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A REVIEW STUDY ON ROLE OF VITAMIN B1, B6, B12 DEFICIENCY CORRECTION IN DIABETIC NEUROPATHY MANAGEMENT

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ABSTRACT
Diabetic neuropathy is a prevalent and debilitating complication of diabetes, characterized by progressive nerve damage that leads to symptoms such as pain, tingling, and numbness, primarily in the extremities. Effective management strategies are crucial for alleviating symptoms and improving quality of life. Recent studies highlight the significance of vitamin B1 (thiamine), B6 (pyridoxine), and B12 (cobalamin) in nerve health, emphasizing their potential role in diabetic neuropathy management. Deficiencies in these vitamins can exacerbate nerve damage due to their involvement in nerve metabolism, myelin synthesis, and neuroprotection. This review explores the mechanisms through which these vitamins contribute to nerve function, examines clinical evidence on the benefits of correcting deficiencies in diabetic patients, and evaluates their use as adjunctive therapies in neuropathy management. By synthesizing data from recent trials and studies, this review underscores the importance of comprehensive vitamin B supplementation as part of a multimodal approach to manage diabetic neuropathy effectively. Further clinical trials are recommended to optimize dosage and combinations for maximizing therapeutic outcomes.

KEYWORDS: Diabetic neuropathy, vitamin B1, thiamine, vitamin B6, pyridoxine, vitamin B12, cobalamin.

INTRODUCTION
Diabetic Neuropathy (DN) refers to a group of nerve disorders that result from damage caused by prolonged or poorly controlled diabetes. It is one of the most common and debilitating complications of diabetes mellitus, and it affects a significant number of individuals with both type 1 and type 2 diabetes. Diabetic neuropathy (DN) can lead to a wide range of symptoms that vary in severity, depending on the nerves affected. These symptoms can include pain, numbness, tingling, and muscle weakness, and in severe cases, it may lead to loss of sensation, deformities, and impaired mobility. Diabetic neuropathy can affect almost every part of the nervous system, including the peripheral nerves, the autonomic nervous system, and the central nervous system, leading to a range of diverse symptoms and complications. Its impact on quality of life is significant, as it can cause chronic pain, functional impairments, and psychological distress. Notably, diabetic neuropathy is one of the leading causes of lower limb amputations, particularly in individuals with advanced or poorly controlled diabetes.

The hallmark of diabetic neuropathy is its gradual progression, often unnoticed in the early stages, which allows for nerve damage to accumulate over time before it is diagnosed.[1] This makes the management of DN particularly challenging, as it can lead to permanent nerve damage if not addressed early on. Early identification and appropriate treatment are crucial in slowing the progression of the disease, alleviating symptoms, and preventing secondary complications like infections, ulcers, and amputations.

EPIDEMIOLOGY
Diabetic neuropathy is a major cause of morbidity among diabetic patients. It is estimated that 25% to 50% of individuals with diabetes will experience some form

of diabetic neuropathy. The prevalence of this condition is higher in patients with long-standing diabetes, especially those who have had the disease for more than 10 years. The risk increases with poor glycemic control, although even those with well-controlled blood sugar may develop neuropathy.

Type 1 diabetes: Diabetic neuropathy often develops after at least 10 years of diabetes, and studies suggest that approximately 50% of individuals with type 1 diabetes may develop some form of neuropathy over their lifetime.

Type 2 diabetes: Diabetic neuropathy is more prevalent in individuals with type 2 diabetes, especially those who have had the condition for many years. Research indicates that between 20% to 40% of patients with type 2 diabetes will develop neuropathy.

The condition is also more common in older adults, with its incidence increasing with age and the duration of diabetes. Additional factors, such as the presence of hypertension, smoking, and obesity, can exacerbate the risk of developing neuropathy.[2]

Causes

Diabetic neuropathy (DN) is a complex complication of diabetes mellitus, resulting from long-term high blood glucose levels that damage the nervous system. Several factors contribute to the development and progression of diabetic neuropathy, primarily involving metabolic, vascular, and inflammatory mechanisms.[3]

Chronic hyperglycemia, or consistently high blood glucose, is the primary cause of diabetic neuropathy. Over time, elevated blood sugar leads to various biochemical processes that directly damage nerves and their supporting structures.

Glucose Toxicity: Chronic high blood glucose leads to the accumulation of glucose within nerve cells. This excess glucose can form advanced glycation end products (AGEs), which bind to nerve cell proteins and disrupt their structure and function, leading to nerve damage.

Polyol Pathway Activation: In high glucose conditions, excess glucose is metabolized via the polyol pathway, leading to the accumulation of sorbitol and fructose. These metabolites attract water into the nerve cells, causing cellular swelling and nerve damage.

Oxidative Stress: High glucose levels lead to increased production of reactive oxygen species (ROS). These free radicals cause oxidative stress, damaging cellular components like lipids, proteins, and DNA, which impairs nerve function.[4]

Inflammation: Chronic hyperglycemia also activates inflammatory pathways in the body. Inflammatory molecules such as cytokines and chemokines contribute to nerve damage by promoting inflammatory responses that interfere with normal nerve function and repair.

Microvascular Damage: Diabetic neuropathy is often accompanied by microvascular damage, which refers to the damage to the tiny blood vessels that supply oxygen and nutrients to the nerves. This damage significantly affects nerve health and can worsen neuropathy, Reduced Blood FlowHigh glucose levels can damage the endothelium (lining of blood vessels), impairing the ability of blood vessels to dilate and constrict properly. This leads to poor circulation, reducing the delivery of oxygen and nutrients to the peripheral nerves, which are highly sensitive to changes in blood supply.[5] Microangiopathy Diabetic microangiopathy refers to the thickening of the walls of small blood vessels, which leads to reduced perfusion to nerve tissue. The poor blood flow results in nerve ischemia (lack of oxygen), which accelerates nerve degeneration. Endothelial Dysfunction Hyperglycemia damages the endothelial cells in small blood vessels, affecting their ability to produce nitric oxide, a vasodilator. This leads to reduced blood flow and nutrient deprivation to nerve cells.[6]

Advanced Glycation End Products (AGEs): AGEs are a direct consequence of chronic hyperglycemia. AGEs form when excess glucose binds non-enzymatically to proteins, lipids, and nucleic acids, creating cross-links that alter the normal function of the affected molecules.AGEs and Nerve DamageAGEs accumulate in various tissues, including the nerves and blood vessels, impairing their normal function. AGEs contribute to oxidative stress, inflammation, and vascular damage, which together accelerate the degeneration of peripheral nerves. And AGEs and InflammationAGEs bind to receptors for advanced glycation end products (RAGEs) on cells, including those in the nervous system. This binding trigger inflammatory signalling pathways that further damage the nerves and worsen the progression of neuropathy.[7]

Inflammation: Chronic inflammation is a key component of diabetic neuropathy. The metabolic disturbances in diabetes, including hyperglycemia and insulin resistance, activate the immune system, leading to persistent inflammation throughout the body, including in the nerves.Pro-Inflammatory Cytokines Elevated blood sugar levels promote the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which play a central role in the development of diabetic neuropathy. Inflammation in the Nervous SystemIn diabetic neuropathy, inflammation in the nerves disrupts normal nerve function. Inflammatory cells, including macrophages, release enzymes and reactive molecules that further damage nerve fibers and interfere with nerve transmission.[8]

Mitochondrial Dysfunction: Mitochondria are the energy powerhouses of cells, including nerve cells. In

diabetes, high blood glucose can impair mitochondrial function, leading to an energy deficit in nerves. Mitochondrial dysfunction contributes toImpaired Nerve Regeneration: Mitochondria are involved in the production of ATP (the energy currency of the cell), and a reduction in their function compromises the ability of nerves to repair and regenerate. This makes nerves more vulnerable to damage and slows the recovery from injuries, Increased Oxidative Stress: Dysfunctional mitochondria generate excess reactive oxygen species (ROS), contributing to oxidative stress. This accelerates the damage to nerve fibres and myelin (the insulating layer around nerves), which impairs nerve function.[9]

Nutritional Deficiencies: People with diabetes, especially those with poorly controlled blood sugar, may experience nutritional deficiencies that contribute to the development of neuropathy. These deficiencies can exacerbate nerve damage. A deficiency in vitamin B12, which is common in individuals with diabetes or those on certain medications (e.g., metformin), can directly lead to nerve damage .and Other B Vitamins Deficiencies in other B vitamins, such as B6 and folate, may also impair nerve function and contribute to the development of diabetic neuropathy.

Genetic Factors: Genetic predisposition plays a role in determining an individual's susceptibility to diabetic neuropathy. Certain genetic factors may make some individuals more vulnerable to nerve damage caused by diabetes. These factors may involveVascular and Inflammatory Pathways: Genetic variants in genes involved in inflammation and vascular function (such as those encoding for RAGE receptors and vascular endothelial growth factor (VEGF)) have been associated with an increased risk of developing diabetic neuropathy, Nerve Regeneration Some genetic variants may influence the ability of nerve cells to repair and regenerate after damage. Defects in genes involved in nerve growth factor (NGF) production can impair nerve recovery, contributing to neuropathy.[10]

Obesity and Insulin Resistance: Obesity and insulin resistance, often present in type 2 diabetes, contribute significantly to the risk of developing diabetic neuropathy. Fatty Acid Toxicity Obesity leads to elevated levels of free fatty acids in the blood, which can damage nerve cells through lipotoxicity. These fatty acids contribute to inflammation and oxidative stress, which exacerbate nerve damage, Insulin resistance (a hallmark of type 2 diabetes) impairs the ability of cells to use glucose properly. This results in higher blood glucose levels, which in turn increase the risk of developing neuropathy through the mechanisms mentioned earlier (e.g., glucose toxicity, AGEs formation).

Smoking: Smoking accelerates the progression of diabetic neuropathy by further impairing blood flow to the nerves and increasing oxidative stress. The harmful substances in tobacco smoke damage blood vessels, contributing to vascular dysfunction and reducing the supply of oxygen and nutrients to the nerves, which worsens the condition.

Alcohol Consumption: Direct Toxicity Alcohol itself can be toxic to nerves, causing alcoholic neuropathy, which can overlap with diabetic neuropathy.[11]

Types of Diabetic Neuropathy

Diabetic neuropathy can be classified into several types, each affecting different parts of the nervous system:

Peripheral Neuropathy (PN): Most Common Form: It affects the nerves in the extremities, such as the feet and hands. Symptoms include Numbness, tingling, burning, or sharp pain, especially at night. In severe cases, this can lead to loss of sensation, making the affected limbs more prone to injury and infection and its Progression Over time, it may lead to foot deformities and ulcers, as the lack of sensation prevents individuals from noticing injuries.

Autonomic Neuropathy (AN): Affects the autonomic nervous system: This system controls involuntary functions like heart rate, digestion, and blood pressure. Symptoms Can include dizziness or fainting upon standing (due to blood pressure instability), gastrointestinal problems (e.g., gastroparesis), urinary problems (e.g., incontinence), and sexual dysfunction. In Severe CasesMay result in cardiovascular issues, such as tachycardia or arrhythmias, and difficulties in regulating blood pressure.[12]

Proximal Neuropathy (Diabetic Amyotrophy): Affects the thigh, hip, or buttock muscles: This form is more common in older adults with type 2 diabetes. Severe pain in the hip, thigh, or buttocks, followed by muscle weakness and atrophy. The Outcome of This condition typically resolves over time, but recovery is slow, and some people may have permanent weakness.

Focal Neuropathy: Sudden onset of nerve damage This type involves sudden, localized damage to a single nerve or a group of nerves. Symptoms may include double vision, pain behind one eye, or sudden weakness in a hand or foot. Prognosis Focal neuropathies often improve over time and may resolve completely within weeks to months.[13]

Symptoms of Diabetic Neuropathy

The symptoms of diabetic neuropathy vary depending on the type of nerve affected, but they commonly include Sensory Symptoms: Numbness Loss of feeling, particularly in the feet or hands, Tingling or "pins and needles" A common early sign and burning or sharp pain. Especially at night, affecting the feet and lower legs. Sensitivity to touch Some patients become hypersensitive to even light touch or clothing. Motor Symptoms include Muscle weakness Difficulty with fine motor skills or walking, Foot deformities Such as

hammertoes or Charcot foot, which are caused by muscle imbalance and loss of sensation. Autonomic Symptoms Dizziness and fainting Due to blood pressure regulation issues. Digestive problems Such as nausea, vomiting, bloating, or diarrhoea. Sexual dysfunction Including erectile dysfunction in men and vaginal dryness in women. Pain is often the most distressing symptom for many individuals with diabetic neuropathy and can be severe and persistent.[14]

Risk Factors

Several factors increase the risk of developing diabetic neuropathy, including Poor Glycemic Control, Chronic high blood glucose is the most significant risk factor. Duration of Diabetes, the longer a person has diabetes, the higher the risk of developing neuropathy. High blood pressure can worsen blood vessel damage. Elevated cholesterol and triglycerides contribute to vascular damage. Smoking accelerates vascular damage and impairs circulation, exacerbating neuropathy. Excess weight increases the risk of metabolic abnormalities that contribute to nerve damage. Older individuals are at higher risk due to the combined effects of aging and long-standing diabetes. Diabetic nephropathy (kidney damage) is often associated with diabetic neuropathy. Genetic predisposition may increase susceptibility to nerve damage.[15]

Role of Vitamin B1, B6, B12

Accumulation of triosephosphates arising from high cytosolic glucose concentrations in hyperglycaemia is one likely or potential trigger for biochemical dysfunction leading to the development of diabetic complications. This may be prevented by disposal of excess triose phosphates via the reductive pentose phosphate pathway. This pathway is impaired in experimental and clinical diabetes by mild thiamine deficiency. The expression and activity of the thiamine-dependent enzyme, transketolase--the pace making enzyme of the reductive pentose phosphate pathway, is consequently decreased. Correction of thiamine deficiency in experimental diabetes by high dose therapy with thiamine and the thiamine monophosphate prodrug, Benfotiamine, restores disposal of triose phosphates by the reductive pentose phosphate pathway in hyperglycaemia. This prevented multiple mechanisms of biochemical dysfunction: activation of protein kinase C, activation of the hexosamine pathway, increased glycation and oxidative stress.[16]

Consequently, the development of incipient diabetic nephropathy, neuropathy and retinopathy were prevented. Both thiamine and Benfotiamine produced other remarkable effects in experimental diabetes: marked reversals of increased diuresis and glycosuria without change in glycaemic status. High dose thiamine also corrected dyslipidaemia in experimental diabetes--normalizing cholesterol and triglycerides. Dysfunction of beta-cells and impaired glucose tolerance in thiamine deficiency and suggestion of a link of impaired glucose tolerance with dietary thiamine indicates that thiamine therapy may have a future role in prevention of type 2 diabetes. More immediately, given the emerging multiple benefits of thiamine repletion, even mild thiamine deficiency in diabetes should be avoided and thiamine supplementation to high dose should be considered as adjunct nutritional therapy to prevent dyslipidaemia and the development of vascular complications in clinical diabetes.

Mechanisms of Action

Impaired Energy Metabolism Thiamine deficiency leads to reduced activity of key enzymes involved in glucose metabolism, such as pyruvate dehydrogenase. In diabetes, where glucose metabolism is already impaired, thiamine deficiency may further compromise nerve function by reducing the energy available to neurons, making them more susceptible to damage. Accumulation of Toxic Metabolites: Reduced thiamine levels result in an accumulation of advanced glycation end-products (AGEs) and other toxic metabolites in the nervous system. AGEs contribute to oxidative stress and inflammatory processes that damage peripheral nerves. Oxidative Stress and Inflammation Thiamine deficiency increases oxidative stress by impairing the pentose phosphate pathway, which is essential for the production of NADPH, a cofactor necessary for antioxidant defence mechanisms. The resultant oxidative damage can lead to nerve injury, demyelination, and pain. Nerve Conduction and Myelin Sheath Damage: Thiamine is involved in maintaining the integrity of the myelin sheath, which is crucial for the proper functioning of nerve fibres. Thiamine deficiency impairs myelin production and repair, leading to nerve conduction abnormalities and the symptoms of diabetic neuropathy.

Clinical Evidence

- Clinical studies have shown that thiamine supplementation in diabetic patients with neuropathy can improve symptoms like numbness, pain, and nerve conduction speed. For instance, a study published in Diabetes Care demonstrated that high-dose thiamine supplementation significantly improved nerve function and reduced neuropathic pain in patients with thiamine deficiency.

Role of vitamin b6 in diabetic neuropathy

Vitamin B6, or pyridoxine, plays several important roles in the body that can be particularly relevant for individuals with diabetic neuropathy. Nerve Function Vitamin B6 is crucial for the synthesis of neurotransmitters, which are essential for proper nerve function. This can help alleviate some symptoms of neuropathy. Glucose Metabolism It assists in glucose metabolism and can help maintain stable blood sugar levels. This is vital for managing diabetes and potentially reducing the risk of neuropathy progression. Anti-inflammatory Effects Vitamin B6 has anti-inflammatory properties that may help reduce inflammation associated with diabetic complications, including neuropathy.

Antioxidant Role It contributes to the body's antioxidant defence system, which can protect nerves from oxidative stress and damage often seen in diabetes. Deficiency Considerations Deficiency in vitamin B6 can lead to peripheral neuropathy symptoms. Ensuring adequate intake may help manage or prevent these symptoms in those with diabetes.

Mechanisms of Action

Neurological Impairment Vitamin B6 is essential for the synthesis of neurotransmitters and the maintenance of normal nerve function. A deficiency in B6 can impair the transmission of nerve signals, contributing to the symptoms of neuropathy, such as pain, tingling, and numbness. Homocysteine and Vascular Damage Pyridoxine is involved in the metabolism of homocysteine, an amino acid whose elevated levels have been associated with increased risk of cardiovascular disease and nerve damage. In diabetes, elevated homocysteine levels may exacerbate endothelial dysfunction, impair blood flow to the nerves, and accelerate nerve degeneration. Oxidative Stress Like thiamine, vitamin B6 plays a role in the reduction of oxidative stress. Deficiency of B6 may enhance the generation of free radicals, which can damage nerve cells, myelin, and blood vessels, worsening the progression of neuropathy. Myelin Production and Nerve Regeneration Vitamin B6 is involved in the biosynthesis of myelin and the regeneration of damaged nerves. Deficiency of B6 can impair nerve repair processes, leading to persistent neuropathic symptoms.

Clinical Evidence

- Pyridoxine supplementation has been shown to reduce neuropathic symptoms in diabetic patients, particularly in those with low levels of the vitamin. For example, a study in *Diabetologia* found that B6 supplementation improved sensory function and reduced pain in patients with diabetic neuropathy.

Role of vitamin b12 in diabetic neuropathy

Cobalamin often known as vitamin B12, plays a vital role in the general metabolic processes and nerve health of people with diabetic neuropathy. The following are some salient points Nerve Health The protective covering around nerves called myelin depends on vitamin B12. A deficit can worsen neuropathy symptoms and cause damage to the nerves. Formation of Red Blood Cells It is essential for the synthesis of red blood cells. For total nerve health, proper oxygenation of tissues, including nerves, is essential. Homocysteine Regulation: Vitamin B12 has a role in the regulation of homocysteine levels, an amino acid that, at high levels, can aggravate cardiovascular disease and cause nerve damage. Reduced homocysteine levels have been linked to a lower risk of neuropathy. Neurological Function Enough B12 is needed to facilitate the manufacture of neurotransmitters, which are essential for nerve-to-nerve communication. This may help lessen diabetic neuropathy symptoms. Deficiency Symptoms Neuropathy symptoms like tingling and numbness can be mistaken for or made worse by a vitamin B12 deficiency. It's crucial to keep an eye on B12 levels, particularly for people following certain diets or using drugs that may interfere with absorption.

Mechanisms of Action

Myelin Synthesis and Nerve Conduction Vitamin B12 is critical for the production and maintenance of myelin, the insulating layer around nerve fibres. B12 deficiency disrupts myelin synthesis, leading to demyelination and nerve conduction abnormalities, which are central to the development of diabetic neuropathy. Homocysteine Metabolism Like vitamin B6, vitamin B12 is involved in the conversion of homocysteine to methionine. Elevated homocysteine levels due to B12 deficiency can lead to vascular damage, impaired nerve function, and increased oxidative stress, all of which contribute to neuropathy. Nerve Regeneration and Repair Vitamin B12 has been shown to play a role in nerve repair and regeneration. In the context of diabetic neuropathy, B12 deficiency may impair the ability of damaged nerves to regenerate, leading to more severe and persistent neuropathic symptoms.

Oxidative Stress and Inflammation B12 deficiency can exacerbate oxidative stress and inflammation, both of which are implicated in the pathogenesis of diabetic neuropathy. Reduced B12 levels may also impair the function of enzymes involved in cellular defence against oxidative damage.

Clinical Evidence

B12 deficiency is common in diabetic patients, especially those using metformin**,** which can impair vitamin B12 absorption. Supplementation with B12 in patients with diabetic neuropathy has been shown to improve nerve conduction and reduce symptoms such as pain, tingling, and numbness. A study in *The Journal of Neurology* found that B12 supplementation in diabetic patients with peripheral neuropathy significantly improved nerve conduction velocities and reduced neuropathic pain.

Vitamin C in Diabetic Neuropathy

Vitamin C, or ascorbic acid, is a powerful antioxidant that helps to mitigate oxidative stress and inflammation—two key contributors to the development and progression of diabetic neuropathy. In diabetic patients, chronic hyperglycaemia leads to increased formation of advanced glycation end-products (AGEs), which can exacerbate oxidative damage to nerve tissues. Vitamin C's role in neutralizing reactive oxygen species (ROS) and its potential to protect endothelial cells and nerves from damage make it a promising candidate for mitigating the damage caused by diabetes.

Mechanisms of Action

Antioxidant Properties Vitamin C scavenges free radicals, thereby reducing oxidative stress in peripheral nerves. Collagen Synthesis It is essential for the synthesis of collagen, a major structural protein in blood vessels. This can improve blood flow to nerve tissues, which may be impaired in diabetic patients. Neuroprotective Effects Vitamin C has been shown to have neuroprotective effects, potentially reducing nerve inflammation and improving nerve conduction velocity.

Clinical Evidence

Several studies have indicated that Vitamin C supplementation may improve symptoms of diabetic neuropathy, including reducing pain and enhancing nerve function. For instance, a study published in *Diabetes Care* found that high-dose Vitamin C supplementation led to a significant reduction in neuropathic pain and improved sensory function in patients with diabetic peripheral neuropathy (DPN). However, results have been mixed, and further studies with larger sample sizes and standardized dosing regimens are needed to establish the efficacy of Vitamin C supplementation in diabetic neuropathy.

Vitamin D in Diabetic Neuropathy

Vitamin D, a fat-soluble vitamin, is essential for maintaining calcium and phosphorus homeostasis, bone health, and immune system function. Increasing evidence suggests that Vitamin D deficiency is common in individuals with diabetes and may contribute to the development and progression of diabetic neuropathy. Vitamin D receptors are present on various tissues, including neurons and glial cells, and it is believed to influence neurogenesis, inflammation, and oxidative stress.

Mechanisms of Action

Neuroprotective Effects Vitamin D plays a role in neuroprotection by modulating the immune system and reducing inflammation, which is crucial in preventing nerve damage in diabetic neuropathy. Regulation of Calcium Vitamin D is involved in regulating calcium levels, which is essential for nerve function. Calcium dysregulation is a known contributor to neuropathic pain. Improvement of Nerve Function Vitamin D receptors in the peripheral nervous system suggest that Vitamin D may directly influence nerve health, improving nerve conduction and regeneration.

Clinical Evidence

A number of studies have shown that Vitamin D deficiency is prevalent in individuals with diabetic neuropathy and that correcting this deficiency can lead to improvements in symptoms. For instance, a study published in *The Journal of Clinical Endocrinology & Metabolism* demonstrated that Vitamin D supplementation improved nerve conduction velocity in diabetic patients with neuropathy. Another trial in *Diabetologia* showed that Vitamin D levels were inversely correlated with the severity of diabetic neuropathy, and patients with low Vitamin D levels were more likely to experience painful neuropathic symptoms.

Vitamin D and Pain Management: Several studies have suggested that Vitamin D supplementation may have an analgesic effect in diabetic neuropathy, particularly in reducing neuropathic pain. This is likely due to the vitamin's role in modulating inflammatory pathways, which are implicated in the pathogenesis of neuropathic pain. Potential Mechanisms Linking Vitamin Deficiency to Diabetic Neuropathy Oxidative Stress and Inflammation Both Vitamin C and D have antioxidant and anti-inflammatory properties, which could counteract the oxidative stress and inflammation that play a central role in the development of diabetic neuropathy.

Vascular Health Vitamin C's role in collagen synthesis and Vitamin D's regulation of calcium homeostasis may help improve vascular health and blood flow to the nerves, mitigating the ischemic damage often seen in diabetic neuropathy. Neurotrophic Support Both vitamins support the function and regeneration of nerve tissues, with Vitamin D potentially influencing the production of nerve growth factors.[17]

DISCUSSION

Brandon Goodwin*et*, al, (2023), Topical Capsaicin for the Management of Painful Diabetic Neuropathy: A Narrative Systematic Review, Painful diabetic neuropathy (DPN) is a serious and common problem affecting those suffering from diabetes. Current treatments of DPN include medications that act on the CNS, rather than the distally affected nerves. Topical capsaicin patches and creams offer potential as alternative treatments to centrally acting neuropathy medications. Topical capsaicin depletes the neurotransmitter for pain signalling at the distally affected nerves. Topical capsaicin in all formulations has been shown to be beneficial in reduction of DPN. However, capsaicin treatments are often irritating to the skin, causing burning and redness at the application site. Topical capsaicin treatments are a potentially beneficial peripherally acting medication. Further research is needed to determine the best means of ameliorating the side effects of treatments. Faisal K. Alkholif *et*, al, (2023) Diabetic neuropathy (DN) is an important risk of hyperglycaemia that damages nerves and causes severe disease, affecting patients' quality of life with symptoms such as tingling of the limb, numbness, muscle weakness, digestive issues (e.g., diarrhoea or constipation), and UTI. Regular glucose monitoring and check-ups can prevent DN in diabetics. DN is a prevalent complication observed in almost 40% of individuals with poorly managed diabetes. Through an exemplary in vivo investigation, diligent researchers have brought to light captivating revelations about the intrinsic capabilities of this molecule. The remarkable findings not only confirm its efficacy but also reveal that it has extraordinary

potential to alleviate some of the most pressing factors associated with diabetes, including hyperglycaemia, oxidative stress, and inflammatory pathways such as NF-κB. These fundamental elements frequently aggravate diabetic complications, elevating this discovery above all others as a groundbreaking development with immense implications for people struggling with this incapacitating ailment. The findings of this study reveal a fascinating connection between Berberine and Tocopherol, demonstrating their ability to significantly impede the advancement of diabetic neuropathy. By skilfully controlling hyperglycaemia levels while simultaneously suppressing inflammation induced by numerous agents such as NF-κB, these two compounds seem to have immense potential to aid in holistic management for diabetes patients. The implications are vast and encourage further research on how these components can become indispensable targets when dealing with diabetes treatment in a comprehensive way.[18]

Kassim SA. Al-Neaimy*et*, al, (2023) The Role of Vitamins B Complex in the Management of Diabetic Peripheral Neuropathy: a Electrophysiological Study, Diabetic peripheral neuropathy (DPNP) is a complication of both type I and type II diabetes mellitus and is the most common diabetic neuropathy, expected to be in 47% of diabetics patients when diagnosed by nerve conductive study. It has been estimated that at least half of patients with DM will develop DPNP in their life, and almost 20% presenting with neuropathic-related pains. The most frequent peripheral neuropathy in diabetes individuals is distal symmetrical polyneuropathy (DSPN). Diagnosis is challenging due to the wide variety of presentations and the fact that over 50% of diabetic peripheral neuropathies have no symptoms. The present study demonstrated that vitamin B complex has a beneficial effect on mild and moderate cases of patients with peripheral diabetic neuropathy, and can be used as an adjunct therapy. Sever cases failed to show improvement using these techniques, alternatively better clinical symptoms could be noticed by clinicians rather than this diagnostic technique.

Kezheng Li *et*, al, (2023)**,** How vitamins act as novel agents for ameliorating diabetic peripheral neuropathy: A comprehensive overview, Diabetes mellitus, a potent metabolic disorder with a skyrocketing prevalence, affects more than half of its sufferers through diabetic peripheral neuropathy (DPN). DPN typically presents as a constellation of symptoms including pain, numbness, tingling, weakness, and impaired balance, and is the most frequent complication of diabetes. The mortality rate associated with DPN escalates due to secondary factors such as diabetic foot ulcers and neuropathic pain. Vitamins hold promise for the treatment of DPN, a debilitating complication of diabetes that results in nerve damage and sensory deficits. As low-cost, widely accessible, and safe substances, vitamins could also help decrease the healthcare costs of patients with DPN. Hence, the exploration of vitamin therapy for DPN is of paramount importance.

Narmin S. Essa *et*, al, (2023) Diabetic neuropathy (DN) is one of the most common and upsetting chronic complication of diabetes mellitus (DM) . It is defined as the presence of signs and symptoms that are suggestive of neuropathy in diabetic patients, after excluding other possible causes of nerve damage. Diabetic neuropathy is classified into two broad classes according to the site and intensity of nerve damage into symmetric (diffuse) and asymmetric (focal) neuropathy. Although neurotropic B vitamins have shown promising effects by improving the symptoms of DN patients and neurophysiological parameters. Furthermore, these vitamins and/or their derivatives had well-illustrated disease-modifying mechanisms on DN. However, large RCTs are needed to approve their use in DN and to be included in national and international guidelines. This was hindered by the fact that vitamins are non-patentable and therefore fewer funds would be allocated for large RCTs furthermore, the manufacturers of dietary supplements distinguish a positive phase 2 trial results as satisfactory to encourage their product marketing without going further to phase 3 trial with its highly costly procedure.

Portia Keabetswe Lekhanya *et*, al, (2023) Exploring the effectiveness of vitamin B12 complex and alpha-lipoic acid as a treatment for diabetes mellitus/ neuropathy: a protocol for systematic review and meta-analysis of randomised controlled trials, Diabetic neuropathy (DN) is a heterogeneous type of nerve damage associated with diabetes mellitus (DM), the condition most often damages nerves in the legs and feet. It presents both clinically and subclinically affecting the peripheral nervous system due to an increase in glucose concentration which interferes with nerve signalling. Following the discovery of insulin as a treatment for DM, the prevalence of DN has since increased significantly due to patients with DM having a longer life expectancy. It has been estimated that at least 50% of patients with DM will develop DN in their life, with approximately 20% experiencing neuropathic-related pains. Nerves are susceptible to changes in glucose concentrations, and insulin treatment makes it impossible for neurons to continue regulating glucose uptake. For many years, vitamin B12 and alpha-lipoic acid (ALA) have been regarded as components that reduce pain and oxidative stress. Vitamin B12 is essential in the metabolism of essential fatty acids involved in the maintenance of nerve myelin and direct scavenging of reactive oxygen species (ROS). This systematic review and meta-analysis focus on vitamin B12 and ALA as monotherapy or dual treatments in DM/DN. These components have shown properties that decrease oxidative stress and increase nerve myelination. A previous meta-analysis assessing the effect of ALA on lipid profiles revealed a significant decrease in lipid profiles; however, this was conducted in patients with various conditions, including diabetes, schizophrenia,

obesity, renal disease and hyperthyroidism. So, there is a need for evaluation of the effects of both ALA and vitamin B12 on lipid profile, glycaemia and inflammation in DM.

Raman Muhamad*et*, al, (2023) Polyneuropathy (PN) is a common neurological disorder that affects the peripheral nervous system. It encompasses a wide spectrum of clinical syndromes, depending on the anatomic regions of the peripheral nervous system that are affected. Patients may present with symptoms such as paresthesia, hypesthesia, weakness, atrophies, reduced or diminished reflexes, and pain. The prevalence of PN is estimated to exceed 5% of the general population older than 50 years of age, with higher rates among older adults and those with underlying medical conditions. Many studies have suggested a subjective improvement of neuropathy symptoms in patients suffering from PN of various etiologies after receiving B6 supplementation. In none of those studies, however, has B6 been administered as a monotherapy but as part of a combination treatment, usually with other vitamins. Therefore, the potential therapeutic role of B6 cannot be confirmed to date. In contrast, supplementation of B6 vitamins, even as part of a nutritional multivitamin supplement, has not proven to be harmful at permitted daily doses in patients who already suffer from PN.

S. Batulwar*et*, al, (2023), Individuals Diagnosed with Type 2 Diabetes Mellitus and the Status of Vitamin B12 Deficiency: A Review, Vitamin B12, also referred to as cobalamin, is a hydrophilic vitamin crucial for the synthesis of DNA, blood cell formation, and neurological functions. Individuals with insufficient B12 intake might need supplements, and signs of deficiency include headaches and fatigue. Despite B12 being stored in the liver for up to five years, inadequate dietary support can lead to depletion over time. Peripheral neuropathy affects more than half of diabetic individuals, elevating the risk of significant complications such as changes in productivity, infections, fractures, amputations, leg ulcers, and increased healthcare utilization. The physiological impacts of vitamin B12 are manifested through two biochemical processes: the methylation process, converting homocysteine into methionine, and the transformation of succinyl-coenzyme A (CoA) from methyl malonyl-coenzyme A (CoA) . A biochemical process is defined as a sequence of chemical reactions that occur within living organisms, driving essential functions such as metabolism, growth, and reproduction. Methylation is a biochemical process where a methyl group (CH3) is added to a molecule, often affecting its function or activity. Metformin's potential to induce vitamin B12 deficiency stems from its ability to diminish the absorption of the intrinsic factor (IF) complex via the enteral cubilin receptor in the terminal ileum. This deficiency can lead to various complications, including nerve damage in the extremities, dysfunction of the autonomic nervous system related to the heart, symptoms affecting the brain and nerves, or blood-related disorders. A specific concern involves the emergence or exacerbation of cardiac autonomic neuropathy, which is associated with a higher risk of cardiac irregularities, heart-related incidents, and mortality. Consequently, individuals using metformin are advised to receive yearly evaluations for vitamin B12 insufficiency. If a deficiency is identified, immediate replacement therapy with intramuscular vitamin B12 is advised to replenish the body's stores of the vitamin.

Stephanie Farah*et*, al, (2022), A systematic review on the efficacy of vitamin B supplementation on diabetic peripheral neuropathy, Diabetic peripheral neuropathy (DPN) is a common complication. To re-evaluate the role of vitamin B supplementation on reducing the signs and symptoms of DPN. Electronic databases such as PubMed, Cochrane Library, and Medline. An Excel spreadsheet was used to report the extracted relevant data. Fourteen randomized controlled trials were selected, comprising a pooled sample of 997 study subjects. Unlike the fibular nerve, the electromyographic motor outcomes of the tibial nerve were in favor of vitamin B supplementation. vitamin B supplementation could improve many symptoms and signs of DPN.

Zsuzsanna Putz *et*, al, (2022)**,** Vitamin D in the Prevention and Treatment of Diabetic Neuropathy, Vitamin D is a secosteroid that differs from most other “vitamins” as it is also synthesized in the body by the skin, kidney, and liver and, in small quantities, is essential for life. There is a wealth of evidence on the various effects of vitamin D other than its known influence on calcium metabolism.1 Studies have reported that vitamin D deficiency may be associated with cardiovascular disease, tumors, and autoimmune diseases, and might play a role in the development of diabetes and neurodegenerative diseases. Vitamin D therapy could be a reliable option for treating patients with diabetic complications; however, further studies are needed to confirm these notions.

Amerta Bai *et*, al, (2021)**,** The Role of Vitamin C in Reducing Pain Associated With Diabetic Neuropathy, Neuropathic pain is a painful condition that arises after a lesion or an insult to the somatosensory nervous system, either in the central or peripheral location. It affects 7%-10% of the general population, producing a spontaneous ongoing shooting or an evoked pain after a noxious or non-noxious stimulus. It is a broad term that includes various types, such as diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, cancer-related neuropathy, and post-stroke pain . Neuropathic pain may be characterized by hyperesthesia, paresthesia, spontaneous ongoing pain, dysesthesia, hyperalgesia, electric shock-like sensations, allodynia, or mechanical and thermal hypersensitivity. Patients usually have abnormal sensations or hypersensitivity in the affected area. Vitamin C plays a synergistic role in reducing pain in patients with diabetic neuropathy. It improves QOL due to its analgesic properties. Moreover, it is cost-

effective and appears to be a safe and adjuvant therapy for specific pain relief. Patients should be encouraged to take vitamin C along with pharmacological management to get maximum relief from pain.

Camelia Oana Iatcu*et*, al, (2021)**,** Gut Microbiota and Complications of Type-2 Diabetes, The gut microbiota is a complex ecosystem made up of a community of microorganisms that include trillions of bacteria spanning at least 1000 different species. The gut microbiota is predominantly composed of bacteria but also contains other commensals such as archaea, viruses, fungi and protists. All of these components are both relevant and important in understanding the relationship between the gut microbiota and the host. Dysbiosis of the gut microbiota is primarily characterized by decreased diversity and abundance of bacteria and fungi, especially those associated with dysfunction and various pathologies. Chief among them are cardiovascular, neuronal, immune and metabolic disorders through the influence of bile acid metabolism, inflammatory status, insulin resistance and incretin secretion. While to date the list of bacteria reported to affect several parameters characteristic of diabetes complications is steadily increasing, very few have been studied as therapeutic approaches in these pathologies. Likewise, efforts should be dedicated toward identification of bacteria signatures and metabolites that will allow early detection of disease risks, and the mechanisms involved, making possible to personalize therapeutic intervention based on individual's needs, stage and particularities of the disease. Therefore, modulation of the gut microbiota through prebiotics, probiotics, synbiotics or fecal microbiota transfer may have beneficial effects in the management of diabetes and associated complications; however, further research involving human trials should be high on the list.

Tina Okdahl *et*, al, (2021), Molecular Aspects in the Potential of Vitamins and Supplements for Treating Diabetic Neuropathy, The incidence of people diagnosed with diabetes worldwide is escalating. Meanwhile, treatment has improved, thus leading to longer life expectancies for affected individuals. Accordingly, the presence of long-term diabetes and macro and microvascular complications is increasing. Currently, it is considered as one of the most important public health issues, as these complications cause negative impact on the individual quality of life and increase socioeconomic expenditure. Among the microvascular complications, polyneuropathy affects up to 50% of adults with long-term type 1 and type 2 diabetes. The pathogenesis is complex and multifactorial and includes immune-mediated, inflammatory, vascular, and metabolic pathways. The role of vitamins and supplements as possible therapy options for DSPN prevention or even reversal has shown promising results in several clinical studies. Further validation in high-quality randomized controlled trials is encouraged. Moreover, research regarding optimal initiation of intervention, duration, dose, and route of administration is warranted.

Triantafyllos Didangelos*et*, al, (2021)**,** Vitamin B12 Supplementation in Diabetic Neuropathy: A 1-Year, Randomized, Double-Blind, Placebo-Controlled Trial, Diabetic neuropathy (DN) is one of the most common microvascular complications of diabetes. Its most prevalent forms are peripheral (DPN), autonomic (DAN, with the most commonly diagnosed form being cardiovascular autonomic neuropathy (CAN). At the time of diagnosis of diabetes, 10–18% of patients present with nerve damage, but neuropathy has also been shown to occur even in prediabetes. Peripheral/distal symmetric polyneuropathy may develop in up to 50% of patients can cause sensory symptoms and is associated with foot infections, ulcers, Charcot arthropathy, fractures, and amputations. The prevalence of CAN is around 7% by the time of type 2 diabetes (DM2) diagnosis and increases with increasing diabetes duration by 4.6% to 6% per year as well as to up to 65% of patients with longer durations of diabetes. This study showed that the increase of B12 levels with an oral dispersible tablet containing 1000 µg methylcobalamin for 12 months in patients with DN improved the patients' neurophysiological parameters, sudomotor function, pain score, and QoL. Future studies will need to address still open questions, such as whether in the absence of B12 deficiency supplementation with the vitamin has any effects on established DN, whether B12 administration has favorable effects on the prevention of DN or the prevention of deterioration of subclinical DN, and which forms of DN are mostly improved by B12 supplementation.[19]

Yang Ou *et*, al, (2021)**,** Association of Diabetic Peripheral Neuropathy with Vitamin D Levels Depends on Vitamin D Status, Many disorders have been confirmed to be associated with vitamin D, such as cardiovascular diseases, metabolic syndrome, cancer, autoimmune diseases, and Alzheimer's disease. Vitamin D insufficiency (VDI) is common in diabetic patients. Several studies have showed that adequate vitamin D intake can prevent or delay the onset of diabetes and reduce complications in diabetic patients. Neuropathy is the most common chronic complication of diabetes; about 50% of diabetic patients have various types of neuropathies Approximately 50% of patients with diabetic neuropathy (DN) experience some degree of neuropathic pain. Diabetic peripheral neuropathy (DPN) is an important cause of non-traumatic foot ulcers and amputations, and also contributes to recurrent hospitalizations, injuries, and decreased quality of life. Relative vitamin D levels in different vitamin D states were reversely correlated with symptoms of DPN. Relatively higher vitamin D levels are associated with neurological symptoms in VDI diabetes mellitus patients. We should consider that vitamin D supplementation may lead to increased neurological symptoms in diabetic patients with VDI; however, if VDI is corrected to

sufficient levels, this risk of increased neurological symptoms may no longer exist.

Aylin Sari*et*, al, (2020), Does Vitamin D Affect Diabetic Neuropathic Pain and Balance? Diabetic neuropathy (DN) is a very common long-term complication of diabetes mellitus (DM) that affects approximately 50% patients with DM and is associated with a significant reduction in the quality of life of patients. DN may induce several symptoms, such as foot and hand muscle weakness, balance disturbance, and neuropathic pain including alterations in touch, pain, or heat sensations; burning; pins and needles; tingling; or numbness. DN involves both small and larger nerve fibers. The small nerve fibers include C-fibers associated with electric shock or burning symptoms. Pathological changes in these fibers cannot be detected by performing EMG. Involvement of the large nerve fibers may impair balance because of their effect on deep senses and can be determined by performing EMG. Vitamin D replacement therapy reduced neuropathic pain and improved balance in patients with DN. However, further studies examining the effects of vitamin D on nerve cells at molecular and electrophysiological levels and prospective studies focusing on the long-term effects of vitamin D replacement therapy on DN are warranted. However, the results of the present study suggest that a vitamin D replacement schedule might be planned in addition to antidiabetic treatment to address vitamin D deficiency in patients with diabetes in order to resolve neuropathic pain symptoms and to alleviate balance impairment associated with DN.

Johannes Stein *et*, al, (2020)**,** Association between neuropathy and B-vitamins: A systematic review and meta-analysis Peripheral neuropathy (PN) is generalized nerve damage of the peripheral nerve system, The age-standardized prevalence of PN in the general population is 9.4%. The etiology of PN is not well characterized. Approximately 31% of patients with PN have diabetes and 46%of neuropathies are idiopathic. Vitamin B12 deficiency causes spinal cord lesion or subacute combined degeneration where a demyelination process leads to decay of the myelin sheath in the dorsal and lateral columns. In older patients with Parkinson's disease, neuropathy could be due to levodopa (L-dopa) treatment that causes vitamin B12 deficiency. Also, toxins such as alcohol and viral infections are associated with vitamin B12 deficiency and neuropathy. Thus, vitamin B12 deficiency could be causally related to PN. The mechanisms could in-volve hypomethylation, phospholipid metabolism, and neurotoxic effects of homocysteine found that neuropathy was associated with lowered vitamin B12 status as indicated by plasma vitamin B12, MMA, and Homocysteine. The associations between neuropathy and vitamin B1 and B6 deficiencies were inconclusive. Treatment of neuropathy is a challenge. The association between vitamin B1 and B12status and neuropathy symptoms or improvement after treatment suggests that treating nutritional deficiencies should be part of the healthcare management of neuropathy and all morbidities associated with high risk of neuropathy.[20]

Thomas Julian *et*, al, (2020)**,** According to the International Association for the Study of Pain (IASP), neuropathic pain is pain caused by a lesion or disease of the somatosensory nervous system. This description applies to a highly heterogeneous spectrum of pain syndromes presenting with a broad range of signs and symptoms, with various underlying pathophysiological mechanisms. Neuropathic pain can be central or peripheral in origin. Aetiologies of primarily neuropathic pain include peripheral pathologies such as chronic alcohol consumption, cancer, drug toxicity, diabetes mellitus, herpes zoster infection, traumatic nerve injuries, as well as central processes including cerebrovascular accidents, multiple sclerosis and spinal cord injuries.A meta-analysis could not be conducted as the studies were too heterogeneous in numerous regards including therapy doses, regimens and route of administration, means of assessing pain, and variety of neuropathic conditions assessed. In addition, many studies used combination regimens often with gabapentinoids and other B vitamins which decreases the certainty with which B12 itself can be assessed. Surprisingly, none of the articles identified in our literature search described central neuropathic pain syndromes, which highlights an area for future research. A significant number of studies did not clearly report adverse events caused directly by B12. For the most part, the included studies in this review have not measured the patents serum B12 level, which is a variable that needs to be checked or adjusted for in future studies. Finally, many studies had a short follow-up duration and, therefore, we were not able to comment on the long-term effects of B12 therapy.

Triantafyllos Didangelos *et*, al, (2020), Efficacy and Safety of the Combination of Superoxide Dismutase, Alpha Lipoic Acid, Vitamin B12, and Carnitine for 12 Months in Patients with Diabetic Neuropathy, One of the most common and costly microvascular complications of diabetes mellitus (DM) is diabetic neuropathy (DN), which, of note, is usually underdiagnosed and undertreated in every day clinical practice. The most common forms of DN are diabetic distal symmetrical sensorimotor polyneuropathy (DPN) and diabetic autonomic neuropathy (DAN). At least 50% of patients Nutrients with Diabetes Mellitus Type 2 (DMT2) and up to 59% of DM type 1 develop DPN, whereas Diabetic Cardiovascular Autonomic neuropathy (DCAN) has a prevalence ranging from 2.5 to 50%. DCAN and DPN are major risk factors for foot ulcers, amputation, and cardiovascular dysfunction. Approximately 30% of patients develop the so-called Painful Diabetic Neuropathy (PDN) with neuropathic pain and symptoms like burning, needles, cold, or heat cramps, electric shock, weakness, and allodynia., in the present study, the administration of the combination of the four elements in one tablet for 12 months in patients with DMT2 resulted

in an improvement in all indices of peripheral neuropathy including neurophysiological parameters, pain, and quality of life, except CARTS and MNSIE, whereas in the placebo group, a deterioration of parasympathetic function was noted.

Pijun Yan *et*, al, (2020), Changes of circulating neuregulin 4 and its relationship with 25-hydroxy vitamin D and other diabetic vascular complications in patients with diabetic peripheral neuropathy, Diabetic peripheral neuropathy (DPN), one of the most common diabetic microvascular complications, is characterized by numbness, pain, weakness and loss of sensation in your hands, feet, or legs associated with peripheral nerve dysfunction. DPN develops quite early during the disease, reaching at least 10–15% and possibly affecting around 50% of all diabetes patients as diabetes duration increases. DPN is a major risk factor for foot ulcers and amputations, resulting in depression, lower life quality, limited mobility, social dysfunction, potential morbidity and mortality, and a huge economic burden. The present study showed that circulating Nrg4 level significantly decreased in nT2DM patients with DPN, and was independently and negatively correlated with the risk of DPN development. Moreover, circulating Nrg4 levels were independently associated with 25(OH)D, but showed no associations with other diabetic microvascular complications [21]. These findings suggest that decreased circulating Nrg4 may trigger the development of DPN through its close interaction with 25(OH)D not with other diabetic vascular complications. However, our findings need to be confirmed by more well-designed prospective studies.

CONCLUSION

The correction of vitamin B1, B6, and B12 deficiencies plays a significant role in the management of diabetic neuropathy, offering a promising adjunctive strategy to conventional treatment approaches. These vitamins are crucial for nerve health due to their involvement in key processes such as nerve metabolism, myelin synthesis, and neuroprotection. Evidence from clinical studies suggests that supplementing these vitamins can help mitigate symptoms, improve nerve function, and potentially slow the progression of neuropathy in diabetic patients. Incorporating vitamin B supplementation into comprehensive treatment plans may enhance overall therapeutic outcomes and improve patient quality of life. However, further research is needed to establish optimal dosages, combinations, and long-term efficacy. Continued exploration and well-designed clinical trials will be essential in refining guidelines for integrating vitamin B therapy into routine diabetic neuropathy management.

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