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Vitamins Supplementation for Nerve Regeneration: A Systematic Review of Clinical Evidence

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Abstract

This systematic review investigates the role of vitamin supplementation on nerve regeneration, a vital process to restore nerve structure and function after injury, focusing on the clinical potential of vitamins B, D and E in supporting repair in central and peripheral nervous systems. Traumatic injuries, chronic diseases, and degenerative conditions are common conditions that can disturb the natural repair capacity of neurons. This review follows PRISMA guidelines, which included a thorough search of the literature using electronic databases such as PubMed, Elsevier and Cochrane databases that focused on human subjects with neuropathic disorders. Nine studies were subsequently included in this review. The risk of bias was identified using a variety of tools chosen based on the study design. A total of 313 participants were involved, with 63 reporting sensory changes following post-operative inferior alveolar nerve (IAN) damage, 33 participants were diagnosed with neuropathy, 40 post-surgery nuclear cataract patients, 27 had vitamin B deficiency, 60 experienced rheumatoid arthritis and neuropathic pain and 30 had Friedreich's ataxia. The results indicated that vitamins B, D and E have different mechanisms to support the recovery process of neurons after injury. B vitamins (B1, B6 and B12) enhance nerve cell metabolism and myelin formation, while vitamin D supports neuroprotection and repair by regulating the transcription process of growth factors and several neurotropic proteins, and also has anti-inflammatory effects, and vitamin E mitigates oxidative stress, protecting nerve cells and promoting structural integrity during repair. Despite the promising results, this review highlights the current clinical guidelines predominantly recommend only vitamin B12 for neuropathy management, indicating a need for further research into the therapeutic potential of other vitamins and diseases before its application on the clinical setting.

Keywords: Vitamins, Supplementation, Neuroregeneration, Neuroprotection, Myelin regeneration

Introduction

Nerve regeneration or neuroregeneration is the regrowth of neural structures, including new neurons, axons, synapses and glial cells [1,2]. It is a crucial process for repairing the neural structure and restoring function after nerve damage or degeneration, both in the central and peripheral nervous systems. In a healthy state, the central nervous system (CNS) requires stability to maintain its extensive functional capabilities, therefore its nerve regeneration ability is limited. In the state of CNS injury, whether it is traumatic or caused by a degeneration process, such as Alzheimer's, it will be difficult for CNS to regenerate on its own. Extensive research is ongoing to find strategies for stimulating neuroregeneration in the CNS [3].

Unlike the CNS, the peripheral nervous system (PNS) can regenerate its axons and reconstruct the damaged circuitry with differing degrees of success depending on the severity of the damage [4]. Despite the regeneration ability of PNS, peripheral nerve injury (PNI) still becomes a global burden. The reported incidence of PNI in Sweden was 13.9/100.000 persons between 1998 and 2006 [5]. Almost similar incidence is also reported in the United Kingdom where 11.2/100.000 persons have PNI [6]. Due to the slow regeneration process of the peripheral axon and on several occasions the regeneration process being incomplete, PNI can result in a poor quality of life and lifelong disability with long-term sequelae, such as chronic pain or motor and sensory impairment [7,8]. Chronic diseases, such as diabetes and hypertension, can also disturb the regeneration process and damage the neurons causing peripheral neuropathy [9].

Biological processes, including nerve regeneration, are heavily influenced by dietary nutrients. Certain micronutrients, including vitamins, have been reported to be important in nerve regeneration [10]. Several studies showed decreasing of serum levels of vitamin A in patients with amyotrophic lateral sclerosis [11] as well as in the patients with cognitive impairment [12]. Moreover, low level of vitamin B12 and folic acid also found to be involved in Alzheimer's disease development [13]. Correlation between low level of vitamins also found in peripheral neuropathic diseases, such as low level of vitamin D in diabetic neuropathic patients [14] and low level of vitamin B12 in fibromyalgia [15].

The importance of vitamins in nerve regeneration have been explored both in central and peripheral nervous system. For example, the neurotropic B vitamin group (B1: Thiamine, B6: Pyridoxine and B12: Cobalamin) are well studied and found to have reconstructive activity and neuroprotective ability that benefit the nervous system [9,16]. The rate of peripheral nerve regeneration has also been shown to improve after daily treatment with vitamin B12, followed by B1 and B6 [17]. Other than vitamin B, vitamin E's antioxidant activity was found to improve nerve morphology and function and expedite peripheral nerve regeneration, which is influenced by oxidative stress [18]. Additionally, a recent study demonstrated that the number of regenerated axons increased and the myelination was boosted after vitamin D supplementation [19]. According to many studies, other vitamins and minerals, such as vitamins A, C and K may also favorably affect nerve regeneration [10]. Although promising, current clinical guidelines primarily recommend only B12 for neuropathy management, notably in diabetes-related cases [20]. Additional vitamins, such as vitamin A, may hold therapeutic potential, although concerns about neurotoxicity and vitamin D's inconsistent findings in the nervous system suggest a need for further evaluation [21,22]. Given these considerations, this study aims to systematically evaluate the clinical potential of vitamin supplementation in the management of patients with nerve injuries. The results of this study are expected to provide more directed recommendations in clinical practice, including its benefits and side effects.

Materials and methods

Literature search strategy

An in-depth search was independently carried out by AMF and AKW in the 3 databases: Elsevier, PubMed and Cochrane in September 2024, using the keywords: ('vitamin' OR 'vitamins' OR 'dietary supplements' AND 'nerve regeneration' OR 'neuroregeneration' OR 'axon elongation' OR 'myelin formation'). The search was restricted to the English language. The screening process and data collection were also performed independently by both reviewers.

Inclusion and exclusion criteria

All papers completed in this process were evaluated by 2 reviewers independently. In the presence of ambiguity or disagreement, a third reviewer was sought to resolve the issue. The included studies must investigate vitamins as a treatment modality in patients with neuropathic disorders or deformations of nerves caused by traumatic injury, chronic diseases or degenerative conditions. Only studies published in the English language and involving humans in their research populations were included. The selection criteria included all race, ethnicity, sex and geographical coverage. The individuals involved in these studies were all characterized by the presence of complex neuropathic disorder and nerve damage employing clinical, neurological and/or biochemical methods to evaluate nerve damage or repair. There were no

restrictions on dosage, route, combinations, length or form of vitamin treatment. The main outcome of interest in the intervention studies was nerve regeneration, which was evaluated based on the improvement of nerve function or other specific regeneration markers. Studies were excluded in case of the presence of case reports, case series of less than 20 participants, pre-clinical or animal studies, systematic review or meta-analyses. Studies that were multiple publications of the same dataset were excluded unless they provide additional or unique insights. Studies involving exclusively pediatric populations or those without clinically confirmed neuropathic conditions, as well as lacked specific metrics related to nerve regeneration (e.g., functional improvement, nerve conduction studies and myelin formation markers) were also excluded.

Data collection process

In order to manage information in an orderly fashion and keep track of all the materials collected, Rayyan AI software was used by the authors for literature management. Before formally screening the articles for compliance with the inclusion criteria, screening of titles and abstracts was done to exclude any studies that would not have contributed any information. Data from the included studies were extracted by 2 independent reviewers onto a predefined data extraction form. The characteristics of the study were gathered with this form, including the title of the study, authors, year of publication, country and design of the study; information on participants, including sample size, demographic data and baseline clinical conditions; and intervention details, including type, dosage, duration and mode of vitamin supplementation, plus comparator treatments, if any. Outcome measures also included the scrupulous recording of primary outcomes of interest in nerve regeneration, such as functional recovery and nerve conduction studies, and secondary outcomes including safety, side effects and biochemical markers. The final assessment of all papers included was conducted over the manuscript preparation.

Synthesis of results

This research was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [18,23]. Owing to the extreme heterogeneity of the studies included in this analysis, the results were synthesized and presented solely in a qualitative manner. The review mainly evaluated the therapeutic effectiveness of vitamins for the treatment of various underlying neurological conditions.

Quality assessment

The quality assessment of the included articles was conducted using tools based on the study design. Two randomized controlled trials (RCTs) were assessed using the RoB 2 tool (Risk of Bias 2) which was specifically designed to evaluate the risk of bias in RCTs. This tool is specifically designed to address the potential biases within key areas: The randomization process, deviations from intended interventions, outcome measurements and reporting of results. The strong focus of this tool is on the integrity of the randomization and the comparability of the intervention groups, which makes it fit for assessing the internal validity of RCTs. In contrast, the MINORS tool (Methodological Index for Non-Randomized Studies) was applied to evaluate the methodological quality of retrospective, pre-post treatment, comparative studies and cross-sectional case-control studies. This tool was chosen because of its flexibility in assessing various non-randomized designs. It appraises the clarity of objectives, appropriateness of control selection, adequacy of follow-up and consideration of confounding variables.

Results and discussion

An electronic comprehensive search yielded 1,732 articles on the subject of vitamins and nerve regeneration. After an initial screening of titles and abstracts, 164 studies were chosen for full-text screening. Finally, 9 studies were included in this systematic review (**Figure 1**), they were 1 retrospective study, 2 randomized controlled trials (RCTs), 4 pre-post treatment studies, 1 cross-sectional case-control study and 1 comparative study. Among them, 7 studies were interventional, to investigate the effect of vitamins on neuroregeneration. While the other 2 studies were observational, to find the correlation between patients' serum vitamin levels and neurological function. All studies have a moderate risk of bias indicated some bias, but not enough to invalidate the results (**Table 1**).

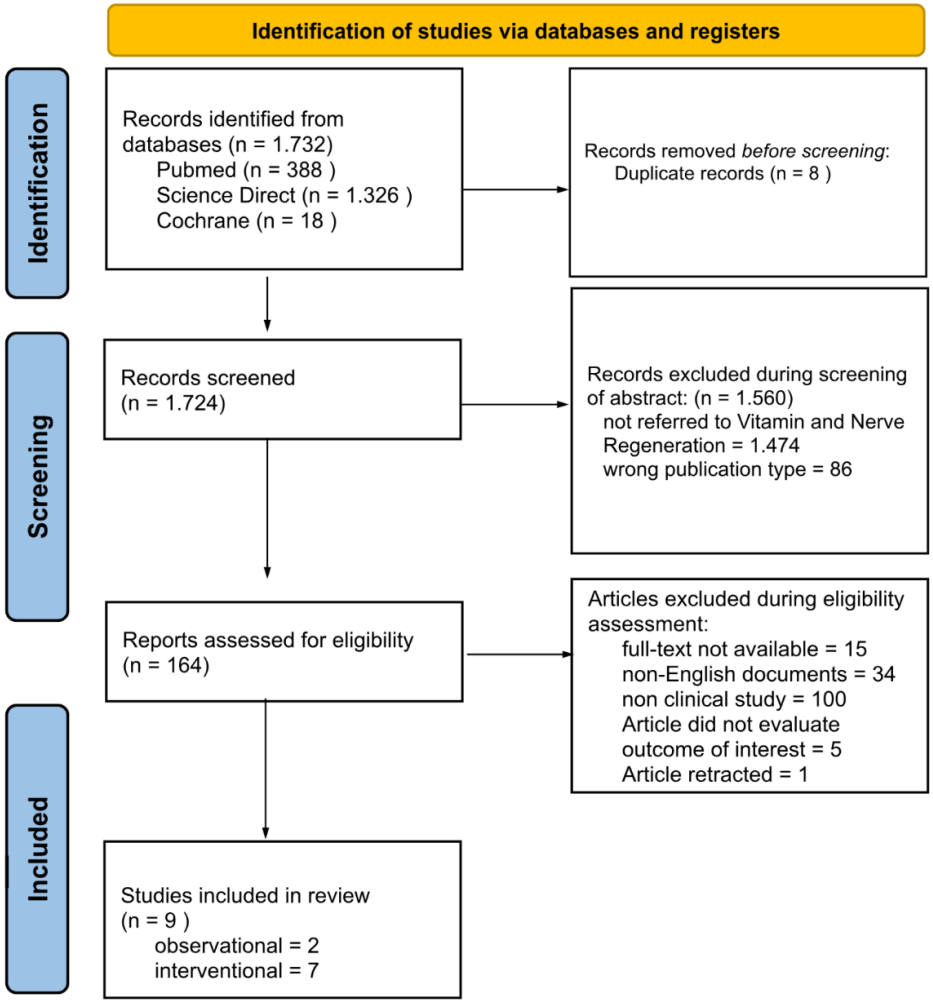

Figure 1 Synthesis of result.

Table 1 Quality assessment.

Author	Study design	Country	Number of patients	Tools	Risk level
Shimura *et al.* [24]	Single-center retrospective study	Japan	33	MINORS	Moderate
Baydan & Soylu [25]	Randomized controlled trial	Turkiye	30	RoB 2	Moderate to high
Shibuya *et al.* [26]	Pre-& post-treatment	Japan	14	MINORS	Moderate
Takahashi & Nakamura [27]	Pre-& post-treatment	Japan	9	MINORS	Moderate
Kuwabara *et al.* [28]	Pre-&post treatment	Japan	10	MINORS	Moderate
Fogagnolo *et al.* [29]	Randomized controlled trial	Italy	40	RoB 2	Moderate
Brito *et al*. [30]	Pre-& post-treatment	Chile	27	MINORS	Moderate
Fathi *et al.* [31]	Cross-sectional case-control study	Egypt	120	MINORS	Moderate
Zouari *et al.* [32]	Comparative study	Tunisia	30	MINORS	Moderate

The 2 observational and 7 interventional studies on vitamins in neuropathic disorders patients included in this review were published between 1976 and 2024, with geographical representation from Asia (n = 4), Europe (n = 2), Africa (n = 2) and South America (n = 1). A total of 313 participants were involved, with 63 reporting sensory changes following post-operative inferior alveolar nerve (IAN) damage [24,25].

Additionally, 33 participants were diagnosed with neuropathy [26-28], 40 were post-surgery nuclear cataract patients [29], 27 had vitamin B deficiency [30], 60 experienced rheumatoid arthritis and neuropathic pain [31] and 30 had Friedreich's ataxia [32]. Serum vitamin level observations are summarized in **Table 2**, while the effects of vitamin and mineral supplementation are summarized in **Table 3**.

Table 2 Serum vitamin level among patients with neurological disorders.

Vitamin	Subject	Comparison	Age (years)	Outcome
25-OHD[a] (ng/mL) NR[b]: 30 - 100	18.3 ± 5.5 (n = 30) [RA[c], NP[d]+]	28.8 ± 17.7 (n = 30) [RA, NP-]	42.4 ± 10.9	*(RA)NP+ with deficient vitamin D had either CTS[e]/MM[f] *(RA)NP+ with deficient vitamin D showed significant delayed latency and reduction of conduction velocity of motor and sensory branches of median, ulnar and tibial nerves (NCVS[g])
Vitamin E (g/mL) NR: 8.67 ± 3.71	Deficient (n = 15) [FAVED]	Sufficient (n = 15) [FA[h]]	21.8 ± 5.9 [FA] 23.7 ± 9.1 [FAVED[i]]	*Mean sensory action potential (SAP) of the median nerve is more reduced in FA than in FAVED. *Mean SAP in the saphenous nerve in the FA group was markedly decreased, while in the FAVED group was within normal limits. *Nerve biopsy abnormalities encountered in FAVED are less severe than in the FA group.

[a]25-hydroxy vitamin D; [b]normal range; [c]rheumatoid arthritis; [d]neuropathic pain; [e]carpal tunnel syndrome; [f]mononeuropathy multiplex; [g]nerve conduction velocity studies; [h]Freidreich's ataxia; [i]Freidreich's ataxia with vitamin-E deficiency.

Table 3 Supplementation of vitamins among populations with neurological disorder.

Vitamin	Supplement	Population	Outcome	Ref
Vitamin B1	10 mg/day	Beriberi neuropathy	Presence of clusters of regenerating myelinated and unmyelinated nerve fibers (nerve biopsy)	[22]
Vitamin B12	3×500 µg/day	Post-operative inferior alveolar nerve (IAN) damage	Reducing hypoesthesia in a median time of 33 days	[24]
	25 mg/day for 10 days followed by monthly 25 mg for 5 months	Immune-mediated or hereditary neuropathy	The 3 out of the 14 patients showed increased CMAP[a] amplitudes after receiving treatment. A patient showed clear improvement in all of the endpoints in the ONLS[b].	[26]
	3×500 µg injection/week for 6 months	Uremic-diabetic polyneuropathy patients	Patients' pain or paresthesia had lessened (neuropathic pain grading), and the ulnar motor and median sensory nerve conduction velocities showed significant improvement.	[28]
	10 mg injection (100 mg pyridoxine and 100 mg thiamin)	Vit B12 deficient	Improvements in conductivity in myelinated peripheral nerves after treatment: Direct correlation between the nerve score and arginine (consistent with the role of arginine in nerve regeneration).	[30]
Vitamin B Complex	10 mg of thiamine-B1, 2 mg of riboflavin-B2, 2 mg of pyridoxine-B6, 20 mg of niacinamide, 3 µg of vitamin B12, 2.5 mg of folic acid and 5 mg of calcium pantothenate (1×1 for 30 days)	Post-operative IAN damage	Statistically significant differences in pre-and post-treatment in neurosensory test.	[25]

Vitamin	Supplement	Population	Outcome	Ref
Vitamin E	Topical formulation of 0.1 % CoQ[c] 10 and 0.5 % vitamin E D-α-tocopheryl polyethylene glycol 1,000 succinate twice per day for 9 months	Nuclear cataract post-surgery	Patients who received treatment had a higher increase in CFD (central fiber densities) than those treated with saline solution.	[29]

[a]compound muscle action potential; [b]overall neuropathy limitations scale; [c]coenzym Q10.

Both observational studies depict the way vitamin deficiency/sufficiency impact on nerve function, and/or neurological outcome (**Table 2**). A study investigated a correlation between vitamin D levels and neuropathic pain (NP) in rheumatoid arthritis (RA) patients revealed vitamin D levels in patients with NP to be significantly lower than those without NP, and the incidence of vitamin D deficiency was higher in RA patients with NP than in RA patients without NP. The mean value of serum 25-vitamin D level in all RA patients with NP was 18.3 ng/mL. RA patients with NP and with deficient vitamin D levels also showed delayed latency and reduced conduction velocity, according to data from nerve conduction velocity studies (NCVS) [31]. Another study conducted in Friedreich's ataxia population compared patients based on their vitamin E status. The details of subjects' serum vitamin E levels are not explicitly mentioned, but subjects were divided into 2 groups: The Friedreich's ataxia (FA) normal vitamin E group and the Friedreich's ataxia vitamin E deficiency (FAVED) group. Interestingly, the sensory action potential (SAP) of the median and saphenous nerves was more reduced in the FA group than in the FAVED group showing a higher degree of sensory nerve dysfunction in FA patients with normal vitamin E levels. Nerve biopsy findings also showed less severe abnormalities in the FAVED group compared to the FA group [32].

Seven interventional studies as summarized in **Table 3**, provide insights into the impact of different vitamin supplementation strategies, particularly vitamin B and vitamin E, on individuals with neurological disorders. The table illustrates the connection between particular vitamin interventions and their effects on nerve regeneration and neurological recovery, underscoring the possible therapeutic benefits of vitamins in managing neuropathies. One trial with vitamin B1, 10 mg, showed clusters of regenerating myelinated and unmyelinated nerve fibers [27], 2 trials with vitamin B12, with 3×500 μg/day, showed an improvement in reduction of hypoesthesia [24] and paresthesia [28], with improved sensory nerve conduction velocities; another trial with higher-dose of vitamin B12, 25 mg/day, achieved an increase in compound muscle action potential [26]. The conductivity in myelinated peripheral nerves was further improved by 1 injection of 10 mg of vitamin B12 [30]. One study with B-complex vitamins showed positive results on some neurosensory tests [25] and lastly, a topical formulation containing 0.5 % of vitamin E gave an increase in central fiber density [29]. The details of each vitamin mentioned in observational and interventional studies will be discussed in each section.

Vitamin B

The water-soluble vitamins B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folate) and B12 (cobalamin) are the 8 different types of vitamin B. They are unrelated and biochemically heterogeneous, but because they usually coexist and are often naturally present in the same food, they are considered the same group. Members of the vitamin B complex primarily act as coenzymes for enzymatic reactions in various biological processes. Some B vitamins carry neurospecific functions in the central and peripheral nervous system, commonly called neurotropic B vitamins, consisting of vitamins B1, B6 and B12. Extensive research has been conducted to understand the role and the potential of vitamin B, especially neurotropic B vitamins, in the nervous system, both as a supplement in healthy conditions and as a treatment for various neurological diseases, including nerve injury [10,33].

Takahashi *et al.* [27] examined the effect of oral administration of vitamin B1 (10 mg/day) supplementation on regeneration and remyelination processes in patients with beriberi neuropathy. Beriberi is a thiamine deficiency commonly caused by inadequate intake of vitamin B1 [34]. The active form of thiamine, thiamine pyrophosphate (TPP), is a cofactor for several TPP-dependent enzymes involved in the metabolism of carbohydrates and fatty acids. In the cytosol, TPP acts as a cofactor for transketolase (TKT) on the pentose phosphate pathway producing ribose 5-phosphate (R5P) and nicotinamide adenine dinucleotide phosphate (NADPH). In the nervous system, R5P and NADPH are important for the production of myelin sheath as both of them are important for fatty acid synthesis [35,36]. Additionally, in fatty acid metabolism, TPP is also a cofactor for 2-hydroxyacyl-coenzyme-A lyase (HACL1) that facilitates the shortening of long fatty acids that cannot undergo a direct β-oxidation catabolism, such as 3-methyl-branched fatty acids (**Figure 2**) [36].

In mitochondria, TPP is a cofactor of 3 important enzymes for carbohydrate metabolism and energy production: pyruvate dehydrogenase (PDH), α-ketoglutarate dehydrogenase (αKGDH) and branched-chain α-ketoacid dehydrogenase (BCKDH). PDH facilitates the oxidative decarboxylation process of pyruvate to produce acetyl coenzyme A (acetyl-CoA) that enters the Krebs cycle. αKGDH catalyzes the production of succinyl-CoA from α-ketoglutarate in the Krebs cycle. These 2 enzymes are very important in glucose metabolism and energy production. Thus, thiamine depletion, resulting in the inability to utilize pyruvate in the Krebs cycle, will greatly affect energy-dependent cells, including neurons. Another TPP-dependent enzyme, BCKDH, acts in the inner mitochondrial membrane to catalyze the essential branched-chain amino acid (BCAA) catabolic pathway, such as leucine, isoleucine and valine (**Figure 2**) [35,36].

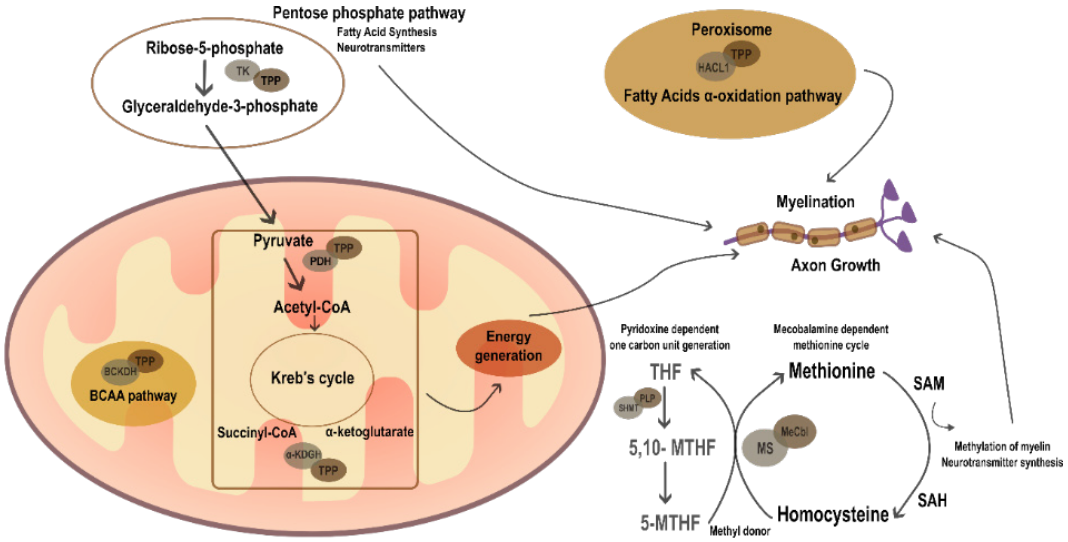

Figure 2 Mechanism of B vitamins in supporting the nerve regeneration.

The active forms of Vitamin B1, B6 and B12 are coenzymes for vital biological processes important for neuroregeneration. TPP serves as a coenzyme for several enzymes involved in glucose and fatty acid metabolism. These processes are essential for myelin production and provide energy for nerve regeneration. Mecobalamin and pyridoxine act as a coenzyme for methionine synthase and SHMT, respectively. These enzymes are crucial for the production of SAM, a methyl donor for the methylation of myelin and neurotransmitter synthesis.

TK: Transketolase; TPP: Thiamine Pyrophosphate; PDH: Pyruvate Dehydrogenase; BCKDH: Branched-Chain α-Ketoacid Dehydrogenase; BCAA: Branched-Chain Amino Acid; αKGDH: α-Ketoglutarate Dehydrogenase; HACL1: 2-Hydroxyacyl-Coenzyme-A Lyase; THF: Tetrahydrofolate; 5-MTHF: 5-Methyl-

Tetrahydrofolate; 5,10-MTHF: 5,10-Methylene-Tetrahydrofolate; SAM: S-Adenosylmethionine; SAH: S-Adenosylhomocysteine.

Due to the crucial role of thiamine in the nervous system, neurological symptoms are common in thiamine deficiency. Three classic neurological syndromes are recognized: Wernicke encephalopathy, Korsakoff's psychosis and dry beriberi (axonal polyneuropathy) [37]. Neurological manifestations of beriberi neuropathy include symmetrical motor and sensory deficits in the extremities and impaired reflexes [34]. Thiamine deficiency also proved to decrease myelin fiber density causing myelin sheath damage and neuronal death as TPP is also thought to be a cofactor for 2-hydroxyacyl-coenzyme-A lyase, required for the production of neural myelin and cerebroside from 2-hydroxy carboxyl substrates [35].

Takahashi *et al*. [27] presented histological evidence from sural nerve biopsies of thiamine deficit patients that demonstrated the differences between untreated patients and after vitamin B1 treatment. The treated patients show several characteristics of axon regeneration, such as clusters of Schwann cells and axons (some even remyelinated), solitary and disproportionately thin myelinated axons that are encased in Schwann cell whorls and redundant basement membranes, and myelinated fibers with minimal Schwann cell process whorl formation. Patients treated with vitamin B1 exhibit prominent regenerative characteristics, corresponding to a significant improvement in clinical symptoms. Thus, confirming the important role of vitamin B1 in nerve regeneration [27]. The definitive treatment of beriberi neuropathy is the administration of vitamin B1 intravenously or orally, depending on the severity of the symptoms [34].

Vitamin B12 was first famous for its role in the hematopoiesis process and is involved in a disease called pernicious anemia. However, vitamin B12 is involved in many essential pathways, and its deficiency could become a tremendous health problem, including in the nervous system. In mitochondria, adenosylcobalamin (AdoCbl), one of the active forms of vitamin B12, acts as a coenzyme of methylmalonyl CoA mutase (MCM) which catalyzes the production of succinyl CoA from methylmalonyl CoA. This methylmalonyl CoA pathway is involved in the metabolism of odd-chain fatty acids and myelin synthesis. In cytosol, vitamin B12 acts as a coenzyme for methionine synthase that catalyzes the methylation of homocysteine (Hcy) to methionine and together with 5-methyl-tetrahydrofolic (5-MTHF) acid catalyzes the formation of S-adenosylmethionine (SAM) [33,38,39]. SAM is highly dependent on vitamin B12 and is a universal methyl donor crucial for the methylation of myelin and neurotransmitter synthesis [39]. SAM synthesis is also dependent on vitamin B6 (pyridoxine) which acts as a cofactor for serine-hydroxymethyltransferase (SHMT). SHMT catalyzes the transfer of 1-carbon units from serine to tetrahydrofolate producing 5,10-methylene-tetrahydrofolate (5,10-MTHF) for nucleic acid synthesis and 5-MTHF for the formation of SAM (**Figure 2**) [33,40].

A previous study using an animal model of TBI (traumatic brain injury) showed the capability of vitamin B12 to promote myelin regeneration as proven by the reduction of myelin sheath destruction in histopathology observation and increase of myelin basic protein (MBP) level after B12 treatment on brain tissue sample. This involvement is related to the inhibition of the endoplasmic reticulum (ER) stress pathway as the study also showed that the vitamin B12 treatment reduces the ER stress signaling pathway proteins and co-treatment with an ER stress inhibitor could increase the MBP expression and MBP positive myelin [33,38]. Thus, the deficiency of vitamin B12 will greatly impact neurological functions, including the nerve regeneration process. Currently, vitamin B12 is widely used in clinical settings for many neurological conditions, such as peripheral nerve injury [33].

In a recent study by Shimura *et al*. [24], the effect of daily supplementation of vitamin B12 on the time to cure hypoesthesia after inferior alveolar nerve (IAN) injury following M3 tooth impaction extraction [19]. IAN injury is associated with refractory hypoesthesia, however, in the study, the time to cure hypoesthesia is significantly reduced as the median is 33 days from the initial treatment of B12. All patients generally may be free of hypoesthesia within 1 month and it is unlikely to be cured beyond 7 months [24]. Another study examined the long-term intravenous administration (3 times/week) of high-dose vitamin B12 (500 ug) for uremic and uremic-diabetic neuropathy in chronic hemodialysis patients. The results showed a significant

reduction in the patient's pain or paresthesia and an improvement in ulnar motor and median sensory nerve conduction velocities [28]. A phase I/II open-label clinical trial has been conducted to observe the efficacy and safety of intravenous ultra-high dose methylcobalamin for peripheral neuropathy. The Medical Research Council (MRC) sum score improved in 7 out of the 12 patients, and no adverse effect was seen in any of the patients, suggesting that high-dose vitamin B12 therapy could become a future treatment of choice for peripheral neuropathy [26].

Neurotropic B vitamins may hold a synergistic action when given together, particularly in the peripheral nervous system, in which several studies have shown evidence. It is postulated that this synergistic action is primarily due to each vitamin's prominent functions and overlapping biochemical pathways [33]. Jolivalt *et al.* [41] demonstrated the ability of neurotropic B vitamins to completely normalize the sensory nerve conduction velocity in diabetic rats. Individual B vitamins did not show the ability to improve the sensory nerve conduction velocity except for vitamin B6 which can partially restore the nerve conduction velocity.

A clinical study by Brito *et al*. [30], on a subclinical B12 deficiency population showed significant improvements in peripheral nerve conductivity and an increase in metabolic markers of myelin integrity (plasmalogens) after treatment with the combination of thiamine, pyridoxine, and cyanocobalamin. Another clinical study on 30 patients with inferior alveolar nerve damage post bilateral sagittal split ramus osteotomy compared the B-complex vitamin treatment with laser treatment. The author concluded that B-complex vitamins could promote nerve regeneration on the inferior alveolar nerve damage and showed improvements in patient symptoms. However, the primary therapy using laser therapy showed more effective treatment than B-complex vitamin treatment alone [25].

While earlier studies suggested a daily intake of 1.8 mg thiamine for moderately active men consuming 3,000 cal [42], more recent recommendations propose a population reference intake of 0.1 mg/MJ (0.4 mg/1000 kcal) for adults, infants, children and during pregnancy and lactation [43]. There are no reports of adverse effects from oral thiamine consumption by food or supplements. Doses of thiamine > 5 mg decline its absorption rate and the excess is excreted in the urine [44]. In contrast to the oral route, parenteral use has been associated with phlebitis and very rarely with hypersensitivity reactions such as pruritus, respiratory distress, nausea, abdominal pain and even anaphylactic shock, which are mainly associated with the administration route [45].

Pyridoxine (B6) intake of 3 to 4.9 mg/day appears consistent with the definition of a Recommended Dietary Allowance for most Americans [46], with a tolerable upper intake level is 12 mg/day for adults, with lower levels for infants and children [47], as doses exceeding 50 mg/day for extended periods may be harmful [48]. Excessive intake of vitamin B6 (pyridoxine) can lead to neurotoxicity, particularly at doses of 1,000 mg per day or more, which is approximately 800 times the typical dietary intake. While the safe upper limit is set at 100 mg per day, there have been reports of toxicity at lower doses of 100 - 300 mg per day [49]. Prolonged high-dose vitamin B6 supplementation can cause ultrastructural changes in the cerebral cortex, including damaged mitochondria, increased lipofuscin granules and decreased synaptic density [50]. However, neurological side effects from vitamin B6 are considered rare and typically occur with high daily doses or extended treatment duration [33].

In persons with normal absorption, an intake of 4 - 7 µg vitamin B12/day is associated with an adequate vitamin B12 status. which indicates that the previous RDI of 2.4 µg vitamin B12/day may be inadequate [51]. The benefit-risk ratio of high-dose vitamin B treatment for conditions like peripheral neuropathy is generally considered favorable, provided dosing recommendations are followed and serum levels are monitored [33].

Vitamin D

Vitamin D, especially in its active form 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), is essential for various biological functions, including the regeneration of nerves. It operates through the Vitamin D Receptor (VDR), a nuclear receptor found in many tissues, including the nervous system. Vitamin D aids in axon regeneration, myelin repair and the overall health of neurons by affecting the growth factors and signaling pathways vital for nerve repair [52]. The most active

form of vitamin D, 1a,25-dihydroxyvitamin D3 (calcitriol), will bind to the VDR and continue to form a heterodimer with another nuclear receptor, the retinoic acid X receptor (RXR). This complex then translocates to the nucleus, triggering the VD response elements (VDRE) and subsequent target gene activation. Through this mechanism, vitamin D is involved in the transcription process of many genes, including nerve growth factor (NGF), glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and the nerve growth factor receptor (NGFR), which is involved in neuron and oligodendrocytes development and differentiation (**Figure 3**) [53]. Oligodendrocytes are members of glial cells responsible for forming and maintaining myelin sheaths. Several studies showed the crucial role of oligodendrocytes on myelin regeneration after demyelination events [54-57]. Despite the extensive event of neuronal injury, approximately 80 % of mature oligodendrocytes survive the event and could promote remyelination. Additionally, oligodendrocyte precursor cells (OPCs) will also differentiate into new oligodendrocytes and were observed to promote remyelination more effectively than the surviving mature oligodendrocytes [54]. In *in vivo* and *in vitro* studies of traumatic spinal cord injury models, vitamin D was demonstrated to have the ability to preserve myelin integration and promote OPCs differentiation by inhibiting the c-Myc signaling, a regulator for cell proliferation and differentiation [57]. Additionally, vitamin D has anti-inflammatory effects, lowering pro-inflammatory cytokines like TNF-α, which can lead to nerve damage. By modulating the immune response, Vitamin D helps reduce inflammation and creates a favorable environment for nerve healing and regeneration. Its role in regulating calcium levels within neurons, which are vital for neurotransmitter release and overall neuronal excitability [52].

Recent studies have demonstrated the potential of vitamin D in promoting nerve regeneration after injury. Both vitamin D_2 and D_3 have shown beneficial effects, with D_3 being more efficient [14]. In peripheral nerve injuries, vitamin D supplementation increases axon number and diameter, improves myelination and enhances functional recovery [58,59]. A cross-sectional, case-control study conducted in Egypt explored the correlation between vitamin D deficiency and neuropathic pain (NP) in 60 rheumatoid arthritis (RA) patients and 60 healthy controls. The presence of NP was confirmed using Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) score, then patients were divided into 2 groups based on the presence or absence of NP. While serum vitamin D levels were measured using enzyme-linked immunosorbent assay (ELISA). The study found that RA patients with NP had significantly lower vitamin D levels than those without neuropathic pain. Furthermore, RA patients with NP and deficient vitamin D levels had delayed latency and reduced conduction velocity in both motor and sensory nerves. Another finding revealed that 85.7 % of RA patients with deficient vitamin D levels were diagnosed with Carpal tunnel syndrome (CTS) and mononeuropathy multiplex (MM). This implies that inadequate vitamin D levels may contribute to deteriorating nerve function in RA patients, potentially exacerbating conditions such as CTS and MM [31].

In clinical settings, the most commonly used form of vitamin D is cholecalciferol (vitamin D_3), with dosage recommendations differing based on deficiency levels and individual patient needs. For maintaining optimal vitamin D levels, daily doses between 800 and 2,000 IU are typically suggested, while higher doses (ranging from 4,000 to 10,000 IU daily) may be necessary for severe deficiencies. When addressing neurological conditions or aiding nerve regeneration, the specific dose can be adjusted according to serum 25(OH)D levels, aiming for a serum level of 30 - 50 ng/mL. Although vitamin D is generally well-tolerated, excessive intake can lead to toxicity, especially at doses over 10,000 IU/day for extended periods. Vitamin D toxicity can cause hypercalcemia, which presents symptoms such as nausea, vomiting, weakness, kidney stones and calcification of soft tissues. Contraindications include conditions like hypercalcemia, sarcoidosis and severe kidney disease, where vitamin D metabolism may already be altered [52].

Calcitriol, the active form of vitamin D, will bind to the VDR and form a complex with RXR before translocating to the nucleus. In the nucleus, this complex will activate the VDRE and subsequent target genes, including the NGF, GDNF, BDNF and NGFR. These genes are involved in neuron and oligodendrocyte development and differentiation. VDRE: Vitamin D Response Element; VDR: Vitamin D Receptor; RXR:

Retinoic Acid X Receptor; NGF: Nerve Growth Factor; GDNF: Glial-Derived Neurotrophic Factor; BDNF: Brain-Derived Neurotrophic Factor; NGFR: Nerve Growth Factor Receptor; OPC: Oligodendrocyte Precursor Cell.

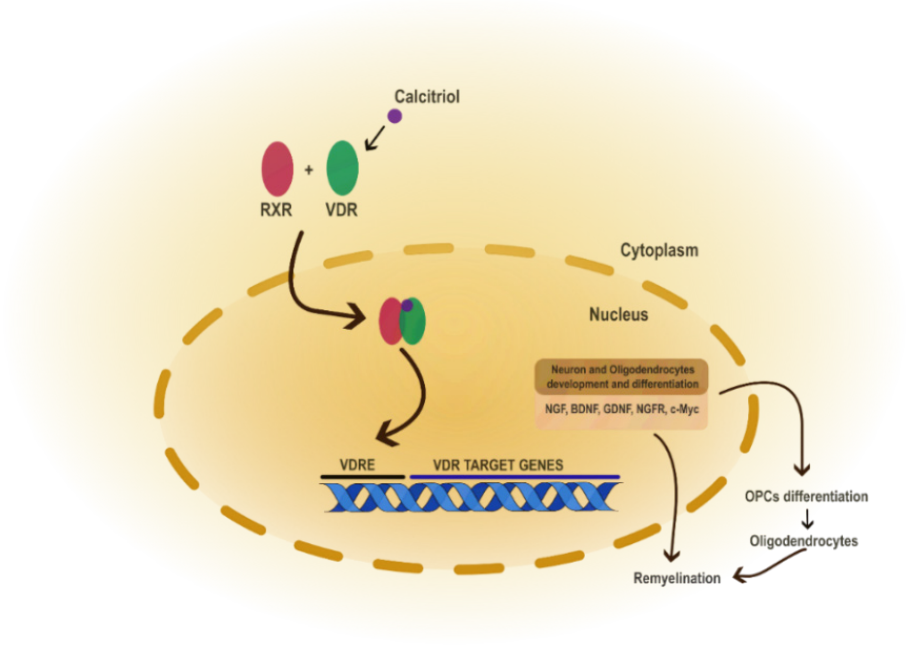

Figure 3 Mechanism of vitamin D in nerve regeneration.

Vitamin E

Vitamin E is well known for its lipid-soluble antioxidant properties and has shown potential in nerve regeneration and neuroprotection. It protects neurons from toxicity by reducing free-radical damage to biological membranes [60]. Research on peripheral nerve injury models indicates that vitamin E offers neuroprotective effects, reducing hyperalgesia and improving functional recovery [13,60]. A deficiency in vitamin E can impair nerve regeneration, resulting in fewer myelinated fibers and changes in fiber caliber distribution [61].

A study conducted in Milan between 2009 and 2011 involved 40 patients who underwent uncomplicated cataract surgery. These patients were randomly assigned to receive either Vitamin E (combined with Coenzyme Q10) or a saline solution, applied topically twice a day for 9 months. The goal was to compare central fiber density (CFD) and temporal fiber density (TFD) in the cornea between the 2 groups using in vivo confocal microscopy, which allows for a detailed assessment of nerve regeneration over time. The results indicated that patients receiving the Vitamin E treatment experienced a more significant increase in both CFD and TFD compared to those in the saline group. Follow-ups were conducted at 3, 6 and 9 months. At the 3-month mark, the CFD in the treatment group rose by 1.5, while the control group saw an increase of only 0.2. For TFD, the treatment group showed an increase of 2.5 compared to 1.0 in the control group at the same time point. This suggests that nerve regeneration occurred more rapidly in the treatment group, with no significant side effects reported over the 9-month period, aside from occasional burning sensations in 10 % of patients during the early postoperative phase. Although cataract surgery is generally safe, it can cause nerve damage in the corneal area, resulting in decreased CFD and TFD. This study provides evidence that Vitamin E not only helps protect nerve structures but also promotes faster nerve regeneration following surgical nerve damage [29].

Vitamin E, especially in the form of α-tocopherol, is a potent antioxidant preventing nerve cells from oxidative stress, which is crucial in the degeneration process of central and peripheral nervous systems. Vitamin E deficiency leads to an increase in free radicals attacking the neuron end and it causes axonopathy and loss of myelin sheath [62]. The nervous system, especially the central nervous system, is susceptible to oxidative stress due to its high metabolic demand,

accumulation of transition metals, and high concentration of polyunsaturated fatty acids which can easily become a target of lipid peroxidation reaction causing extensive damage to membrane lipids of neurons. ROS also can target the nucleic acids and break the backbone of proteins resulting in neuronal damage and functional declines in the nervous system [63].

Lanza *et al*. [64] demonstrated the decrease of several antioxidant properties, such as metallothioneins (MTs), catalase (CAT), Cu, Zn-superoxide dismutase (SOD) and glutathione transferase (GST), after peripheral nerve injury, specifically in the proximal portion of the neurons. Inadequate antioxidant properties will further weaken the endogenous antioxidant defense and cause progressive degeneration and hinder the repair process [65]. Vitamin E, especially α-tocopherol, acts as an antioxidant by scavenging free radicals, such as lipid peroxyl radicals, by hydrogen atom transfer reaction, thus preventing lipid peroxidation (**Figure 4**) [66].

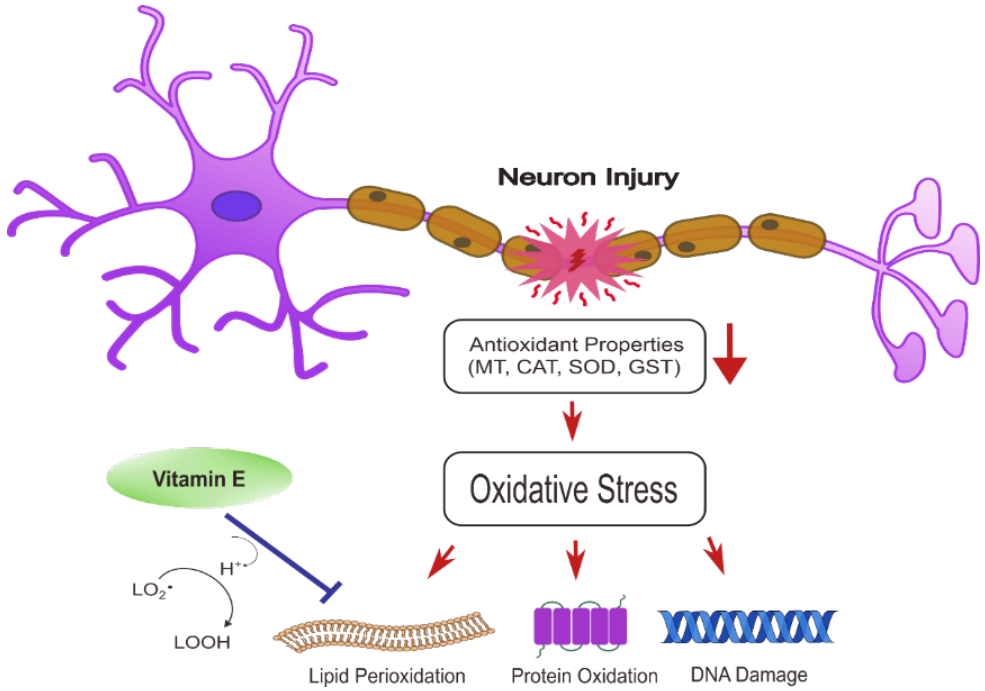

Figure 4 Mechanism of vitamin E in nerve regeneration.

Inadequate antioxidant properties in the neuron can cause progressive degeneration and slow down the repair process. Vitamin E, a potent antioxidant, will act as an antioxidant by scavenging free radicals and preventing lipid peroxidation. MT: Metallothionein; CAT: Catalase; SOD: Cu,Zn-superoxide dismutase; GST: Glutathione transferase.

In the study comparing Friedreich's ataxia (FA) and Friedreich's ataxia vitamin E deficiency (FAVED) in Tunisia, electrophysiological testing, as well as nerve biopsies, were utilized to evaluate the structural and functional differences in nerve regeneration between the 2 groups. The results revealed that the FA group, which had normal vitamin E levels, showed more decreased nerve function and severe abnormalities compared to the FAVED group [32]. This paradoxical finding can be explained by their distinct underlying mechanisms. The FA group showed more decreased nerve regeneration than the FAVED group because of the genetic and mitochondrial-driven nature of FA, leading to more severe and irreversible nerve damage [67,68]. In contrast, nerve damage in FAVED is primarily caused by vitamin E deficiency, which is more responsive to treatment with antioxidant supplementation, allowing for greater nerve regeneration [32].

Intake recommendation for vitamin E is provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the Institute of Medicine of The National Academies (formerly National Academy of Sciences). The FNB's vitamin E recommendations are for alpha-tocopherol alone; the only form maintained in plasma is 15 mg [69]. The 15

mg of natural alpha-tocopherol would equal 22.4 IU while synthetic alpha-tocopherol would be equal to 33.3 IU [70]. A study on healthy Japanese male adults found that high-dose supplementation of 1,200 IU daily for 28 days showed no adverse effects, significantly increasing plasma and platelet α-tocopherol concentrations without affecting platelet aggregation, coagulation or clinical parameters [71]. However, appropriate dosing should consider factors such as oxidative stress and lipid intake. Although supplementation in high doses has proved inconsistent, some studies have suggested that it may enhance the risk of all-cause mortality owing to influences on cytochrome P450s and MDR1 [72]. Increased levels of vitamin E have effects that influence the kidneys negatively, causing them to become more inflammatory and more oxidative in nature and these levels are influenced by the amount ingested [73]. For example, α-tocopherol has been noted to activate osteoclast fusion, stimulating bone resorption, culminating in the induction of osteoporosis-like disease in mice [74].

Comparison of efficacy

Energy metabolism and antioxidant role of B1, co-enzyme action of B6 and myelin maintenance and neurotropic function of B12

Thiamine's main role is to act as a cofactor for enzymes that catalyze metabolic pathways of carbohydrates like the one that converts pyruvate to acetyl-CoA which is essential for the production of ATP in neurons. Such an energy source is necessary for the functional activity of a neuron and for cell repair. Additionally, thiamine also has antioxidant action which decreases the oxidative stress in the neuronal cells which could be caused by mechanical damage to the cell [35,36]. Pyridoxine, acts as a coenzyme in over 100 enzymatic reactions, including those involved in amino acid metabolism and the production of neuroactive substances that facilitate nerve repair [33]. Cobalamin is vital for synthesizing and maintaining myelin, supporting efficient nerve signal transmission and regeneration. Vitamin B12 promotes the production of neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which support neuronal survival and regeneration. It also plays a significant role in inhibiting endoplasmic reticulum (ER) stress-induced apoptosis in neurons [38]. ER stress can lead to cell death following injury; thus, vitamin B12's ability to mitigate this stress enhances neuronal survival. Furthermore, studies indicate that vitamin B complex supplementation can modulate neuroinflammation by influencing macrophage polarization. This shift from pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages supports a more favorable environment for nerve healing [75].

Calcium homeostasis and gene expression modulation by vitamin D

Vitamin D regulates calcium levels within neurons, which are vital for neurotransmitter release and overall neuronal excitability. Additionally, it activates nuclear receptors that regulate gene expression related to neurotrophic factors and cytokines involved in repair processes [53]. Research involving animal models has shown that vitamin D enhances the recovery of peripheral nerves following injury by promoting Schwann cell proliferation and migration towards injury sites. Moreover, vitamin D reduces the expression of pro-inflammatory cytokines such as TNF-alpha and IL-6 while promoting anti-inflammatory cytokines like IL-10. This modulation helps create a more favorable environment for regeneration [52].

Antioxidant properties of vitamin E

Vitamin E functions primarily as a potent antioxidant, protecting neuronal cells from oxidative damage during nerve injury. Its lipid-soluble nature allows it to integrate into cell membranes, where it protects polyunsaturated fatty acids from peroxidation. The antioxidant effects of vitamin E are crucial for maintaining cellular integrity during nerve healing by preventing lipid peroxidation, which helps maintain the structural integrity of cell membranes in neurons and glial cells [62-64].

Table 4 Comparison of vitamin B, D and E in nerve regeneration.

Vitamin	Nerve regeneration mechanism	Recommended dose	Ref
B1	Enhances nerve cell metabolism and myelin formation, facilitating nerve repair.	0.4 mg/1,000 kcal	[43]
B6	Supports neurotransmitter synthesis and myelination, crucial for nerve function.	3 to 4.9 mg/day	[47]
B12	Promotes myelin regeneration and reduces neuropathic symptoms through neuroprotection.	500 μg 3 times a day	[51]
D (Chole-calciferol)	Regulates growth factors and neurotropic proteins, providing neuroprotection and anti-inflammatory effects.	800 - 2,000 IU/day (4,000 - 10,000 IU/day for severe deficiency)	[52]
E (alpha-tocopherol)	Acts as an antioxidant, mitigating oxidative stress and promoting structural integrity during nerve repair.	4 - 7 μg/day	51

The recommended dosages can vary based on individual needs, clinical conditions, and specific study protocols. The doses listed are derived from clinical evidence and common practices observed in the reviewed studies.

Clinical vs preclinical results

Research on vitamin supplementation for nerve regeneration shows promising results in animal studies. However, there are significant discrepancies between animal studies and human trials in this field. While numerous supplements, particularly vitamins B12 and E, have shown success in animal models of peripheral nerve injury, similar evidence in human patients is limited [76].

Vitamin B

Preclinical research indicates that vitamins B1, B6 and B12 are crucial for nerve regeneration. For example, vitamin B12 has been shown to enhance nerve repair and functional recovery after traumatic brain injury by inhibiting endoplasmic reticulum (ER) stress-induced neuron injury [9,38]. Studies demonstrate that vitamin B1 can improve nerve conduction velocity in diabetic rats and protect peripheral nerves from damage induced by hyperglycemia. Vitamin B6 has also shown neuroprotective effects by counteracting glutamate-induced neuronal damage in rat models. In humans, the evidence for the efficacy of vitamin B supplementation in nerve regeneration is less consistent. While some studies show benefits, such as increased conduction velocity in patients with carpal tunnel syndrome from vitamin B6 supplementation, overall findings are mixed. A meta-analysis indicated that while vitamin B12 is essential for neurological health, its direct impact on nerve regeneration in humans remains less clear compared to animal studies [9,77]. The differences in outcomes may stem from variations in dosage, individual metabolic responses, and the complexity of human health conditions compared to controlled animal models. The variability in human populations complicates the translation of animal study results to clinical settings.

Vitamin D

Vitamin D has been shown to promote axonal regeneration and improve recovery following nerve injuries in various animal models. For instance, studies indicate that vitamin D enhances the expression of nerve growth factors and supports neuronal survival after injury (Chabas, Erdem). Clinical data on vitamin D's role in nerve regeneration are limited and often inconclusive. While some observational studies suggest a correlation between low vitamin D levels and neurological disorders, definitive clinical trials demonstrating its effectiveness in promoting nerve regeneration are lacking. Large randomized controlled trials have generally not shown significant effects on primary outcomes related to neurological health [78]. The translational challenge here lies in the differences between species regarding vitamin D metabolism and action. Human trials often involve diverse populations with varying baseline vitamin D levels and health conditions, which can obscure potential benefits observed in animal studies.

Vitamin E

Research on vitamin E supplementation for nerve regeneration and injury shows mixed results between preclinical and clinical studies. In animal models, vitamin E combined with vitamin B12 or pyrroloquinoline quinone demonstrated improved functional recovery and histopathological outcomes in peripheral nerve injuries [18,79]. However, translating these promising preclinical findings to human trials has been challenging. While vitamin E supplementation showed neuroprotective effects in patients undergoing cisplatin chemotherapy, reducing the incidence and severity of peripheral neurotoxicity [80], other clinical trials, such as those for Parkinson's disease, have failed to demonstrate significant benefits [81]. The discrepancies between preclinical and clinical outcomes may be attributed to factors including inadequate understanding of the drug's mechanism of action in human disease and failure to conduct preclinical studies using clinically relevant parameters [81].

These differences highlight the complexities of translating animal research into effective human treatments. The overwhelming use of rat models in nerve regeneration research may compromise the design of treatments for humans due to differences in injury types, difficulties in interpreting functional outcomes and inter-species variations in pathophysiology [82]. Addressing these challenges requires more robust clinical trial designs that consider individual variability and optimize dosing strategies based on insights gained from preclinical studies.

Limitations

This systematic review has several limitations that may affect the interpretation and generalizability of the findings. The majority of the included studies, had methodological variability and a moderate risk of bias. Many of the studies included in this review are small in sample sizes, which reduce the statistical power. Small cohort studies cannot represent larger populations, leading to limitation in terms of generalizability. This aspect is more critical in clinical research since small numbers cannot reflect variability in patients' responses. One of the major limitations is that most studies are not randomized, which could increase the risk of selection bias. Non-randomized designs do not control for confounding factors, which may be unbalanced between intervention and comparison groups. Some studies have also lacked an appropriate comparison group, undermining valid comparisons and the ability to attribute observed effects specifically to the intervention. Another serious limiting factor is that a number of studies included did not blind either participants or researchers. In the absence of blinding, the risk for performance and detection bias, especially subjective outcomes such as reduction of pain or sensory improvements is extremely high, which makes the reported outcomes less reliable.

While the search over databases was very wide, the review restricted its results to the English language only. In the process, it must have missed important studies which have been published in another language, which introduces a language bias into the review. These biases in included studies and limitations in the search strategy could affect the strength and generalization of this review's conclusions. Moreover, the heterogeneity among the included studies, especially regarding interventions, outcome measures, and populations, precludes any quantitative synthesis, such as meta-analysis, thereby limiting generalization of findings across diverse clinical settings. Although the findings provide valuable insights, caution should be applied in interpreting them and considering them indicative rather than definitive evidence in relation to the role of vitamin supplementation in nerve regeneration.

Clinical implications

The findings of this review highlight the potential clinical utility of vitamin supplementation in promoting nerve regeneration. For clinicians, these findings suggest strategies to integrate vitamin supplementation into clinical practice. Patients with nerve injuries, chronic neuropathic pain, or conditions such as diabetic neuropathy could benefit from targeted supplementation, particularly when deficiencies in these vitamins are identified. Screening for vitamin levels as part of the diagnostic workup in patients presenting with neuropathic symptoms or recovering from nerve injuries is recommended. Correcting deficiencies may enhance recovery, alleviate symptoms and improve functional outcomes. In cases where deficiencies are detected, clinicians should tailor supplementation to the needs of a patient based on efficacy and safety to avoid complications associated with over-supplementation.

Moreover, although vitamin B12 is widely recognized and used in the treatment of neuropathic conditions, this review illustrates the potential benefits of other vitamins which remain underutilized in clinical practice. The evidence encourages a broader application of these vitamins, especially in patients with conditions characterized by oxidative stress or inflammation affecting nerve health. For example, supplementing with vitamin D may offer additional beneficial effects on cytokine modulation and neuronal repair in inflammatory neuropathies. These interventions also have variable levels of evidence to support their use, and all should be undertaken with caution, using a heuristic approach. Supplementation should be incorporated as an adjunct into standard therapy, not used as an alternative, and any progress or side effects of the patient should be followed up closely. These findings serve a rationale for proactive, evidence-based approach to integrating nutritional interventions into the management of neuropathic conditions.

Conclusions

This review strongly emphasized the important role of supplementation with vitamins in nerve regeneration across all the above-mentioned neurological disorders. Overall, they were shown to possess remarkable neuroprotective and neuroregenerative roles, especially for accelerating nerve healing. Some of the key processes of neuroregeneration that help maintain and repair damaged peripheral nerves such as myelin repair, axon growth and reduction of oxidative stress, which ensues from a higher production of reactive oxygen species (ROS), are central to the protective properties of the vitamins. This means that besides stimulating nerve regrowth and myelin repair, they are also participating in various other pathways to help counteract the harmful effects of oxidative stress. B-vitamins in particular were seen to exert important influences on neuronal function and bring about accelerated axon elongation and remyelination. Collectively, the observational and interventional studies across all these neurological conditions paint a consistent and positive picture. The beneficial effect of these vitamins in promoting nerve regeneration is underpinned by their well-documented role in energy metabolism and neurotransmission. It is crucial to note that certain cytokines released by RA joint inflammation can mimic the effects of nerve injury by creating nerves that act as if there is one [83]. Which, the nerve repair and regeneration could be extremely challenging, thus there is always room for multivitamins to help these processes. Despite their positive findings, studies included in this review have several limitations that could undermine the strength of findings on vitamin supplementation in nerve regeneration. Key limitations include small sample sizes, lack of randomization and limited control groups increased susceptibility to biases. Also, in non-randomized studies, the absence of blinding could potentially affect subjective measures like pain and sensory examination.

Thus, this systematic review underscores the importance of vitamins in nerve regeneration processes and suggests that broader clinical recommendations may enhance patient outcomes in neuropathic conditions. Future research could greatly benefit from conducting larger RCTs with careful blinding methods to minimize biases. It's also essential to establish consistent dosing parameters and more standardized outcome measures to enhance compatibility across studies. Incorporating more objective assessments such as neuroimaging or electrophysiological tests would also support the evidence to establish robust clinical guidelines for managing nerve injuries effectively. Moreover, for future directions, expanding research on vitamin combinations might bring benefits in neurological diseases. While individual vitamins have been studied extensively, there is growing interest in the synergistic effects of vitamin combinations. Research may explore the combined benefits of B vitamins, antioxidants and other vitamins in preventing or slowing the progression of neurological diseases. Furthermore, future research may aim to identify individual vitamin needs based on genetic factors, lifestyle and medical history, which has not been explored in this review. This could lead to more targeted and effective vitamin supplementation strategies for individuals with neurological diseases.,

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