-rich fraction of the herb coronaria and its consistent glaucine may be used for DNP in the future as it has shown promising antihyperglycemic and antinociceptive potential.[76] Naturally obtained hybrid molecules that are synthesized when active compounds of these natural plants are conjugated together. These hybrid molecules are a novel and effective approach used to treat a lot of diseases including diabetes complications.[77]

Thymosin β4

As shown in Table 1, Thymosin β4 (Tβ4) is a protein with

anti-inflammatory activity and neurons recovery efficiency induced by diabetes during PN. Dysregulated microRNA assembly, which among other serious complications also causes inflammation and is a cause of DN. miR - 146a regulates IRAQ1, tumor necrosis protein -adapting factor 6 and kappa Nuclear Factor - light -chain activated B cell enhancer and transcription factor; Nuclear factor kappa - light chain - activated B cell enhancer. The activation of NFkB downregulates proinflammatory mediators and suppresses the TRAF6 communicate to the cells of spinal cord, which reduces the neuropathic pain. An animal model proved that administration of miR-146a reduces the DPN. It does so by upregulating the Tβ4 and stimulates oligodendrocyte differentiation by repression of pathways that aid the inflammation. It was found by RT - PCR, hyperglycemic mice reduced miR - 146a expression and this was reversed with Tβ4 treatment. DPN treatment with Tβ4 enhances the neurovascular remodeling, which benefits the loss of neurological functions. miR-146a may facilitate the beneficial effects of Tβ4 by suppressing proinflammatory mediators.[82]

Tau proteins are the proteins that stabilize the microtubules of cytoplasm and are abundantly present in neurons of CNS. The hyperphosphorylation of this protein causes neurodegeneration disorders. Glycemic variability (GV) is also thought to induce DN through the same mechanism by inhibiting Akt cell signaling and GSK3Beta. GV also induces DPN through oxidative stress and apoptosis in neurilemma cell, which causes inflammation by activating NF-kB pathway. An experiment on diabetic rats was conducted to determine the effect of GV on DN. Nevers of both CNS and peripherical nervous system are damaged during diabetes, which is characterized by progressive cognition impairment, dementia, and Alzheimer's.[45] During diabetes, the neuronal damage induced by oxidative stress and apoptosis of hippocampus occur, which is a cognitive organ. GV disrupts hyperglycemia by promoting the hyperphosphorylation of Tau protein and effects the cognitive function in rats.[83]

Antiepileptic medicine

Cutaneous diabetic microangiopathy is associated with impaired vascular endothelial growth factor (VEGF)-A expression in patients with type 2 diabetes. Epidermal VEGF-A confirms that VEGF-A expression significantly decreases in patients with diabetes with neuropathy compared to subjects without diabetes.[84] The chances of developing painful DN increase with hyperglycemia, the longer duration of period the patient has diabetes, and sedentary lifestyle of an individual.[85,86] One of the suggested treatment options to consider that is clinically recognized is the administration of pregabalin. It relives pain and inflammation commonly experienced in DN. It decreases the sensation of pain by binging strongly to alpha-2-delta subunit of voltage-gated calcium channels at the presynaptic terminals.[87]

Anticonvulsants

Gabapentin reduces DN pain in DPN to a significant number in 50% in large population of patients. It is similar in chemical structure to that of pregabalin, but it has sixfold higher affinity for receptor binding and therefore more effective in reducing the pain from DPN.[38] Animal model r shows that the use of retigabine (ezogabine) activates voltage -gated potassium channels. The analgesic effect of the antiallodynic (anticonvulsant) retigabine was reversed when blockers of channels were used. Voltage-gated potassium channels are in the process and the drugs designed to target these channels can be effective in treating DPNP.[88] A study performed showed that activation of Kv7 channels can be reversed with retigabine, an activator of these channel, in a dose-dependent manner and this helps reduce the DPN; thus, targeting activation of kv7 activation channel can be effective. These voltage-gated potassium channels are considered to be involved in majority of the diabetic peripheral neuropathy (DPN) associated with diabetes.[89]

The role of hGAT1 has long been known to be involved in the mechanism of NP, and the use of GAT1 is known to be effective in controlling pain. The analgesic action of TGB which works on a similar mechanism by inhibiting GAT1 was studied in a rat model by inducing them to use DPN using STZ and standard oxaliplatin. It was found that it works on GABAergic system by making GABA more available at synaptic loci. Thus, TGB can also be used as a clinical trail medicine for controlling neuropathic pain.[90] A group of three compounds of 3,3-diphenyl-propionamides previously known to possess anticonvulsant agent was checked for its analgesic action. A rat model of acute pain that is a hot plate was used to determine its antinociceptive activity. The result suggested that two of these three compounds JOA 122 and JOA 123 showed significant antinociceptive activity in the mode of tonic pain when tested in neuropathic model using mouse induced with DN using STZ-induced PN and formalin test using oxaliplatin. These compounds are thought to act via voltage-gated sodium channels (Nav1.2) to which it shows high affinity.[91] Another study showed that the painful DN can be improved using duloxetine and venlafaxine, pregabalin and oxcarbazepine, TCAs, atypical opioids, and botulinum toxin.[92] Reducing the production of Chondroitin Sulfate genetically suppresses apoptosis signals and controls the development of diabetes -associated neuropathy.[93]

The use of anticonvulsant such as pregabalin to control DPN has also been suggested and the clinical data demonstrated that the use of more than 300 mg/day have proven effective in some patients and therefore approved as a monotherapy for DPN. Opioid use, lidocaine patches and capsaicin creams are also recommended but there are not enough clinical trials to support them.[94]

A study was performed on randomly categorized 457 patients suffering with diabetes into placebo and duloxetine drug group to determine the effect of drug in its inhibition of neuropathic pain. The results showed a significant decrease in pain score of 50% with <20% discontinuation of medication due to drug -related complications and side effects. It is the reabsorption

of serotonin and norepinephrine (5HT and NE) and this double inhibition makes it an effective pain reliever in DPN. Effective dosing duloxetine can be considered a useful drug for treating pain, inflammation, and mostly pain in the DN.[95]

Antinociceptive

Docosahexaenoic acid is a polyunsaturated fatty acid which shows antinociceptive effect by oral administration of mice; it also shows antiallodynic effect with preventive thermal hyperalgesia mechanism adopted in a STZ-induced neuropathic pain model. It decreased the excitability of dorsal root ganglion neurons by decreasing sodium and increasing potassium currents. Female Wister rats caused diabetes by injecting STZ, hyperalgesia and tactile allodynia test performed. Ipsilateral local peripheral administration of DHA produced a dose-dependent antihyperalgesic effect on formalin-induced hyperalgesia. A maximum effect was observed for 562 μg/paw of DHA and 1000 μg/paw of gabapentin Peripheral administration of DHA or gabapentin exhibited an antihyperalgesic effect against thermal-induced hyperalgesia. After 14 weeks, the diabetic and nondiabetic rats were compared and tactile allodynia was induced. DHA and gabapentin were introduced which attenuated tactile allodynia. The local administration of DHA reverted the hyperalgesia and allodynia in neuropathic pain in SID rats. The μ and δ receptors are involved in the antihyperalgesic effect of DHA in neuropathic pain induced in diabetic rats. This effect is likely due to a purely local peripheral action.[96]

Metformin is used as an antidiabetic drug for type 2 diabetes and shows hypoglycemic activity. Mice were given metformin and exposed to a hot plate to measure its increased latency for the nociceptive response. Injured sciatic nerve and mechanical allodynia appeared only after one day, The therapeutic effect was observed after eight days of surgery, and it was found that three doses of metformin weakened the mechanical allodynia caused by chronic narrowing injury. Another similar experiment proved that metformin treated in high doses of PWT increased significantly compared to the control group. The antinociceptive activity of metformin can be facilitated by activation of opioidergic pathway. It, however, should be further investigated aiming its repositioning in the treatment of patients with different painful conditions.[97]

Tricyclic antidepressant drugs

TCAs or γ-aminobutyric acid (GABA) analogs are the most common treatments used for the treatment of neuropathic pain. They are used for decades and found to be effective in treating diabetic neuropathic pain.[98] There are few reports regarding its ability to increase the risk of falling down or fracture in older patients suffering with type 2 diabetes having DNP.[99] Despite these contradictory reports, it is widely used for the treatment of neuropathic pain. Antidepressants and antiepileptic drugs inhibit the ion channels and its neurotransmitter as a mechanism to contract the pain developed.

High doses of non-selective anti-inflammatory COX inhibitors such as nonsteroidal anti-inflammatory drugs have adverse side effects while selective COX-2 inhibitor drugs such as celecoxib (Celebrex) however have fewer side effects. Vioxx increases the risk of heart attack and was shortly banned after its production in the market. When the peripheral nerve is damaged or compressed, an ideal drug stabilizes as well prevents the progression of central sensitization to pain. Antidepressants and antiepileptic are those drugs that work by blocking the ion channel and thus the transmission of pain. These drugs, however, are not without side effects and effect the nervous system in one or other way.

Electric current is produced by nerves and muscles, the speed of this current down the nerve activates the muscle. Julius Bernstein called this as action potential. This action potential generates depolarizes and nerve self-propagate. It occurs because the nerve fiber is electrically charged with the outer surface of the nerve fiber positive compared to the inner surface and this supports self -propagation. Nerves have ions and these ions move through selective ion channels embedded in the membrane. These ion channels are closed while the axons are at rest, but when the action potential arrives through the nerve cell body, this causes voltage changes and these channels like sodium and potassium are voltage gated. The difference in potential opens up the sodium channel allowing the charged sodium to move through into the nerve fiber and this causes the membrane potential to change from negative to positive. This positive potential causes the sodium gates to close and opens the potassium channels allowing positive potassium ions to flow down the nerve making membrane potential to a negative. The ion channel proteins also work alongside these gates to maintain the concentration of these ions at a hemostasis level by pumping the sodium ions out and potassium into the nerve. A high concentration of potassium ions inside the axon and a high concentration of sodium ions outside the axon is maintained by these proteins.

When a nerve is damaged, the concentration of these ion channels increases in the damaged area of the finer nerve and it alters the depolarization characteristics of these fibers. Therefore, medications that target this channel such as seizure medications and antidepressants are commonly used for the treatment of neuropathic pain. The neurotransmitter acetylcholine targets muscle cell membrane receptors. The transmission can be a fast electrical or slow chemical transmission. There are both excitatory and inhibitory synaptic chemical transmission in the brain. The membrane potential of the target neuron is reduced by the stimulus emitter and increases b. The balance between these two determines whether an action in the target neuron will occur or not. The brain contains amino acids as stimulus transmitters and glutamate because the main inhibitory transmitters are amino acids, GABA. The voltage-gated calcium ions are opened up when the action potential reaches the axon terminal allowing the calcium ions to flow in the neuron. This releases tiny synaptic vesicles filled with neurotransmitter which fuse with the surface membrane releasing their neurotransmitter contents into the synapse. Receptors such as acetylcholine function

with ion channels and activate the second messengers of target neurons, activating protein genes. The neurotransmitters hold the ability to alter the density of synaptic receptors on the target neuron over time. Simple electrical transmissions can carry information more diverse and faster through synapses than chemical receptors.[100] Calcium voltage gates are reported to be involved in DPN. A report suggested the use of pregabalin to be effective in relieving the pain and improving the sleep more than that of placebo when the drug is administered in a dose-dependent manner.[101] However, it is also reported to increase the weight gain, cause dizziness, tiredness, alter vision, euphoria, etc.[102] Mirogabalin monobenzone sulfonate is an alternative supplement drug for the treatment of painful DN. This indicates a binding affinity for the 2 d - 1 and 2 d - 2 subunits of the voltage -dependent Ca2 + channel and a slower separation rate. In a clinical trial, 834 DPN patients with type 1 or 2 diabetes and older than 20 years were selected for the trial and grouped into the mirogabalin and placebo groups. Depending on the dose given to the patient during the experiment while the average pain score was assessed at the end of the 14th week.The overall result indicated reducing the pain and associated sleep interference in patients with DPNP.[103] Serotonin-norepinephrine reuptake inhibitors, TCA, and gabapentin have also been reported to reduce NUP. Use of opioid drugs is associated with the risk of over dosage, addiction, and subsequent addiction to it.[104]

Alpha-lipoic acid and acetyl-L-carnitine

Alpha-lipoic acid and acetyl-L-carnitine (all placebo controlled) is a supplement for DN. Alpha-lipoic acid was more effective than placebo for the outcome of pain.[105]

Nonpharmacological treatments

The use of nonpharmacological treatment options is often less explored and can be beneficial in relieving diabetic neuropathic pain.

Surgical treatment

Surgical treatment such as nerve decompression surgery to relieve pain at the nerve root is one of the proven ways to reduce DPN pain. One study was performed on participants who had type or two diabetes and experienced DN pain. Patients who were part of this experiment rated the average pain experienced greater than five on the ten-point McGill Pain questionnaire and the total neuropathy score value was greater than or equal to 2 for the visual analog item. Intervention group underwent surgery procedure where decompression of the common peroneal, tibial, and deep peroneal nerves was performed. Control group received usual care. Patients included in both control and groups were checked after three, six, and then after 12 months. The group that performed the surgery reported an improvement that was threefold more than that of control group. Thus, the use of surgical procedure for the betterment of DPN to decompress lower limb nerves can be used as a treatment option.[106]

Hemoglobin HbA1c glycation occurs when blood glucose rises and attaches to hemoglobin, DPN in diabetes 2 and its association with increased glycemic levels and HbA1c requires optimization to control neuropathy. Trans -renal pancreas (SPK), an insulin -providing agent can normalize HbA1c but it is often accompanied by hypoglycemia in patients with type 2 diabetes. The normalized HbA1c levels and its relation with retinopathy and nephropathy in patients with poorly controlled type 2 diabetes were investigated using 671 patients with hyperglycemia.[107]

Supplement

Folic acid supplement shows protective effect against diabetic peripheral neuropathy in rats. A study was conducted in which over a period of 16 weeks 38 patients suffering from DPN were given | temporary folic acid supplementation 37 was characterized as a placebo group and at the end of the experiment the nerve conduction velocity related to folic acid and homocysteine concentrations was determined. The result indicated that decreased homocysteine was accompanied by increased serum levels of folic acid. Nerve conduction velocity was highly effected by folic acid intake.[108] The use of folate administration along with Vitamin B to patients with DN and type 2 diabetes may improve insulin resistance and homocysteine (hcy) level.[109]

Diabetic retinopathy (DR) leads to loss of vision and is the most commonly associated complication of diabetes. Current treatment options include controlling blood pressure and glycose level in the blood with constant eye checkup and photocoagulation in advance stage. Postsurgery treatment usually involves the use of VEGF inhibitors; however, majority of patients respond low to these inhibitors. Members of the NOX family are associated with ROS production and oxidative stress on DR. This ROS is also responsible for expression of VEGF and cytokine, an inflammatory mediator. Hcy, an amino acid, is present in high level in the blood of DR and induces ROS production. Vitamin B9/folic acid is known to decrease hcy accumulation along with downregulation of genes that are linked with angiogenesis, inflammation, and oxidative stress in a diabetic mouse suffering from type 2 diabetes. It decreased retinal thinning and the serum level of hcy.[110]

The daily use of Vitamin B complex that comprises nonenzymatic antioxidants such as Vitamin B1, Vitamin B6, and Vitamin B12 in the treatment of pediatric patients with type 1 diabetes for decreasing the effects of DN has been investigated. 80 children were included in the study; they were divided into two groups of 40 in each group, with one group receiving the complex drug and the other matching placebo. Microalbuminuria was observed in all patients from the last 6 months included in the study, all of whom were Vitamin B deficient and had low HSY levels compared with controls. The administered drug of Vitamin B complex tablet decreased the total cholesterol and triglyceride level and decreased the hcy level, cystatin C, and glycose level by decreasing HbA1c.[111]

Increased magnesium level along with low level of Vitamin B6 is found to be elevated in patients with DN. Lipid peroxidation induced by oxidative stress in patients with DN can be treated

with antioxidant vitamins. Magnesium with zinc and Vitamin E and C was administered to patients suffering from DN having type 2 diabetes. The Michigan Neuropathy Screening instrument questionnaire determined that the severity of DN. Magnesium supplementation with micronutrients did not improve the nerve conduction velocity in patients and the low dose of Vitamin B group supplementation also had no effect in improvement of the symptoms. However, the use of Vitamin C and Vitamin E with zinc, magnesium can increase the severity in DN patients by reducing oxidative stress.[112]

The use of Vitamin B is, however, not appreciated by all studies. One study showed that the use of Vitamin B complex (B6, B12, and folic acid) can do more harm in patients suffering from both type 1 and 2 diabetes showing symptoms of DN. The oral administration of the complex decreased hcy level but also decreased the glomerular filtration rate and renal function and increased the risk of MI and stroke and was found to be associated with renal and vascular toxicity.[113] Another study showed that the use of folic acid, Vitamin B6, and Vitamin B12 lowers hcy level, but it did not decrease the risk of developing the type 2 diabetes among women at high risk for CVD.[114] High doses of Vitamin B_6 and Vitamin B_{12m} can cause an increase in hip fractures in postmenopausal women.[115] However, the use of Vitamin C, Vitamin B_2, and folate has been reported to reduce the risk of developing diabetes in Japanese women.[116]

Homocysteine is a by-product of transmethylation reactions and detoxified by methionine synthetase, which is dependent on Vitamin B12 and folate as coenzymes for its proper function. Low folate and vitamin concentrations reducing homocysteine damage are also associated with an increased risk of cardiovascular complications. It acts as an indicator in DN. Vitamin B DR and its association with homocysteine were determined by clinical trials. The deficiency of B6, B12, and folic causes hyperhomocysteinemia; however, only B12 deficiency was found to be associated with DR. Supplementation of B12 and folic acid can reduce hcy level. Lower B12 level increased hcy in DR patients, suggesting it as an independent risk factor. It was also found that B12 level was significantly lower in DR than DNP.[117]

Endothelial cells, pericytes, and Muller cells are three important components of the inner blood–retinal barrier (iBRB), playing a key role during the development of DR. Thiamine can decrease the progression of retinopathy and the metabolic damage caused in microvascular cells due to hyperglycemia. Thiamine protects the iBRB from inner stress and apoptosis.

Different types of human cells were exposed to hyperglycemic conditions in the presence and absence of thiamine supplementation. IntHG elevated the MMP2 and MMP9 expression and normalized by thiamine in all cell types, whereas TIMP-1 increased in HRP only. The expression of angiotensin 2, VEGF, and HIF-1α in HMEC increased when hyperglycemic conditions were provided to cells. These expressions were encountered by thiamine. Thiamine supplementation can neutralize the damage caused to the nerve due to diabetes and can be further investigated for its effect as a DN agent.[118]

Acupuncture

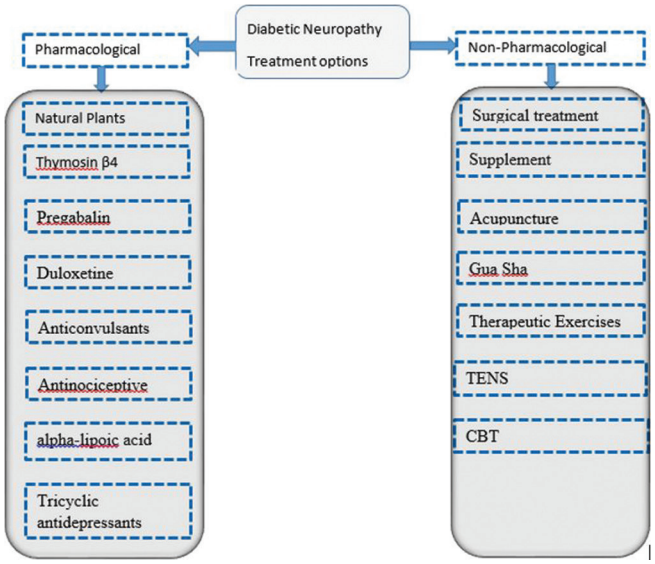
A study was performed to analyze the effective of electroacupuncture for the treatment of DPN. The study was designed to allot the participants into two groups randomly. One group received the electroacupuncture with needle connected to the electroacupuncture device passing current of 2 Hz-120 Hz and 80% of the bearable intensity at different 12 points. The needle was inserted at the acupuncture point with deqi sensation. The placebo group receiving a superficial needle (3-5 mm) was performed without a deqi sensation, creating a false motion like rotating the acupuncture at a non-acupuncture point matched to each of the actual acupuncture points. The needles were connected to the device with similar light and sound heard by the participants, but no electric current was passed through the needles.[119]

The use of electroacupuncture in treating DPN (in Chinese "xiaokezheng") has proven to be effective. DPN is considered as a peripheral nerve injury due to hyperglycemia-induced oxidative stress with endoplasmic reticulum stress (ERS)-induced apoptosis as the major apoptotic mechanism involved in the process. Under the condition of oxygen-deficient environment, entrance of reactive species or disturbance of calcium hemostasis, errors in protein folding, and alteration of calcium hemostasis will cause an ERS. This ERS can induce apoptosis by activating unfolded protein responses, completing signal transduction with a combination of 3 types of transmembrane proteins (protein kinase R - such as Endoplasmic Reticulum Kinase, Inositol Requires Enzyme 1a, Activating Transcription Factor - 6 and glucose regulated protein) 78 (GRP78). The GRP78 is associated with protein folding and transduction. Its overexpression occurs during stress and it stabilizes ER and prevents apoptosis. Caspase-12 of caspase family member involves the apoptotic pathway of ER. Acupuncture is long known to treat pain and discomfort, which is appreciated over Western medicine because of no toxicity. Manual twirling, low-frequency electrical stimulation of the inserted needles (electroacupuncture) has found to be effective in DPN treatment. GRP78 and caspase-12 were used as targets to investigate the intervention effect and mechanism of "adjusting internal organs and dredging channel" electroacupuncture act on DPN by immunofluorescence staining technique and Western blot technique in STZ-diabetic rats to elucidate its action mechanism. The sciatic nerves of rats were assessed for the levels of GRP78 and caspase-12 after 12 weeks of consecutive treatment; electroacupuncture reduced pathological injury of sciatic nerves in diabetic rats with effectively downregulated GRP78 and caspase-12 and reduced cell apoptosis of sciatic nerves in DPN rats. Electroacupuncture treatment improved DPN by downregulating GRP78 and caspase-12 and reducing cell apoptosis of sciatic nerves in diabetic rats, further inhibiting the occurrence of endoplasmic reticulum stress and thus preventing sciatic nerve injuries.[120]

Table 1: Natural compounds effective against diabetic neuropathy pain

Active compounds	Mechanism	References
Cephalendra indica	Inhibition of oxidative stress, AGE's level in sciatic nerve was also found to be significantly reduced in diabetic rats	[78]
Deguelin	Deguelin attenuated DN by decreasing oxidative stress and plasma glucose levels via the Nrf2 signaling pathway	[69]
SalA	SalA protected against DPN by antioxidative stress, attenuating neuroinflammation, and improving mitochondrial function via Nrf2	[79]
Naringenin	Combination with naringenin attenuated the diabetic condition but also reversed neuropathic pain through modulation of oxidative-nitrosative stress, inflammatory cytokine release and MMP inhibition in the diabetic rats	[80]
Quercetin	Quercetin alleviate diabetic neuropathic pain by inhibiting mTOR/p70S6K pathway - mediated changes of synaptic morphology and synaptic protein levels in spinal dorsal horn neurons of *db/db* mice	[81]

AGE: Advanced glycated end products, DN: Diabetic neuropathy, Nrf2: Nuclear respiratory factor 2, DPN: Distal polyneuropathy, MMP: Matrix metalloproteinases, SalA: Salvianolic acid A, mTOR: Mammalian target of rapamycin, p70S6K: p70 ribosomal protein S6 kinase



Graphical Abstract

Acupuncture for DPN appears to improve symptoms. However, the application and type, duration, and time of acupuncture have an effect on reduction of pain in DN.[121] One report suggested that the use of Japanese acupuncture Kiiko-Matsumoto decreased neuropathy-associated pain more than those whose received traditional Chinese acupuncture technique. However, using one of these types still results in an overall decrease in pain assessed by the McGill Short Form Pain Score.[122]

Gua Sha

Gua Sha or *caogio* is a traditional Chinese therapy also known as coining. It is often studied for pain relieving technique to cure back and neck pain.[123-126] It involves press stroking an area of the body with a smooth-edged instrument to intentionally create transient petechiae and ecchymosis. One report suggested its benefit in reliving DN pain. 119 patients were selected for the study; they were divided into two groups with 60 received the Gua Sha treatment and 59 received the normal care. Dropout from both groups was low and did not significantly altered the result. The Toronto Clinical Scoring System (TCSS) was used to assess clinical neuropathy. Clinical neuropathy was determined using TCSS which ranged from a score of 0, indicating no neuropathy and the highest score was 19. The performance sensory function was used to determine the Vibration Perception Threshold. The device used produced vibration amplitudes with the highest representing the worse performance of sensory dysfunction. The ankle brachial index and fasting plasma glucose were also determined for patients with normal values equal to or higher than 0.97 and fasting plasma glucose was 3.9-6.1 mmol / L. After Gua Sha intervention. There were significant differences between the test and control groups. Sha Cave treatment has reduced the symptoms of neuropathy and improved sensory function. It also decreases peripheral artery disease and was effective in controlling the plasma glucose level. It was shown that the therapy seems to increase microperfusion and produces a response against inflammation and protects the immune system by upregulating the heme oxygenase-1, which has both cytoprotective and antinociceptive effects as well as anti-inflammatory and immunoregulatory properties. Animal models proved its effectiveness in the treatment of DN and it seems to reduce the associated pain symptoms with it. Another possible mode of action that is proposed for the Gua Sha therapy is that the skin receptors and nociceptors may possibly be involved in the meditation effects of Gua Sha therapy.[127]

Therapeutic exercises

Moderate exercise is usually recommended for type 2 diabetes patients, especially those with DPN symptoms. The amount of exercise is essential for proper nerve function. Usually, 3 sessions a week each ranging between 90 and 180 min has proved to be effective. High level of physical activity such as exercise enhances the microvascular function in T2DM. Balance with combination of resistance exercises has shown to be effective in improving the impaired balance that is associated with DN and is recommended to be included in the exercise regime as a part of therapy.[128] Meditation and techniques to relax muscles are found to be effective in relieving the pain.[129]

Lifestyle interventions are designed for weight loss intentions with a recommended diet and moderate -intensity aerobic physical activity. The participants were compared with general care group that received general dietary and exercise advice. This lifestyle intervention in DN, an improvement in mobility and the nerve fiber density, was observed in the group that received DN physical activity intervention as compared to standard care intervention group.[130]

Transcutaneous electrical nerve stimulation

Recently, TENS has been used to treat DN pain. To study the potential for increased leg pain in patients with PF, DN, and CN with the use of Trans Cutaneous Magnetic Stimulation (TCMS). Of the 17 patients enrolled in this trial, 14 patients with PF, DN, and CN experienced an increase in pain 24 hours after treatment with a single TCMS treatment without adverse events. A sham treatment arm and duration of response is planned.[131] Simultaneous use of ENS and amitriptyline is found to be beneficial in reducing pain in DN patients. In another study, the experiment patients were treated for approximately 1.7 years with sessions averaging 34 min and lasting 1.9 times a day. The result indicated that about 76% of patients reported great improvement in NP. Another study was performed by German scientists where 19 patients were used as a treatment and that experiment also reported positive results.[132]

Controlling hyperglycemia would logically control the DN. However, one study suggested its effect to be significant in patients with type 1 diabetes and less to no effect on type 2 patients. Bariatric surgery and afterward weight loss also improved the symptoms of DN, but not enough literature is available to establish a relationship between the two.[133]

Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) is a phycological treatment approach, conducted to study the effect of CBT in DN pain. The participants were all over 18 years old and suffering from diagnosed type 2 diabetes with reported chronic neuropathic pain for at least 3 months. A self-assessment scale, West Haven Yale Multidimensional Pain Inventory (WHYMPI), was used to measure the degree of neuropathic pain. The patients were randomly sorted into the group of treatment as usual and CBT. The 4-month follow-up showed that the patients who received CBT recorded a lower pain severity as compared to that of control and this may be an effective treatment in reducing pain that is associated with DNP.[134]

Conclusions

The DN is a common complication experienced with patients suffering from diabetes for a longer time. The pain that results due this DN is discomforting and effects the quality of individual life. There are a number of ways this can be relieved; this includes the use of medical plants or more followed traditional pharmacological paths that include allopathic medicines such as antidepressants, anticonvulsants, or antinociceptive agents. Some of these are FDA approved, whereas other are in clinical trial. The nonpharmacological treatment options are often less discussed and highlighted; however, research indicates that it can be effective; this includes techniques such as Gua Sha, acupuncture, and therapeutic exercises.

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Conflicts of interest

There are no conflicts of interest.

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