Rev. Fac. Med. Hum. 2024; 24(3):132-138.
DOI: 10.25176/RFMH.v24i3.6686
REVIEW ARTICLES

ISSN Versión Online: 2308-0531
Facultad de Medicina Humana URP
RFMH

VITAMINS B1, B6, AND B12 AND PERIPHERAL NEUROPATHIES: A SYSTEMATIC LITERATURE REVIEW

VITAMINAS B1, B6, B12 Y NEUROPATÍAS PERIFÉRICAS. REVISIÓN SISTEMÁTICA DE LA LITERATURA

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ABSTRACT

The term peripheral neuropathy includes very varied and complex conditions that present difficulties in their diagnostic and therapeutic approach. One of the factors underlying these entities is the deficiency of neurotrophic vitamins B1, B6 and B12. Given the uncertainity and poorly known extremes of this subject and the empirical approach when using the therapeutic resources, a systematic search of the literature has been carried out trying to organize and base on scientific evidence the ideas and conflicting points that have presided over the approach to the issue by the professionals concerned by it. This study serves as the basis for an attempt at expert consensus that promotes a series of recommendations that rationalize and facilitate the management of the issue in clinical practice.

Keywords: Peripheral neuropathies; B vitamin deficiency; Systematic review. (Source: MESH-NLM)

RESUMEN

Bajo el término neuropatía periférica se agrupan condiciones muy variadas y complejas que presentan dificultades para su abordaje diagnóstico y terapéutico. Uno de los factores que se encuentran en la base de esas entidades es el déficit de las vitaminas neurotróficas B1, B6 y B12. Dado los extremos oscuros o mal conocidos de este asunto y el empirismo con el que se han utilizado los recursos terapéuticos, se ha realizado una búsqueda exhaustiva de la literatura intentando ordenar y basar en evidencia científica las ideas y puntos conflictivos que han presidido la aproximación al tema por parte de los profesionales concernidos por él. Este estudio sirve de base a un intento de consenso de expertos que promueva una serie de recomendaciones que racionalicen y faciliten el manejo del tema en la práctica clínica.

Palabras clave: Deficiencia vitamina B1,B6,B12; Neuropatía periférica; Revisión sistemática. (Fuente: DeCS-BIREME)

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Cite as: Longa López JC, Dinamarca-Montecinos JL, Mejía-Rojas K, Bernaola Cuadros AC, Ampuero Bárcena JB, Palacios-Sánchez L, Fernandez-Fairen M. Vitamins B1, B6, and B12 and Peripheral Neuropathies: A Systematic Literature Review.. Rev Fac Med Hum. 2024;24(3):132-138.
doi 10.25176/RFMH.v24i3.6686

Journal home page: http://revistas.urp.edu.pe/index.php/RFMH

INTRODUCTION

Under the generic heading "peripheral neuropathy" (PN) falls a series of complex neurological conditions involving peripheral nerve injury, with varied causes and forms, presenting motor, sensory, and autonomic manifestations in different patterns. PNs are among the most common neurological problems. Their prevalence in the general population is estimated between 1% and 13.5%, with the highest rates in the elderly population[1-3].

The most common type is diabetic neuropathy. It occurs in 50% of diabetics, while diabetes accounts for 18-49% of all PN cases[1]. The overall prevalence of PN in adults aged 40 and older was 28.4% in people with diabetes and 11.8% in those without diabetes[3]. Between 25% and 62% of patients with idiopathic PN are prediabetic. Among prediabetic individuals, 11-25% present PN[4]. Only 10-15% of diabetic patients with PN are symptomatic[5]. The prevalence of painful PN is three and a half times higher in the population with oral glucose intolerance than in the normal population, seven times higher when there is impaired fasting glucose, and ten times higher in diabetics, clearly indicating the impact of metabolic dysregulation on the nervous system from very early stages[4]. Chronic painful distal symmetrical sensorimotor polyneuropathy is present in 13-26% of diabetic patients[6,7].

Studies show that patients with type 1 or type 2 diabetes have up to a 75% reduction in plasma thiamine levels, resulting in 40-70% of diabetes mellitus patients having decreased vitamin B1 levels[8]. In diabetic patients without PN, the vitamin B12 level is below normal in 17%, while this figure rises to 64% among patients with PN[9]. The use of metformin in diabetic patients significantly increases the risk of vitamin B12 deficiency[9-14]. Between 2% and 16% of PNs are inflammatory. Still, 20-30% of PNs remain "idiopathic"[1]. One-third of PNs present with neuropathic pain[15]. Nutritional deficits are a significant cause of PN, especially deficiencies in vitamin B12, thiamine, niacin, pyridoxine, and folate. These conditions are related to malabsorptive gastrointestinal disorders and advanced age[16].

Up to 15% of people aged 60 or older have some vitamin B12 deficiency, mostly secondary to gastritis and associated disorders[17]. Another at-risk group includes patients undergoing bariatric or gastric surgery, who can develop clinically significant vitamin B12 deficiency due to insufficient intrinsic factor production. Between 10% and 33% of these patients present PN[18]. For many years, vitamins B1, B6, and B12 have been empirically and widely prescribed in clinical practice worldwide, particularly in Latin America, to treat peripheral neuropathy symptoms and restore nerve health. Some studies suggest a possible favorable effect of these vitamins on PN symptoms[19-22], but many aspects remain unresolved.

In an effort to clarify these issues, a systematic review of the topic was conducted and is presented in this paper. This literature search will serve as the basis for a subsequent expert consensus.

METHODS

Two experts in bibliographic searches conducted a systematic review of the literature in the PubMed database from 2010 to the present (2024), using the following terms in English: ((((((peripheral neuropathy) OR (diabetic neuropathy)) AND (vitamin b deficiency)) OR (vitamin b1 deficiency)) OR (vitamin b6 deficiency)) OR (vitamin b12 deficiency)) AND (("2010"[Date - Publication] : "3000"[Date - Publication]), finding 7540 references, and in Spanish using ((((neuropatía periférica) OR (neuropatía diabética)) AND (déficit vitamina b)) OR (déficit vitamina b1)) OR (déficit

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vitamina b6)) OR (déficit vitamina b12), gathering 41 more references. An initial screening was carried out by reading and analyzing the title and abstract of each identified reference. There was no limitation on the type or quality of the works. 173 articles were selected and reviewed, of which 87 were deemed relevant for in-depth study for this review by two independent experts (JC and PS). The interobserver agreement was $\kappa = 0.90$. Discrepancies were resolved by the consensus coordinator (MFF).

RESULTS

Vitamin B12 and diabetic neuropathy (DN) are by far the most cited and studied in this field, each in its category, as will be seen throughout this exposition.

A) Vitamin B1, B6, B12 deficiency, and peripheral neuropathy

PN is common in conditions associated with vitamin B1, B6, and B12 deficiencies. While this relationship is indisputable regarding vitamin B12, it is inconclusive for B1 and B6, as there are not enough studies in this regard[22]. Vitamin B1 and B6 deficiencies are not always symptomatic or easily diagnosable, and vitamin B12 status is a good parallel indicator of B1 and B6 status.

Low plasma levels of vitamin B12 and high levels of methylmalonic acid (MMA; a metabolite associated with vitamin B12) and homocysteine (tHcy) may be associated with PN due to peripheral nerve demyelination[23], hypomethylation, altered phospholipid metabolism, and neurotoxic effects of homocysteine. Patients with PN more frequently exhibit reduced vitamin B12 and elevated MMA and tHcy levels compared to patients without PN. However, the causal role of low vitamin B12 levels or elevated MMA or tHcy levels in PN is uncertain, although some studies suggest this relationship, significantly recorded after 2011 but not before[22].

Vitamin B12 and B6 deficiencies may favor the initiation and development of PN, so administering these neurotrophic B vitamins may be beneficial for preventing and treating this condition. Certain groups are at risk of B vitamin deficiencies, as shown in Table 1, depending on the deficient vitamin: B1 [24], B6 [25,26], or B12.

Table 1. Risk Conditions for Vitamin B1, B6, and B12 Deficiencies.

B1. Thiamine Deficiency
Poor intake: i.Diets mainly rich in polished rice/processed grains ii.Chronic alcoholism iii.Parenteral nutrition without adequate thiamine supplementation iv.Gastric bypass surgery, gastrectomy
Poor absorption: i.Malnutrition ii.Bariatric surgery, gastrectomy iii.Malabsorption syndrome

Increased losses:
i.Diarrhea
ii.Hyperemesis (gravidarum or non-gravidarum)
iii.Use of diuretics
iv.Renal replacement therapy

Increased utilization:
i.Pregnancy
ii.Lactation
iii.Hyperthyroidism
iv.Refeeding syndrome

B6. Pyridoxine Deficiency

Reduced intake:
i.Severe malnutrition

Reduced absorption:
i.Elderly over 60 years old
ii.Intestinal disease
iii.Bariatric surgery

Increased clearance:
i.Liver disorders
ii.Hepatitis
iii.Medications such as anticonvulsants, isoniazid, hydralazine, levodopa, altretamine, barbiturates, corticosteroids, or penicillamine

Increased degradation:
i.Elevated alkaline phosphatase levels

Sideroblastic anemia:
i.Hematologic pathway enzymes with low affinity for pyridoxine

Complex formation:
i.Isoniazid, certain fungi, antiquitin deficiency (α-aminoadipic semialdehyde dehydrogenase)

Low maternal levels

B12. Cobalamin Deficiency

Gastric alterations:
i.Auto-antibodies against intrinsic factor or parietal cells (e.g., pernicious anemia)
ii.Gastrectomy
iii.Bariatric surgery
iv.Autoimmune metaplastic atrophic gastritis

Small intestine diseases:
i. Malabsorption syndrome
ii. Ileal resection or bypass
iii. Inflammatory bowel disease (e.g., Crohn's disease)
iv. Celiac disease
v. Intestinal dysbiosis
vi. Blind loop syndrome
vii. Dibothriocephalus latus (fish tapeworm)

Pancreatitis
i. Pancreatic insufficiency

Pharmacological agents:
i. Neomycin
ii. Biguanides (ej. metformin)
iii. Proton pump inhibitors (ej. omeprazole)
iv. Histamine 2 receptor antagonists (e.g., cimetidine)
vi. Nitrous oxide (N2O), used for anesthesia or recreationally

Diet:
i. Strict vegan diet
ii. Vegetarian diet during pregnancy

Hereditary diseases:
i.Hereditary transcobalamin II deficiency

In older adults, for example, the Framingham Study cohort [27] reported a prevalence of B12 deficiency of 40.5% among individuals aged 65 to 99, compared to 17.9% among those aged 22 to 63. It is noteworthy that there is a functional insufficiency of cobalamin, common in the elderly and of unknown cause, with normal plasma levels of vitamin B12 but elevated levels of MMA or tHcy[28].

The intake of medications such as metformin, anticonvulsants, calcium antagonists, 5-amino-salicylates, and chemotherapy can decrease the levels of these vitamins. Medications that reduce gastric acid, such as proton pump inhibitors (PPIs), antacids (antiH2), or histamine-2 receptor blockers, may reduce vitamin B12 absorption, especially when used long-term. Gastric acid is involved in the dissociation of vitamin B12 from food proteins, a step prior to binding to intrinsic factor (IF). Some authors recommend monitoring vitamin B12 concentrations in patients receiving prolonged treatment with PPIs or antiH2, but there is no consensus on whether this should be done. In cases of vitamin B12 deficiency in patients taking PPIs or antiH2 chronically, it should be assessed whether it is appropriate to continue treatment with these medications.

Chronic administration or high doses of colchicine can alter the absorption of vitamin B12 and thus increase its requirements. This seems to be due to the fact that this substance acts on the receptors of the terminal ileum to which the vitamin B12-IF complex binds for absorption. Monitoring of vitamin B12 concentrations is recommended in patients on long-term colchicine treatment, but there is no consensus on the frequency of this monitoring. Vegans or strict vegetarians are susceptible to this deficiency and may need to resort to vitamin supplements taken orally. Patients undergoing bariatric or gastric surgery are predisposed to vitamin B12 deficiency due to reduced gastric parietal cells and,

therefore, insufficient IF production. In the early stages of PN, there is a subclinical neuropathy scenario where there are still no symptoms or clinical signs (stages 0 and 1a) [29]. In the subsequent stage 1b, neuropathic damage can already be documented, still in its initial phase, through neurophysiological or morphometric tests, which allow early diagnosis of small fiber alterations, even before the appearance of neuropathic pain. This opens a window of opportunity, necessitating preventive interventions for the early and still reversible pathophysiological disorders of the PN continuum before reaching a point of no return[30].

The detection of these situations should be as early as possible, despite all the difficulties and drawbacks such as the existence of the initial subclinical phase and the limited availability and feasibility of precise analytical determinations. In cases where analytical tests are not possible and symptoms of PN appear with normal vitamin concentrations, PN screening should be based on clinical criteria. The proposal by Hin et al. is valid, defining a PN patient as one who meets more than two neuropathy symptoms and more than two abnormalities detected in the neurological examination of the lower limbs, among the parameters described by those authors in their study[31].

Treatment with vitamin B1 can be associated with a significant improvement in PN symptoms [22], with neurological imbalances due to vitamin B6 deficiency usually reversible through adequate supplementation [32]. Although in the study by Stein et al., the improvement of symptoms after administering B12 alone or a combination of B1, B6, and B12 was not significant[22], multiple observational and experimental clinical studies have indicated that neurotrophic B vitamins can improve PN symptoms [33-39]. The most recent evidence comes from a study where patients with PN for various reasons received 100 mg of oral thiamine mononitrate, 100 mg of pyridoxine hydrochloride, and 5000 µg of cyanocobalamin once a day for three months, improving the primary outcome (Total Symptom Score, TSS), and secondary outcomes such as relief of clinical manifestations of pain, burning, paresthesias, numbness, and tingling, improved quality of life (QoL), and safety assessed by adverse effects.

The greatest mean reduction in TSS (66%) was observed in the subgroup of diabetic patients, followed by carpal tunnel syndrome (64.7%), neuropathy with more than one cause (64.3%), other causes of neuropathy (62.7%), and idiopathic neuropathy (57.7%). The mean relief in the visual analog scale (VAS) of pain, burning, paresthesias, numbness, and tingling in the overall population was 69.1%, 63.5%, 89.6%, and 57.8%, respectively. The TSS had improved within 8-14 days of starting treatment, and there was also a significant reduction in all VAS parameters and a considerable increase in quality-of-life scores (physical and mental components) at 12 weeks [33]. A randomized controlled trial (RCT) also demonstrated a significant improvement in DN in patients with vitamin B12 deficiency (< 400 pmol/l) after administering 1000 µg/day of vitamin B12 for 12 months [34]. Three systematic reviews of the literature on this topic [35,36], one of them with a meta-analysis of RCTs [37], have presented favorable conclusions for the administration of vitamin B12 in DN, providing a level I of evidence. The combination of methylcobalamin, methylfolate, and pyridoxal phosphate relieved pain and improved the quality of life of diabetic patients with PN, despite not correcting the vibration sensitivity threshold [38]. In patients with DN, the number needed to treat (NNT) with a B1, B6, and B12 vitamin supplement was 5.08 for pain reduction[39].

B) Determination of Vitamin B1, B6, B12 Deficiency

The diagnosis of these conditions is based on three fundamental pillars: analysis of risk factors, clinical screening of symptoms and signs, and biochemical

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screening of vitamin levels studied here. However, the latter is not always determinative alone of the decision to supplement a patient. Additionally, the concept of "relative deficiency" must be considered, referring to the context in which a patient may have seemingly normal or sufficient levels of vitamins B1, B6, and B12 to meet physiological requirements, as long as they are not under physical and/or mental stress that increases demands, potentially leading to clinical deficiency manifestations in such circumstances.

Evidently, in all cases, plasma vitamin B12 levels should be measured as a potential collateral indicator of B1 and B6 deficiency. If a deficiency is suspected, specific determination and management of their levels should be initiated. Analytical determination of vitamin B1, B6, and B12 levels is crucial for diagnosing deficiencies and monitoring their evolution and treatment. It should be emphasized that the values of these determinations vary greatly depending on the analytical method and laboratory used, lacking universally applicable cut-off points.

Plasma levels below which Vollbracht et al. considered "deficiency" for vitamins B1, B6, and B12 are 35 µg/l for vitamin B1, 4.1 µg/l for B6, and 193 pg/ml (142 pmol/l) for serum vitamin B12[40]. Classically, deficiency levels of vitamin B12 have been estimated between 160 and 245 pg/ml (120 and 180 pmol/l), with the most commonly accepted limit being 200 pg/ml (148 pmol/l) [41,42]. Setting the cut-off point defining vitamin B12 deficiency at 200 pg/ml (148 pmol/l), the prevalence of low serum B12 levels in the non-institutionalized US civilian population was 2.8%. If this point is set at 271 pg/ml (200 pmol/l), this percentage rises to 10.5% and to 25.6% if the limit is elevated to 350 pg/ml (258 pmol/l) [43]. Most laboratories consider serum values below 200 or 250 pg/ml (148 or 185 pmol/l) to be abnormal. According to WHO criteria, serum vitamin B12 levels ≤ 200 pg/ml (≤ 148 pmol/l) are compatible with deficiency, between 201 and 300 pg/ml (149-221 pmol/l) are borderline values, and levels above 300 pg/ml (> 221 pmol/l) are considered "sufficient" or "adequate"[44]. The most frequently taken cut-off point defining the "normality" of vitamin B12 levels is 350 pg/ml (260 pmol/l), with levels below this considered "deficient" and those below 200 pg/ml (148 pmol/l) as "deficiency." Below this value, more than 15% of subjects had elevated plasma MMA concentrations, significantly different from those with vitamin B12 above 350 pg/ml (260 pmol/l) [27]. The prevalence of vitamin B12 deficiency, using this cut-off point (350 pg/ml or 260 pmol/l), is 17.1%[23].

Vitamin B12 is mainly stored in the liver. The average B12 content in liver tissue is approximately 1.0 µg/g in healthy adults [45,46]. The hepatic reserve varies between 1000 µg and 3000 µg, depending on liver size. The minimum reserve compatible with health is 300 µg [47]. Daily losses of the hepatic B12 reserve are 0.1 to 0.2%, regardless of the reserve magnitude [45,48-50]. A person with a B12 reserve of 1200 µg and a loss of 0.1% excretes 1.2 µg of B12 per day. Since 50% of dietary B12 is absorbed, the required daily intake to replenish reserves is 2.4 µg of B12[51].

Considering that the hepatic vitamin B12 reserve gradually and steadily declines, if absorption/intake/supplementation ceases entirely, the reserve will sustain the situation for three years, reducing plasma levels by about one-third per year until reaching 400 µg/ml at the end of the second year, close to the 300 µg hepatic reserve limit compatible with health [70]. This is consistent with the average three-year period in which B12 deficiency signs appear following total gastrectomy [52]. Dinamarca-Montecinos and Vásquez-Leiva categorized vitamin B12 deficiencies based on thirds of the highest normal plasma value (1200 pg/ml or 885 pmol/l), proposing the following gradation: ≤ 400 pg/ml (≤ 295 pmol/l) = suboptimal; between 401 and 800 pg/ml (296-590 pmol/l) = at risk; and > 800 pg/ml (> 590 pmol/l) = optimal. Thus, 'suboptimal' would include patients with vitamin B12 deficiency according to WHO cut-off points, as well

as a previously unclassified group (301-400 pg/ml or 222-295 pmol/l) [53]. Over three years without intake, there will be hepatic reserve depletion, maintaining vitamin B12 levels between 350 and 450 pg/ml (258-332 pmol/l). Histological and pathological studies have shown that these levels correspond to the threshold of peripheral nerve structural damage and neurological symptoms due to this damage. Although it was traditionally considered that neuropathy associated with vitamin B12 deficiency occurred with levels below 250 pg/ml (184 pmol/l), it has been indicated that the threshold for developing nerve conduction alterations is 450 pg/ml (332 pmol/l) [23,54].

Adults with concentrations between 200 and 340 pg/ml (150-250 pmol/l) have already exhausted their vitamin B12 reserves, with individuals in "deficiency" and at greater risk of clinical and metabolic dysfunction. Approximately 50% of the population with vitamin B12 levels below 100 pg/ml or 75 pmol/l (severe deficiency) and 40-50% of those between 100-200 pg/ml (75-150 pmol/l) will have clinically diagnosable symptoms [55].

Given all the above, vitamin B12 levels above 400 pg/ml (295 pmol/l) could be considered "normal" and "low" below that figure. This would also be the "normality" for Langan and Goodbred, who also label values between 150 and 399 pg/ml (111-294 pmol/l) as "low-normal" and below 150 mg/ml (111 pmol/l) as "low" [56]. Since vitamin B12 concentrations do not accurately reflect intracellular concentrations, plasma MMA or tHcy levels are considered more precise indicators of this status[57]. MMA is the most sensitive marker of vitamin B12 status, with levels above 0.271 µmol/l suggesting deficiency [23]. If MMA levels are normal, the appropriate cut-off point to define vitamin B12 insufficiency may be 340 pg/ml (250 pmol/l) [55]. Experts have suggested that if a patient's serum vitamin B12 level is below 150 pg/ml (110 pmol/l), MMA levels should also be checked to confirm deficiency [56].

Total blood homocysteine level is another marker, less specific than MMA, which increases rapidly as vitamin B12 levels decrease. A homocysteine level above 15 µmol/l suggests B12 deficiency [58]. It is considered "metabolically significant" when vitamin B12 levels are < 200 pmol/l and tHcy > 20 µmol/l [41]. In cases where levels are close to insufficiency but "normal," the study should be conducted serially to determine if levels are stable or decreasing, in which case the cause should be investigated, managed, and supplemented accordingly.

c) Indication for Vitamins B1, B6, B12

It is obvious that the administration of neurotrophic B vitamins should be considered when there is a demonstrated deficiency of these vitamins. Conversely, there is no need to administer them if the patient is in the "normality" condition already expressed. The primary therapeutic objective in the face of such a deficiency is logically to treat that situation, but even in the absence of it, other therapeutic purposes worthy of consideration may advise their administration.

Sometimes, even if there is no actual deficiency, but plasma levels are declining due to insufficient intake and/or progressive use of hepatic reserves, they may be indicated to prevent the development of the deficiency. The attitude of "normal levels, asymptomatic patient, do nothing until levels drop more and/or become symptomatic" should not be adopted. Evidently, in at-risk populations and/or those with PN, robust plasma levels are desirable, indicating good hepatic reserve levels capable of bypassing this process. When plasma B12 levels depend exclusively on cellular metabolism due to the absence of absorption and constant use of hepatic reserves, levels above 800 pg/ml[15,21]. (15 ET

and 21 RN; NIIIC, NIVE) would be robust and desirable as they indicate that only one-third of the hepatic reserve has been used, with a margin of another third guaranteeing similar cellular metabolism to when absorption is normal[53], before symptoms begin[54], and reaching the minimum reserve level compatible with health[53].

If the values are close to their lower limit and for whatever reason the deficiency cannot be confirmed with certainty through other determinations, neurotrophic vitamins can be administered to at-risk patients, with close follow-up of the case. This indication should be based on the etiology and dimension of the deficiency and the patient's risk factors, such as predisposition to deficiency or PN, as seen in patients with diabetes, chronic kidney disease, or advanced age [59]. The decision is a function of the patient's belonging to a risk group and the presence of compatible symptoms and/or signs. Supplementation of B1, B6, B12 should be considered in patients with or without clinical, neurophysiological, and/or morphometric manifestations of PN with biochemically demonstrated levels in the deficiency range, and in patients at risk of deficiency, with clinical, neurophysiological, and/or morphometric manifestations of PN, even if the deficiency has not been biochemically demonstrated. Given the systemic and complex nature of the involvement, besides identifying deficiency risk factors, it is crucial to stratify the patient's overall risk, including pro-oxidative comorbidities, cardiovascular risk associated with increased homocysteine levels, quality of life (pain, sleep quality, etc.), and socioeconomic status. All this must be considered when deciding whether to supplement a patient or not. A recent consensus unanimously determined that neurotrophic vitamins should be considered for patients:

•Over 60 years old
•Diagnosed with diabetes
•Diagnosed with HIV or TB
•On certain medications such as metformin or isoniazid
With chronic kidney disease undergoing dialysis On restrictive diets due to their high risk of developing PN [59].

For most individuals following a balanced diet, there is no need to consider preventing a deficiency of these vitamins. If there is a risk of deficiency for any other reason, it should be prevented with oral supplementation. Similarly, the storage capacity of vitamin B1 in skeletal muscles, brain, heart, liver, and kidneys is limited to 30 mg. An insufficient dietary intake or excessive demand for this vitamin can lead to a deficiency state within just three weeks, which is why dietary supplementation may be required[60].

d)Diabetes, Vitamin B1, B6, B12 Deficiency, and Peripheral Neuropathy

As mentioned before, these conditions often overlap, so for patients with prediabetes and diabetes, three relevant issues must be considered:

· Screening and diagnosing neuropathy, which is not always symptomatic.
· Differentiating the etiology of PN, which, paradoxically, is not always diabetes. Up to 10% of cases can be due to other causes that must be considered [55], as vitamin supplementation would fail in such cases.
· Determining the cause of possible or confirmed neurotrophic B vitamin deficiencies to establish the appropriate dosage and duration of treatment.

Glycemic control has limited efficacy in developing PN. Therefore, an effective intervention is needed to act causally or modify the pathophysiology of DN. Vitamin B12 may be the most used[6], as its deficiency is common in patients with type 2 diabetes mellitus (DM2), causing a series of neurological disorders that resemble, accompany, or accelerate DN. Several studies have investigated the effect of B12 supplementation on DN, some with favorable effects. However, many of these studies have significant biases. Most were conducted in patients with poorly controlled DM2.

Others administered not only vitamin B12 but various combinations of B12 with different supplements or substances. Additionally, there is significant variation in these studies regarding baseline blood levels of vitamin B12 (200-600 pg/ml or 150-450 pmol/l), dosage (25 to 2000 µg), duration (12 to 24 weeks), molecular form (cyano-, methyl- or hydroxycobalamin), administration mode (oral or parenteral), and participant selection (with or without established DN, peripheral or painful).

Diabetic patients, especially those over 60 years old, may present signs of neurological dysfunction even if B12 levels are above 150 pmol/l, considered normal by many authorities. According to this, B12 levels between 200-542 pg/ml (150-400 pmol/l) should be considered a "relative" B12 deficiency in people with diabetes and managed accordingly [61]. Given the generally favorable effect of B12 administration on DN[34], and since almost 95% of participants had this "relative" B12 deficiency, it is reasonable to recommend supplementation with this vitamin in all patients with DN and B12 levels below 542 pg/ml (400 pmol/l)[61].

The relationship between metformin administration and B12 deficiency is well-known[11-14,61,63], but it remains controversial whether diabetics treated with this drug should receive preventive B12 supplementation. The American Diabetes Association (ADA) recommends closely monitoring patients receiving metformin to avoid B12 deficiency, especially due to the high risk that diabetics have of developing this deficiency and PN, regardless of whether they take metformin[64]. Vitamin B12 levels < 200 pg/ml (150 pmol/l) and between 200-300 pg/ml (150-400 pmol/l) were observed in 24.5% and 34.5% of metformin users, respectively, significantly higher than in non-metformin users (17.3% and 22.6%, respectively; $p < 0.001$). Overall, the B12 level was < 300 pg/ml (400 pmol/l) in 52.2% of patients[65].

The Metformin Usage Index (MUI), defined as the product of the metformin dose administered in mg and the duration of treatment in years divided by 1000, is useful for evaluating the risk of B12 deficiency. There was a significant association between MUI > 5 and high risk of B12 deficiency ($p < 0.01$). The highest risk was observed among patients with MUI > 15 [odds ratio (OR) 6.74, 95% CI 4.39-10.4], followed by patients with MUI > 10 (OR 5.12, 95% CI 3.12-8.38). Therefore, an MUI > 5 suggests a high risk of B12 deficiency[65]. Patients aged 50 or older, treated with metformin for at least 18 months, have a two to three times higher risk of developing PN [66].

e) Management of Vitamins B1, B6, B12 in Their Deficiencies and Peripheral Neuropathy

Once a vitamin B deficiency is identified, treatment should begin as the first step in preventing PN without waiting for symptoms to appear. The "clinical silence" or symptom-free phase is a major issue. For example, 50% of patients with DN have no symptoms, with clinical practice guidelines recommending "pathogenic therapy" aimed at correcting the condition's mechanisms before symptoms develop[67]. This high percentage of "clinical silence" opens two significant gaps in DN management: early underdiagnosis and undertreatment.

Neuropathy often starts insidiously and progresses slowly over the years. Symptoms take months to appear and develop, and considerable time may pass before neuropathy is diagnosed, delaying treatment initiation and losing the opportunity to prevent or slow its progression. It is advisable to start treatment at the beginning of neuropathy or, if possible, even before it becomes symptomatic[19]. Up to 50% of chronic sensory-motor polyneuropathies progress silently, and only 20% of DNs are painful, requiring early diagnosis and treatment before evolving into more advanced stages and causing severe definitive disorders[68,69].

Although it has been considered that PN associated with vitamin B12 deficiency occurs when its level is below 250 pg/ml (184 pmol/l), the threshold for developing nerve conduction alterations is 450 pg/ml (332 pmol/l), requiring the vitamin's administration much earlier than those 250 pg/ml (184 pmol/l)[54]. The earlier the intervention, the greater the benefits for patients.

Once decided, it depends on the magnitude and type of deficiency, the severity of symptoms, the possibility of reversibility, and the response to the implemented management. According to all this, doses and treatment duration should be sufficient to optimize and maintain plasma levels and hepatic reserves as much as possible. It must be defined whether the condition associated with the deficiency and/or PN is transient or permanent, and whether it affects the absorption pathway or not. If it does not affect it, oral supplementation can be used at a sufficient dose to ensure the absorption of 2.4 µg of vitamin B12 per day. Given the percentage absorbed of orally administered B12, the daily dose should be around 500-1000 µg/day (0.5-1 milligrams/day) until symptoms improve, generally for 2-3 months, but depending on the underlying cause of the deficiency and the duration of the underlying disease or condition. If it is permanent, that regimen should be maintained. If it affects the absorption pathway, the intramuscular (IM) route should be used, ensuring 2.4 µg daily of vitamin B12 as long as the disease or originating condition persists.

An injection of 10,000 µg every 4 months should be sufficient to maintain plasma levels above 400 pg/ml (295 pmol/l). If this situation is persistent, supplementation should be prolonged over time [19]. The specific daily requirements of each patient must be considered, thinking that depending on symptoms and the type of associated pathology, they may have higher requirements. The recommended daily intake (RDI) of vitamin B1 for the healthy population is 1.2 mg per day for men and 1.1 mg per day for women who are not pregnant. In Latin America, doses of oral vitamin B1 up to 600 times higher than the RDI are recommended to treat insufficiency states [19]. For vitamin B6, the RDI is 1.3 mg per day for men and women aged 19 to 50, but adults over that age need 1.7 mg per day. Vitamin B6 is normally well tolerated in doses up to 200 mg per day in adults. It is commonly prescribed in Latin America for therapeutic purposes in oral doses 50-60 times higher than the RDI [19].

The RDI for vitamin B12 is 2.4 µg. The estimated daily body loss is 2 to 5 µg. This "loss" results from the difference regarding the total ingested vitamin B12, including enterohepatic loss of the absorbed portion and non-absorbed due to saturation of ileal receptors. Saturation is reached with 2000 µg of vitamin B12[19].

f) Route

Vitamin B12 can be administered orally or IM. It is evident that the route can affect the absorption and bioavailability of the vitamins, but the choice depends largely on the specific considerations of each patient. The choice of one route or another should be made considering the patient's characteristics (advanced age, swallowing problems, etc.), adherence to treatment, preferences, and cost. In clinical practice, vitamin B12 treatment often begins with IM injections, once or twice a week for three weeks, and when the patient shows improvement, maintenance treatment is given orally [19]. For parenteral supplementation of vitamin B12, 1000 µg (1 mg) of cobalamin on alternate days for two weeks is recommended, followed by IM injections of 1000 µg of cobalamin every three months for those without neurological compromise.

In the case of neurological compromise, the same dose is administered until symptomatic improvement is observed, followed by IM injections every two months. In cases of irreversible neurological damage, it should be administered for life. Logically, for long-term treatment, oral administration is preferable. However, certain at-risk groups may require injections, such as if there is decreased absorption.

If urgent correction is needed, the parenteral route is the norm, particularly in four scenarios:

- Symptomatic or severe anemia (Hb < 8 g/dl)
- Contexts with neurological or neuropsychiatric symptoms where delaying correction of the deficiency could leave permanent sequelae
- Concerns about treatment adherence
- When absorption failure is due to pernicious anemia or intestinal blind loop syndrome, entities in which optimal absorption concentrations are feared not to be reached orally. However, literature reports the effectiveness of oral cyanocobalamin in cases of pernicious anemia with a result similar to the parenteral route.

Precisely in this regard, a 2018 meta-analysis evaluated the effectiveness of oral versus IM vitamin B12 for treating this vitamin's deficiency, finding no statistically significant difference in the outcomes evaluated (serum vitamin B12 levels, hemoglobin levels, total homocysteine, and serum MMA)[70]. In general, there is a consensus that B1, B6, and B12 vitamins should be given IM to patients with PN who present a specific deficiency of these vitamins, gastrointestinal tract disorders, and those with acute or severe conditions[59].

The IM route has traditionally been the most used to overcome any FI deficiency because oral bioavailability was considered poor. However, the oral route has advantages, such as greater respect for patient autonomy, higher patient satisfaction, lower treatment costs, and fewer risks in patients on anticoagulants. On the other hand, studies investigating its effectiveness have indicated that oral administration has effects equal to IM in compensating for and improving the biochemical and clinical manifestations of deficiency [71-74]. The oral absorption of high-dose vitamin B12 is as effective as the IM injection [70,75]. A daily oral dose of 1000 µg methylcobalamin normalized serum vitamin B12 levels, making it recommendable for patients with absolute or relative deficiencies of this vitamin [34]. There is now evidence that both IM and oral routes, when there are no absorption disorders, at high doses, are equally effective for this purpose.

It should be noted that the stability of neurotrophic B vitamins in injectable formulations varies depending on the specific formulation and storage conditions. Given that there are preparations that include all three vitamins and that B12 denatures when mixed with B1 and B6 in injectables, systems that ensure their separation must be available. This problem does not exist with oral formulations. When administered orally as a dietary component, vitamin B12 is absorbed in the ileum and requires IF and calcium to cross the intestinal mucosa. Ileal receptors are saturated with contents between 1.5 to 2.5 µg in food, so greater absorption than this amount is physiologically limited[50]. A second relevant absorption mechanism for high therapeutic doses is passive diffusion, which represents 1-2% of total absorption.

It is accepted that the absorption of orally administered B12 by healthy adults with normal gastric function is 50%[76]. It should be noted that there are dispersible tablet formulations with improved bioavailability. Other routes of administration of these vitamins have also been used. The sublingual route can avoid the complex absorption process of vitamin B12, reaching the bloodstream directly through sublingual veins[77]. Due to its relative ease and painless nature of administration, it should be considered especially for the pediatric population where available. Although studies testing this route report promising results, it is important to note that almost all include patients with mild and subclinical vitamin B12 deficiencies, over short periods, with the vitamin administered sublingually under "laboratory" conditions without missed doses. It

is therefore difficult to extrapolate to the "real world," where patient compliance is usually not as good. Like the sublingual route, the intranasal route can also avoid the complex absorption process of vitamin B12 and reach the bloodstream directly[77]. Its ease of administration has the same advantages for patients as sublingual therapy and has been shown to be preferred over IM in latitudes where available. However, the evidence for this route's efficacy compared to more classic treatment routes remains limited.

Occasionally, vitamin B12 is used subcutaneously, especially in patients with congenital errors of cobalamin metabolism requiring high pharmacological doses to maintain normal biochemical and metabolic processes. Efficacy studies for the subcutaneous route are limited.

g) Dose

The effect of neurotrophic B vitamins is dose-dependent. To achieve a minimum effective concentration and reach a rapid therapeutic response, a high initial dose is necessary, while the maintenance dose ensures that concentration in the medium and long term. In patients over 70 years old with a mild vitamin B12 deficiency (135-405 pg/ml or 100-300 pmol/l), B12 absorption is dose-dependent, and serum levels increase more with a 1000 µg dose than with 200 µg, with a 167% increase in 16 weeks[78]. Regarding vitamins B1 and B6, the improvement in symptoms in patients with symptomatic DN is greater when administering 25 mg of B1 and 50 mg of B6 than 1 mg of vitamin B1 and 1 mg of B6, with a higher percentage of improved patients.

The treatment of a mild-moderate vitamin B12 deficiency ("insufficiency," 200-400 pg/ml or 148-295 pmol/l) can be initiated orally with 500 to 1000 µg per day. The response should be monitored after two months, and if concentrations do not significantly increase, it is advisable to switch to the IM route and assess the possible causes of the deficiency. Severe deficiency, or "deficiency" (< 200 pg/ml or < 148 pmol/l), or specific patient groups such as older people, hospitalized patients, diabetics with neurological symptoms, and diabetic PN, can be treated with higher doses, more frequent applications, or both. The recommended initial dose in these cases is 1000 µg once a day for a week, followed by 1000 µg/week for 4-8 weeks until the deficiency is corrected. Once corrected, the use of the oral route for maintenance treatment can be considered.

Patients with significantly reduced absorption may initially receive doses of up to 10 mg or 25 mg once or twice a week for three weeks, depending on the patient's condition, to ensure reinforcement. If necessary, 25 mg can be administered once a month long-term.

Table 2 references the recommended doses for various conditions.

Table 2. Vitamin B12 Dosages for Different Conditions.

Condition	Dosage	Route
Severe Malabsorption		
Pernicious anemia (autoimmune gastritis)	1000 µg/day for 1 week,	IM
Total or partial gastrectomy	then once/week for 4-8	
Gastric bypass or other bariatric surgery	weeks, then once/month	IM
Ileal resection or reconstructive surgery (ileal bypass or ileocystoplasty)	for life or 1000-2000 µg for life	IM
Inflammatory bowel disease, tropical sprue		
Imerslund-Gräsbeck syndrome and other syndromes		oral

Mild Malabsorption		
Protein-bound vitamin B12 malabsorption Mild atrophic gastritis Metformin use Use of gastric acid inhibitors	500-1000 µg/day or 1000 µg/day or alternate days for 1 week, then once/week for 4-8 weeks, then once/month for life	oral IM
Dietary Deficiency		
Strict vegan or vegetarian diet	50-150 µg/day or twice/week	oral
Low meat or dairy diet	Supplements with > 2 µg of vitamin B12 or fortified foods with vitamin B12	oral
Mothers with vitamin B12 deficiency	Supplementation 1-2 µg/day	oral
Severe Malabsorption		
Pernicious anemia (autoimmune gastritis) Total or partial gastrectomy Gastric bypass or other bariatric surgery Ileal resection or reconstructive surgery (ileal bypass or ileocystoplasty) Inflammatory bowel disease, tropical sprue Imerslund-Gräsbeck syndrome and other syndromes	1000 µg/day for 1 week, then once/week for 4-8 weeks, then once/month for life or 1000-2000 µg for life	IM
Mild Malabsorption		
Protein-bound vitamin B12 malabsorption Mild atrophic gastritis Metformin use Use of gastric acid inhibitors	500-1000 µg/day or 1000 µg/day or alternate days for 1 week, then once/week for 4-8 weeks, then once/month for life	
Dietary Deficiency		
Strict vegan or vegetarian diet	50-150 µg/day or twice/week	oral
Low meat or dairy diet	Supplements with > 2 µg of vitamin B12 or fortified foods with vitamin B12	oral
Mothers with vitamin B12 deficiency	Supplementation 1-2 µg/day	oral

No dosage adjustments for vitamin B12 are required in patients with renal or hepatic insufficiency[79]. In contrast, the Estimated Average Requirement (EAR)[55] in pregnant women should be increased by 0.2 µg/day to meet fetal demands. The key criteria for adjusting the loading and maintenance doses of neurotrophic B vitamins are symptom improvement and safety profile [51]. The work of Hakim et al.[33] provides an idea of the time frame to consider for evaluating the therapeutic response to these vitamins, which also depends on the indicator to be assessed, the etiology and severity of the neuropathy, and the idiosyncratic characteristics of each patient.

Specifically, the dosage of neurotrophic B vitamins depends on the type of vitamin in question and the underlying cause of the vitamin deficiency, which will determine the duration of treatment based on its reversibility. When these vitamins are administered in combination, there is a tendency to establish the dose based on cobalamin, but it should not be forgotten that the other two neurotrophic vitamins also have particular prescription profiles.

In PN, generally speaking, if the vitamin B12 level is below 450 pg/ml (332 pmol/l), oral vitamin B12 supplementation (2000 µg/day) can be initiated, or 1000 µg per day IM/subcutaneously for 7 days, followed by 7 more doses on alternate days for 2-3 weeks, and when the patient shows improvement, maintenance treatment orally. When patients have moderate or severe symptoms or persistent neuralgia, high doses of up to 10-25 mg are normally prescribed. In PN, when neurotrophic vitamins are given in high doses for 4 weeks, they are more effective than lower doses, reducing pain and other clinical problems[80]. In any case, so far, there is no data to demonstrate that vitamin supplementation reduces neuropathy in the absence of frank deficiency [54].

Evidence has suggested that the combination of B1, B6, and B12 is therapeutically effective, especially in high doses [33]. The pharmacological synergy and therapeutic effects of using these vitamins in the peripheral nervous system are facilitated and potentiated by the intrinsic functions of each vitamin with a main mechanism of action and other complementary ones. Therefore, the combined administration of these vitamins enjoys these advantages and justifies the availability of formulations with this combination and their widespread use.

h) Duration

Even in patients who experience symptom relief after a few weeks of treatment, maintenance therapy is advisable to prevent relapses, possibly requiring long-term treatment. Regarding PN, it is a chronic entity that requires long-term management and treatment[59]. Daily administration of a 1000 µg dispersible tablet of methylcobalamin for 1 year produced significant improvements in pain, neurophysiological parameters, and QoL, with a substantial increase in vitamin B12 levels [34].

Long-term is not necessary in certain acute instances such as those induced by drugs or inflammatory neuropathies. Symptoms seen with taxanes, antimycobacterials, immunosuppressants, and azoles are often reversible and completely resolved by reducing doses or stopping the administration of these drugs. Patients with conditions in remission or controlled, i.e., those where the cause, such as diabetes or neurotrophic B vitamin deficiency, is being adequately treated, may not require further attention.

I) Treatment Control

People with vitamin B12 deficiencies should undergo regular checks to assess the effectiveness of treatment and adjust doses as necessary. Long-term treatment should always be monitored to ensure its effectiveness and safety [19].

Regarding the toxicity risk of neurotrophic B-complex vitamins, only vitamin B6 presents it[81]. Prolonged treatment with high doses of vitamin B6 can cause adverse effects, such as dermatological reactions, vomiting, or "burning mouth" syndrome[82]. In rare cases, extreme overdosing of vitamin B6 for months, exceeding an average of 500 mg daily for more than 6 months or doses of more than 2000 mg per day in less

than 2 months, can cause sensory-motor neuropathies, which are generally reversible after discontinuation of treatment[81,83]. This side effect is reported in multiple instances but is very rarely observed in daily practice.

Regarding vitamin B12, when its circulating rate exceeds its binding capacity with transport proteins, such as after injection, the excess is excreted in the urine [84]. Studies have suggested an association between serum vitamin B12 levels and mortality risk, discouraging the use of B12 supplements. However, public health studies of the general North American population (NHANES) provide assurance that high B12 levels are not per se the cause of this risk [85].

DISCUSSION

Information and knowledge are keys to success, and that is what this work aims to convey. The term "peripheral neuropathy" has been widely and generally used to refer to a broad category of conditions that structurally and/or functionally compromise peripheral nerves, expressed by a collection of symptoms and signs equivalent to their diagnosis. Over 100 different causes of peripheral neuropathies are cited[1], including diabetes, alcohol consumption, nutritional deficiencies, malabsorption syndromes, bariatric surgery, oncological treatments, HIV, leprosy, etc. In 20%-30% of cases, the cause is not identified, and idiopathic neuropathy is discussed [1].

The prevalence of PN is 2.4% in the general population, increasing with age up to 8%[86]. In Colombia, the prevalence ranged between 4.8% and 8.5% depending on the region[87,88]. In the North American population, the prevalence of PN was 10.4% among those aged 40 to 69, and 26.8% in those aged ≥ 70 years[3]. In diabetics, this figure rises to 28%[89], with the expectation that 50% of diabetics will develop it in the next 25 years[90]. In DM2, the prevalence is 31.5% (95% CI 24.4–38.6%) vs. 17.5% in DM1 (95% CI 4.8–30.2%) [91].

In Latin America, studies show an estimated prevalence of peripheral diabetic neuropathy of 46.5%[92], and specifically 44.2% in Lima (Peru)[93]. However, as a counterpart to the importance of the problem, as pointed out by Calderón-Ospina et al. in a very recent work[20], the literature on the recognition and management of these clinical pictures is scarce in Latin America. Given that one of the causes of PN can be a deficiency state of vitamins B1, B6, B12, that therefore the administration and supplementation of these seem a logical approach to managing the problem, and that today this is frequently done irregularly and anarchically, the current emergence of several studies [20,22,59,67,80,94,95] aims to rationalize the clinical use of these resources.

Given the limited efficacy of the available treatments for PN, optimizing the therapeutic arsenal to combat it remains an area of significant unmet medical need. The evidence of interventions in PN, derived from systematic literature reviews and expert experience on which recommendations are based, is often inconclusive. Knowledge must be harmonized and constantly renewed to promote appropriate and effective treatments in daily practice. This literature review has highlighted the dark points, many under discussion, and the weaknesses, paradoxes, and contradictions of the subject, obtaining a knowledge base on which to try to develop a rational consensus based on the evidence currently provided by the literature. All the points raised in this study will be widely analyzed and discussed by the authors in an attempt to achieve a consensus on how to use vitamins B1, B6, B12 in situations of their deficiency and in PN, leading to a subsequent publication.

CONCLUSION

This work has aimed to define and clarify a whole series of confusing and discussed aspects in the field of applying vitamins B1, B6, B12 in peripheral

neuropathies. The situations have been defined, their limits specified, the possible indications for the use of these substances and in what form and time to do so have been clarified, preparing the ground for discussing these points and stating pertinent recommendations.

Authorship contribution: Dr. M. Fernandez-Fairen: conception and design of the article; material collection; data analysis and interpretation; manuscript writing. All authors contributed to the conceptualization and development of the work, provision of study material, critical review of the article, and approval of the final version.

FUNDING: This work was financially supported by P&G. The sponsor had no role in the development of the content of this manuscript.

Conflict of interest: The authors declare no conflicts of interest.

Received: February 29, 2024.
Approved: July 10, 2024.

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REVIEW ARTICLE

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