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VITAMINS B1, B6, B12 AND PERIPHERAL NEUROPATHIES: INTERNATIONAL EXPERT CONSENSUS

VITAMINAS B1, B6, B12 Y NEUROPATÍAS PERIFÉRICAS. CONSENSO DE EXPERTOS.

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ORIGINAL PAPER

ABSTRACT

Introduction: Based on a bibliographic review of the literature, a consensus of international experts has been carried out on the use of vitamins B1, B6, B12, in their deficiencies, and in the peripheral neuropathy that may be associated with them, to optimize the management of these conditions. **Methods:** Several questions considered important and worthy of being addressed and clarified were raised, retaining nine of them for further discussion to achieve consensus. **Results:** Forty one recommendations on the management of these conditions have been proposed, with unanimity of the participants in the consensus. **Conclusions:** This has been an attempt to clarify controversial points, assisting the clinician's attitude in current medical practice.

Keywords: Peripheral neuropathies; B vitamin deficiency; Expert consensus. (Source: MESH-NLM)

RESUMEN

Introducción: A partir de una revisión bibliográfica de la literatura se ha planeado y desarrollado un consenso de expertos internacionales sobre la utilización de las vitaminas B1, B6, B12 en sus déficits y en la neuropatía periférica que puede estar asociada a la misma, como tema que precia de esa aproximación aclaratoria para optimizar su manejo. **Métodos:** Se plantearon varias cuestiones de discusión que se consideraron importantes y dignas de ser abordadas y aclaradas, conservando nueve de ellas para su discusión ulterior buscando el consenso en tres rondas consecutivas. **Resultados:** Se han propuesto 41 recomendaciones sobre el manejo de estas condiciones, con unanimidad por parte de los participantes en el consenso. **Conclusiones:** Con ellas se ha intentado aclarar puntos oscuros o controvertidos, facilitando la actitud del clínico ante ellos en la práctica médica actual.

Palabras clave: Deficiencia vitamina B1,B6,B12; Neuropatía periférica; Consenso de expertos.
(Fuente: DeCS- BIREME)

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INTRODUCTION

Peripheral neuropathy (PN) is one of the manifestations of pathological conditions associated with a deficit of neurotrophic B vitamins, namely B1, B6, B12 [1]. These vitamins are neuroprotective, preventing, mitigating, or delaying neurodegenerative processes and are widely used worldwide. However, they are often perceived by physicians and patients as dietary supplements rather than drugs, which is simply a misconception that does not do justice to these vital substances, not only for the peripheral nervous system but also for the central nervous system and other systems and organs.

It is worth noting that their use, however common, has not been preceded or followed by optimization and rationalization, with scant and poor evidence regarding this matter. The complexity of the topic, the imprecision and heterogeneity of the terminology used, and its lack of contextualization through rigorous conceptual analysis have complicated the issue. Recently, significant work has been published in this field, notably increasing theoretical and practical knowledge, constituting a solid foundation on which to continue work. In light of this, after conducting a systematic review of the existing literature to encompass and update the issue, it was decided to bring all that content to a consensus of experts to develop and establish a series of recommendations applicable to clinical practice, which until now has been somewhat empirical.

METHODS

Consensus was chosen as the method to address the issue, given the advantage of combining the general background present in the literature, not always abundant and of quality, with the knowledge and personal experience of professionals well-versed in the subject, in a dynamic and lively process of discussion and agreement on certain fundamental aspects of it.

Expert Committee

The committee consists of seven members, all recognized experts in the field. They have regularly dealt with the dual problem of the clinical use of neurotrophic B vitamins (B1, B6, B12) and PN throughout their medical practice, with extensive experience as clinicians, educators, and researchers. Specialties represented include a diabetologist, an endocrinologist, a physiatrist, a geriatrician, two neurologists, and an orthopedist, from Chile, Colombia, and Peru, as the work has focused on these countries.

Systematic Literature Review

As the bibliographic basis for this consensus, the systematic literature review conducted in a previous study was used [2]. In the study of the literature for the consensus, studies were prioritized logically based on their quality and level of evidence, randomized controlled trials (RCTs), systematic literature reviews, with or without meta-analysis, and published consensuses[1,3-9].

The study field is the adult individual, considered as such from 18 years of age. The members of the consensus were also asked to provide any additional studies and references that might be relevant in addition to those mentioned. Throughout the consensus process, secondary literature of interest has been added whenever the delegates have deemed it valuable. In this way, 12 additional articles were annexed, which were also evaluated by two independent reviewers (JC and PS), to assess their quality and relevance according to the purpose of the consensus. The value of the collected works as bibliographic support for the consensus has been given based on their type and category, quality, and level of scientific evidence following a system based on the guidelines of the AHCPR (Agency for Health Care Policy and Research) and the Cochrane method[10]. (Table 1).

Table 1. Levels of Evidence (NE, by its Spanish acronym) and Quality of Employed Works.

NE	Characteristics
I (NIE)	High evidence of the assertion or fact analyzed, based on consistent findings in systematic reviews and meta-analyses (SRMA) or high-quality randomized trials (RCTs), well-conducted, with low risk of bias, with high statistical power; consistent significant findings (≥ 75%) in at least two high-quality studies.

ORIGINAL PAPER

II (NIIE)	Moderate evidence of the assertion or fact analyzed, based on the findings of systematic reviews (SR) or controlled or cohort studies (CC), of moderate quality, with risk of bias, limitations or low statistical power; consistent significant findings (≥ 75%) in at least one high-quality study and other low-quality studies.
III (NIIIE)	Low evidence; observational descriptive level III studies, cross-sectional studies (CSS), case series or reports (CR), or narrative review of the topic (NR); inconsistent findings; low evidence of the assertion or fact analyzed; significant findings in one high-quality study or consistent significant findings (≥ 75%) in low-quality studies.
IV (NIVE)	Expert opinion or consensus (OC), clinical practice guidelines (CPG). Insufficient or nonexistent evidence; significant findings in fewer than 3 low-quality studies or inconsistent, uncertain, or inconclusive significant findings regardless of study quality, or no studies on the particular topic.

ORIGINAL PAPER

The reference numbers of the different cited works will appear in the text within brackets [], followed by the corresponding abbreviations for the type of work and its level of evidence in parentheses. If there are multiple works referred to in the point discussed, the overall level of evidence granted by that conjunction will come after enunciating the respective works, followed by a semicolon. The recommendation grade of doing or not doing has been stratified as strong, moderate, weak, or not recommended (SR+, MR+, WR+, NR+, SR-, MR-, WR-, NR-)[11].

This consensus has relied, both in the formulation of the questions and in the responses to them, on assertions and data well-supported by reason and scientific evidence, applicable and updated according to the changes that have occurred over time in such evidence regarding the topics addressed.

Questions to Address

From the literature review, 16 questions were proposed that seemed pertinent and important initially. These were outlined as guidance to ensure the inclusion and discussion of the most prominent and unresolved issues on the subject. These questions were modified, combined, and reduced to 9 by the expert committee in a plenary round where consensus was reached unanimously on this aspect. Each primary question (Q) carries behind it a series of considerations, points, or specific secondary questions to be agreed upon (Qn.1,2,3…), which could be addressed, modified, added, or removed at any stage of the process if the committee deemed it necessary. In drafting the questionnaires, the MonkeySurvey™ system was utilized.

Consensus Method

A quasi-anonymous Delphi iterative method was followed in three rounds, either entirely or partially online. The first round included multiple-choice, open-ended qualitative questions, and "check-box" type questions, using dichotomous responses and a Likert scale, to gather information about the clinical practice of the expert panel and to formulate proposals for algorithms and recommendations to be included in the consensus. Consensus was considered achieved when 4 or more panel members (≥ 57.1%) selected the same option or voted "agreement" regarding a specific point, with 4/7 representing weak consensus (57.1%), 5/7 (71.4%) moderate, 6/7 (85.7%) strong, and 7/7 unanimity (100%)[12].

Statements that promoted a "strong" or "unanimous" consensus were maintained and used as resolutions or recommendations, while those that obtained moderate or weak consensus, or those on which there was no consensus, were reconsidered and discussed in the next round. In the second round, the refined and consensualized questions from the first round and the recommendations derived from the discussions were addressed. In the third round, the analysis and discussion of all points to be agreed upon were concluded, and each conclusion was voted on by panel

members using a dichotomous scale (yes or no, agreement or disagreement).

Consensus Editing

As mentioned earlier, editing this work has been important regarding the terminology and taxonomy of the conditions treated in it. Extreme thoroughness and rigor have been applied to these aspects since the exact identification of what is being discussed and what is meant by each concept and term used are fundamental. The expressions used were primarily in Spanish, accompanied in certain cases by their English equivalents. Words, abbreviations, and acronyms used in Anglo-Saxon literature were inserted in the text when their use and dissemination in that language are customary, thus facilitating universal understanding.

Another aspect standardized was the units in which different parameters susceptible to measurement are expressed, such as levels, cutoff points, and doses. They were reported in the text using the most common units in clinical practice and in the literature, but in some cases, they were also converted and expressed in other values that are also widely used in the everyday world. Plasma levels of vitamin B1 were expressed in µg/l (micrograms per liter), ng/ml (nanograms per milliliter) for B6, and pg/ml (picograms per milliliter) for vitamin B12, or pmol/l as recommended by the British Society for Haematology Guidelines [13]. (CPG, NIVE, WR+). The conversion from pg/ml to pmol/l is 1 pg/ml = 0.7378 pmol/l[14]. Vitamin B12 values will be given in both scales since both are widely used to refer to the concentrations of that substance in the performed tests.

Once the manuscript was drafted, the draft was sent to all consensus members to obtain their final comments and definitive approval for publication.

RESULTS

The questions developed and agreed upon throughout the process, and all points generated from them, have been answered, as mentioned, based on the exhaustive analysis of the literature and the open discussion by the consensus participants.

The following will present and analyze these questions one by one, the comments gathered from the fundamental references used to support the consensus or raised by the consensus members throughout the process, which have constituted the basis of the argumentation of the questions to be agreed upon, and the response to these as positions taken and exportable proposals, the consensual points, and the strength of the consensus in each of them.

C1.- Does the deficiency of vitamins B1, B6, B12 cause peripheral neuropathy?

C1.1: PN is common in conditions associated with deficiencies of vitamins B1, B6, B12. (Unanimity). [1] (SRMA, NIIEE).

C1.2: The association between PN and deficiencies of vitamins B1 and B6 is inconclusive. (Unanimity). [1] (SRMA, NIVE).

C1.3: PN is associated with low levels of vitamin B12 in plasma/serum. (Unanimity).

The evidence of this association is strong and is attested in an SRMA[1] and a CSS[15], measuring deficiency solely by vitamin B12 concentration (NIIEE; p = 0.003), or associating its decrease with the elevation of blood levels of methylmalonic acid (NIIEE; p = 0.005) or total homocysteine (NIIEE; p < 0.001)[1].

C1.4: Vitamin B12 deficiency could be causally related to PN. (Unanimity).

Low levels of vitamin B12 are significantly associated (OR [95% CI]: 1.51 [1.23-1.84]) with the development of PN [1] (SRMA, NIIEE).

C2.- What is considered a deficiency of vitamins B1, B6, B12?

Some terminological clarifications to keep in mind:

"Deficit": Lack or shortage of something judged necessary (Royal Spanish Academy – RAE, by its Spanish acronym).

"Deficiency": It refers to the significant lack of a certain substance or a set of them.

"Shortage" or "shortfall states": Same as deficiency.

“Insufficiency": Levels of the substance in question do not reach the necessary physiological values to properly fulfill its function. Its severity will be in relation to the magnitude of the deficit. Obviously, "insufficiency" is less relevant and severe than "deficiency."

ORIGINAL PAPER

"Functional deficit": Levels are within normal range but are not capable of fulfilling their role.

"Relative deficit": Levels are within normal range but are not sufficient to meet increased demands.

"Subclinical deficit": Biochemical deficit without clinical translation (asymptomatic).

Often considered synonymous, but it is clear they are not entirely so. Inappropriate use of terms can cause confusion.

ORIGINAL PAPER

C2.1: Levels of B1, B6, B12 should be categorized as normal, insufficient, and deficient. (Unanimity).
Following the criteria of the WHO expressed by different authors[16], Denmark-Montecinos and Vásquez-Leiva[17], Langan and Goodbred [18], and Leishear et al. [15], it is recommended by consensus to categorize the situation of these vitamins at these levels (15, 16, and 17 CSS and 18 NR; NIIEE).

C2.2: Serum B12 determination is sufficient to diagnose normality or deficiency. (Unanimity).
Although diagnosing vitamin B12 deficiency rigorously is improved by adding MMA determination to that of the vitamin itself[18,19]. (NR, NIVE), the determination of B12 alone is sufficient for this [15] (CSS, NIVE).

C2.3: Plasma levels above 400 pg/ml (> 295 pmol/l) are considered "normal" for vitamin B12, levels between 200 and 400 pg/ml (148-295 pmol/l) are considered "insufficient," and levels below 200 pg/ml (< 148 pmol/l) are considered "deficient." (Unanimity).

"Normal" levels of vitamin B12 are considered plasma levels above 400 pg/ml in at least 2 measurements separated by 4 months, with a stable or rising curve (never descending), in a population whose diet includes foods rich in vitamin B12 or supplements in adequate doses periodically. A plasma level of 400 pg/ml of vitamin B12 is close to one-third of the hepatic reserve threshold of health [20] (SRMA, NIIEE) and neuropathic alteration of peripheral nerves[15,21]. (15 CSS and 21 NR; NIVE).

C2.4: B1 deficiency is considered ≤ 35 µg/l of thiamine. (Unanimity).

C2.5: B6 deficiency is considered ≤ 4.1 ng/l of pyridoxal 5-phosphate. (Unanimity). [22] (CSS, NIVE).

C3.- When is screening for deficiency of vitamins B1, B6, B12 recommended?
The measurement of plasma levels of these vitamins could be recommended in Public Health as a marker of the risk of deficiency of these in the general population, taking into account on the positive side that these states are not always symptomatic or easily diagnosable by other means, and considering the cost-benefit factor of it. Taking into account that the analytical determination of the levels of these vitamins is scarcely used in Latin America due to the limited availability, affordability, and reliability of the analytical tests, it would be advisable to recommend the universalization, standardization, and quality control of these.

Furthermore, in clinical practice, systematic determination of vitamin B12 in asymptomatic individuals is not recommended, although 50% of patients with PN are asymptomatic, with a normal blood count, without risk factors for deficiency, or receiving oral supplements of vitamin B12 or folate unless there is suspicion of discontinuation of that supplementation.

C3.1: Measurement of plasma vitamin B12 levels is suggested for the population at risk of deficiency, when there is suspicion of risks and/or related symptoms. (Unanimity).
Screening for vitamin B12 deficiency is strongly recommended (SR+) in patients at risk of deficiency of that vitamin. The prevalence of deficiency is 40.5% between 65 and 99 years, compared to 17.9% between 22 and 63 years[23]. In diabetic patients, the prevalence for values below 150 pg/ml has been up to 33% [24]. Exogenous nutritional disorders such as strict vegan or vegetarian diets, or endogenous disorders such as bariatric surgery, or the use of drugs such as metformin [25,26]. (25 RST and 26 CC; NIIE), anticonvulsants, calcium antagonists, 5-aminosalicylates, proton pump inhibitors [27]. (CC, NIIE), colchicine, and chemotherapy require monitoring of vitamin B12 levels.

It is recommended to measure serum cobalamin levels in the presence of neurological symptoms such as pain, paresthesia, numbness, motor coordination deficit, memory or cognitive problems, personality changes, high blood glucose, and peripheral trophic disorders, regardless of the result of the blood count.

C3.2: Four possible scenarios should be considered: cases of vitamin deficiency with/without symptoms and cases with normal analytical values with/without symptoms. (Unanimity).

The combination of the possibility of clinical symptoms and the determination of the levels of these vitamins allows for establishing diagnostic and therapeutic guidelines. In symptomatic cases with deficient analytical values, analytical control allows monitoring the effectiveness of treatment. If the deficiency is analytically evident but there are no symptoms, it should be monitored to see if the levels are stable or decreasing, in which case the cause, management, and corresponding supplementation should be studied. Symptoms may appear with normal concentrations of these vitamins. In this situation, screening should be based on clinical symptoms, opening a window of opportunity for preventive interventions for the physiopathological disorders that may be starting.

When concentrations of the vitamins are at normal levels and there are no clinical symptoms, active follow-up of the subject is not necessary except in those subjects and situations that present a blatant risk.

C3.3: Screening for deficiency of vitamins B1, B6, B12 is recommended primarily in patients over 60 years of age, diabetics, especially if treated with metformin, post-bariatric surgery, and/or with fragility fractures. (Unanimity).

At the age of 60, up to 15% of people have some vitamin B12 deficiency, mostly secondary to gastritis and associated disorders [28]. Diabetic patients, especially those over 60, may present signs of neurological dysfunction even if B12 levels are above 150 pmol/l. According to this, B12 levels between 200-542 pg/ml (150-400 pmol/l) should be considered as "relative" B12 deficiency in older people with diabetes and managed accordingly[29]. Diabetics treated with metformin exhibit vitamin B12 levels below 200 pg/ml (150 pmol/l) and between 200-300 pg/ml (150-400 pmol/l) in 24.5% and 34.5% of cases, respectively, a significantly higher percentage than among non-users of metformin (17.3% and 22.6%, respectively; $p < 0.001$) [26] (CC, NIIE). Diabetic patients with specific risk factors for vitamin B12 deficiency should be screened analytically annually to rule out that deficiency [30]. (NR, NIVE).

Patients undergoing bariatric surgery are at high risk of vitamin B deficiencies[30] (NR, NIVE). Prior to surgery and despite their obesity, 12-25% of patients already have a deficiency in vitamin B12, 20% in folate, and 1-8% in thiamine [31,32]. (NR, NIIIC, NIVE). After surgery, and depending largely on the technique used, vitamin B12 deficiency is found in 30% of patients [29], with PN in 10-33% of cases[32].

Low levels of vitamin B12 are associated with elevated tHcy with decreased bone mass and increased bone fragility. Older adults with these types of fractures should be considered a risk group for vitamin B12 deficiency and therefore it is advisable to measure plasma levels of this vitamin in these patients. In a series of hip fractures ≥ 65 years old, 90% of them showed suboptimal or at-risk B12 levels [17] (CSS, NIVE).

C3.4: Once the risk and/or deficiency are suspected, screening should be done as early as possible. (Unanimity).

Detection of these situations should be as early as possible to implement preventive interventions for incipient and potentially reversible peripheral nerve alterations before reaching a point of no return in the continuum of PN [33].

C3.5: Additional analytical determinations may be necessary. (Unanimity).

It should be noted that there is functional insufficiency of cobalamin, common in the elderly and of unknown cause, with normal B12 levels but elevated MMA or tHcy levels[23].

If possible, vitamin B12 and folic acid levels should be measured in at-risk patients. If the vitamin B12 level is close to its lower normal value, MMA determination may also be performed. If folic acid is close to its lower normal value, serum homocysteine can be requested to identify specific deficiencies, which is clinically very difficult, and provide appropriate specific recommendations.

Patients with persistently suboptimal cobalamin levels should undergo tests to detect intrinsic factor antibody titers [13,14,34] (13 CPG, 14 and 34 NR; NIIE).

C4.- When should the prescription of vitamins B1, B6, B12 be considered?

C4.1: The administration of neurotrophic B vitamins should be considered when there is a demonstrated deficiency of them. (Unanimity).

It is obvious that the administration of neurotrophic B vitamins should be considered when there is a demonstrated deficiency of them, in an attempt to correct or compensate for that deficiency [13,35] (13 CPG, NIVE, SR+ and 35 NR, NIVE). Low levels of vitamin B12 are significantly associated with the development of PN [1] (SRMA, NIIE), and therefore, normalization should be attempted. Administration of vitamin B12 is effective in correcting biochemical, hematological, and clinical deficiencies in the short term [36-42] (36 and 37 RCT, 38 SRMA, 39 SC, 40 CSS, 41 and 42 CPG; NIE).

C4.2: The administration of neurotrophic vitamins should be considered in patients without clinical, and/or neurophysiological, and/or morphometric manifestations of PN, when biochemically demonstrated deficiency levels are present. (Unanimity).

In patients with biochemically demonstrated subclinical vitamin B12 deficiency in two consecutive tests, empirical treatment with 50 µg of oral cyanocobalamin daily for 4 weeks can be administered [13]. (CPG, NIVE, MR+).

C4.3: Supplementation with these vitamins should be done in patients belonging to risk groups for deficiency, with clinical and/or neurophysiological and/or morphometric manifestations of PN, even if the deficiency has not been biochemically demonstrated. (Unanimity).

In a recent consensus, the administration of neurotrophic B vitamins B1, B6, B12 in symptomatic patients, with risk factors predisposing them to vitamin deficiencies, even if such deficiencies have not been demonstrated, was strongly recommended [8] (C, NIVE).

C4.4: In populations at risk of deficiency of vitamins B1, B6, B12 and/or PN, robust plasma levels indicating good hepatic reserves capable of obviating that deficiency are desirable. (Unanimity).

Levels above 800 pg/ml would be robust and desirable [17]. (CS, NIIE), as they suggest that only one-third of the hepatic reserve has been consumed, with another third margin that would guarantee, despite the absence of absorption, a cellular metabolism similar to that existing when absorption is normal [17], before the situation becomes symptomatic [28]., and before reaching the minimum level of reserves compatible with health[17].

C4.5: In at-risk populations, if levels of B1, B6, B12 are close to their lower limit and deficiency cannot be confirmed by other determinations, these vitamins may be administered with close monitoring. (Unanimity).

Sometimes, even if there is not yet a proper deficiency of these vitamins but plasma levels are decreasing due to insufficient intake and/or progressive reduction of hepatic reserves, they may be indicated to prevent the development of deficiency.

C4.6: The patient should be considered holistically, complementing the administration of vitamins B1, B6, B12 with other interventions as important as rehabilitative treatment of PN. (Unanimity).

The combination of physical exercise with pharmacological treatment has proven to be an excellent adjunct, significantly improving the local and general condition of patients with PN [43-46]. (43 and 44 RCT, 45 and 46 SRMA; NIIE).

C5.- Can the administration of vitamins B1, B6, B12 benefit patients with deficiency of vitamins B1, B6, B12 and/or with PN?

C5.1: The administration of vitamins B1, B6, B12 can benefit patients with deficiency of vitamins B1, B6, B12 and/or with PN. (Unanimity).

Treatment with vitamin B1 was associated with a significant improvement in PN symptoms [1]. (SRMA, NIIE).

Neurological imbalances caused by vitamin B6 deficiency are usually reversible with adequate supplementation [1,47] (1 SRMA, 47 SRMA; NIIE).
Regarding vitamin B12, there is ample literature supporting this assertion with a high level of evidence [7,36-42,48,49] (49 SRMA, 36 and 37 RCT, 7 and 38 SRMA, 39 SC, 40 and 48 ET, 41 and 42 CPG; NIE), and strong recommendation for the administration of vitamin B12 in these patients.

C5.2: Evidence shows that the combination of the three neurotrophic B vitamins is therapeutically effective. (Unanimity).
There is sufficient quality evidence to support this statement [48,50-52] (50 RCT, 47 and 51 SRMA, 52 SC and 48 ET; NIE).

C5.3: The administration of vitamins B1, B6, B12 significantly benefits PN in diabetic patients. (Unanimity).
Many of the studies cited previously regarding the efficacy of administering these vitamins in PN were conducted in diabetic patients [7,37,42,48-51] (49 SRMA, 37 and 50 RCT, 7 and 51 SRMA, 48 ET, 42 CPG; NIE).

C6.- What should be done in the following risk groups: people with diabetes, people with prediabetes, or older adults, in relation to the deficiency of vitamins B1, B6, B12?
These patients are included by their own right in the risk groups mentioned above. The first thing to do in all of them is, as mentioned, to objectify the levels of vitamin B12 to confirm or rule out its deficiency and as a possible collateral indicator of the deficiency of vitamins B1 and B6. If such deficiency is suspected, the study and specific determination of the levels of these vitamins and the corresponding management of the specific situation should be initiated.

C6.1: In view of the favorable effect of vitamin B12 administration and the high index of relative deficiency of it in diabetic patients, it is reasonable to recommend supplementation with vitamin B12 in all patients with diabetic neuropathy and vitamin B12 levels below 542 pg/ml (400 pmol/l). (Unanimity).
This consensus point was reached knowing that there are studies showing that patients with type 1 or 2 diabetes mellitus have up to a 75% decrease in plasma thiamine levels [53] (SRMA, NIIC, NIVE), resulting in up to 40-70% of patients with diabetes mellitus having levels below the norm and in diabetic patients with PN, the level of vitamin B12 is below the norm in 64% of them [54] (SRMA, NIVE), considering, as mentioned in question 3, that this deficiency predisposes to PN, taking 400 pg/ml (295 pmol/l) as the cutoff point for "normality" in adults for that vitamin (C2 PC3) and the favorable effect of its supplementation in diabetic peripheral neuropathy (DPN) as seen in C5.3.

C6.2: Diabetic and prediabetic patients receiving metformin should be closely monitored. (Unanimity).
The American Diabetes Association (ADA) recommends close monitoring of patients receiving metformin to avoid vitamin B12 deficiency, especially given the high risk that diabetics have of developing such deficiency and PN, regardless of whether they take metformin or not [55] (C, NIVE). Patients aged 50 or older, treated with metformin for a minimum of 18 months, have two to three times the risk of developing PN [56] (CC, NIIIE). The relationship between metformin administration and vitamin B12 deficiency is well known [4,57-63] (4, 57 and 58 SRMA, 61,63 CC, 59, 60, 62 ET; NIE).

C6.3: The metformin usage index (MUI) is suggested as a tool to assess the risk of vitamin B12 deficiency. (Unanimity).
There is a significant association between an MUI > 5 and a high risk of vitamin B12 deficiency ($p < 0.01$). The highest risk was observed among patients with an MUI > 15 (OR 6.74, 95% CI 4.39-10.4) followed by patients with an MUI > 10 (OR 5.12, 95% CI 3.12-8.38). An MUI > 5 thus suggests a high risk of vitamin B12 deficiency [63] (RCT, NIVE).

C6.4: In adults over 60 years of age, vitamin B12 levels should be maintained above 400 pg/ml (295 pmol/l). (Unanimity).
This figure is proposed as "normality" in C3.3. There is a strong recommendation to supplement the vitamin in cases of demonstrated deficiency (C4.1).

C7.- When should the administration of vitamins B1, B6, B12 be initiated?

C7.1: Once the deficiency of vitamins B1, B6, B12 is identified, treatment should be initiated early to try to stop or at least delay the progression of the

process, without waiting for the appearance of symptoms. (Unanimity).

Once the vitamin B deficiency is identified, treatment should be started, which is the first step in preventing PN. Symptoms should not be awaited. The "clinical silence" or phase without symptoms or signs is a major issue in this matter. It is essential to shorten this period as much as possible.

The onset of neuropathy is often insidious and progresses very slowly over the years. Symptoms take months to appear and develop, and a considerable amount of time may pass until diagnosis, delaying the initiation of treatment and missing the opportunity to prevent or delay its progression. It is advisable for treatment to start early in neuropathy or, if possible, even before symptoms appear[64]. (C, NIVE). Up to 50% of chronic sensory-motor polyneuropathies progress silently, and only 20% of DPN cases present with pain, so they should be diagnosed and treated as early as possible in this asymptomatic phase, before their evolution leads to more advanced stages and definitive severe disorders [65,66]. (65 SRMA and 66 C; NIVE). Intervention in these early stages is the most important gesture regarding PN since once the degenerative process is underway, it tends to be irreversible, making all measures that can alleviate or delay this situation fundamental [20]. (SRMA, NIIE). Therefore, the earlier the intervention, the greater the benefits for patients[14].

C7.2: In order to reduce the risk of neuropathy, vitamin B12 should be administered if levels are below 450 pg/ml (332 pmol/l). (Unanimity).

The threshold for developing nerve conduction abnormalities is 450 pg/ml (332 pmol/l) [15,21]. (15 ET and 21 SRMA; NIVE), and vitamin administration is necessary long before reaching this level.

C8.- What route, dose (range/frequency), and duration of treatment with vitamins B1, B6, B12 should be employed?

C8.1: They will depend on the patient's requirements, magnitude and type of deficiency, intensity of symptoms, possibility of reversibility of the condition, and response to treatment. (Unanimity).

The doses and duration of treatment should be sufficient to optimize and maintain plasma levels and reserves of these vitamins as much as possible. In principle, the standard daily requirements of the patient should be considered, bearing in mind that those with symptomatic deficiency and depending on the type of pathology may have higher requirements. It should 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 may be used, at a dose sufficient to ensure absorption of 1.2 mg/day of vitamin B1, 1.3 mg of vitamin B6 below 50 years old and 1.7 mg/day in those older than that age, and 2.4 µg of vitamin B12 per day[67]. (C, NIVE).

C8.2: Treatment of 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, assessing the response after two months and considering switching to IM route or evaluating other possible causes of deficiency if concentrations do not increase significantly. (Unanimity).

To ensure absorption of those 2.4 µg of vitamin B12 per day, and given the percentage absorbed of the orally administered vitamin B12, the daily dose should be around 500-1000 µg/day (0.5-1 mg/day). A daily dose of only 250 µg of cyanocobalamin is not sufficient to normalize B12 levels within a year[37]. (RCT, NIIE). Based on this and after analyzing and discussing the wide variety of proposals in the literature, in light of the committee members' experience, it was unanimously agreed to accept the recommendation reached at the Mexico City meeting in 2019[64]. (C, NIVE).

If the deficiency does not improve with this regimen after two months and vitamin B12 levels remain suboptimal, the cause may be an absorption disorder, in which case IM route should be used for vitamin administration [34]. (SRMA, NIVE). In the presence of intrinsic factor antibodies, treatment should be for pernicious anemia[34]. (SRMA, NIVE).}

C8.3: In severe deficiencies ("deficiency," < 200 pg/ml or < 148 pmol/l), or specific patient groups, the recommended initial dose is 1000 µg IM once daily for a week and then 1000 µg/week for 4-8 weeks until the deficiency is corrected. Once compensated, the oral route may be considered for maintenance treatment. (Unanimity).

This statement is based on the treatment of a specific condition, pernicious anemia, characterized by severe alteration of the enterohepatic circulation of B12 due to

intrinsic factor deficiency. There are many other conditions where the deficiency becomes severe but recovers rapidly with oral supplementation or fewer injections with higher doses. In general, regarding parenteral supplementation of vitamin B12 in patients with neurological involvement, 1000 µg (1 mg) of cobalamin IM every other day is recommended until improvement of symptoms is observed, followed by IM injections of 1000 µg of cobalamin every two months.

C8.4: Vitamins B1, B6, B12 should be given via IM in patients with altered, or suspected alteration, of the oral route, and in those who require rapidly increasing plasma levels. (Unanimity).

It is obvious that if there are absorption disorders of these vitamins, the route of choice will be other than oral. Intrinsic factor deficiencies also fall into this indication.

In patients where it is necessary to safely and rapidly increase vitamin levels, bypassing absorption and bioavailability problems, the IM route is standard [13,68]. (CPG, NIVE). In clinical practice, treatment with vitamin B12 often begins with injections once or twice a week for 3 weeks, and when the patient shows improvement, maintenance treatment is given orally [64]. (C, NIVE). If correcting the situation is urgent, 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 a delay in correcting the deficiency could lead to permanent sequelae.

Doubts regarding treatment compliance

When there is absorption failure due to pernicious anemia or blind intestinal loop, nosological entities in which optimal absorption concentrations may not be reached orally. However, there is literature reporting the efficacy of oral cyanocobalamin in cases of pernicious anemia with a result similar to that of the parenteral route[20]. (SR, NIIE).

C8.5: In the case of PN, initiate treatment with between 1000 and 2000 µg per day of vitamin B12 orally or 1000 µg per day by intramuscular/subcutaneous route for 7 days, followed by 7 additional doses every other day for 2-3 weeks, and then, when the patient shows improvement, maintenance treatment orally. (Unanimity).

Patients with PN, especially if due to metabolic disorders, the use of certain medications or drugs, or nutritional deficiencies, should be treated with high loading doses of neurotrophic B vitamins (B1, B6, B12) at the beginning of pharmacological intervention, followed by lower maintenance doses once neuropathy symptoms are relieved [8]. (C, NIVE). High doses of B neurotrophic vitamins given for 4 weeks are more effective than lower doses, reducing pain and other clinical problems[3].

In cases of PN, generally, if the level of vitamin B12 is below 450 pg/ml (332 pmol/l), supplementation with oral vitamin B12 (2000 µg/day) can be initiated.

C8.6: Even with PN, if robust plasma levels of vitamin B12 are present, there is no need to manage it with this vitamin since clearly, the cause of the PN must be something other than the deficiency of that vitamin. (Unanimity).

It has been mentioned that for the participants in this consensus, vitamin B12 levels above 800 pg/ml are considered "robust" and desirable for the reasons outlined in C4.4. These levels are far from the 450 pg/ml that initiate the neuropathy process [15,21] (15 CSS and 21 SRMA; NIVE).

C8.7: Maintenance therapy is recommended in PN to prevent recurrences, which may be required long-term if deficiency, insufficiency, or risk levels persist, and if the cause of the deficiency is permanent. (Unanimity).

Even in patients who experience symptom relief after a few weeks of treatment, maintenance therapy is advisable to prevent recurrences and may require long-term treatment [64]. (C, NIVE). The maintenance dose ensures the concentration of the corresponding vitamins in the medium and long term.

C8.8: Long-term treatment should always be monitored to ensure its effectiveness and safety. (Unanimity).

People with vitamin B1, B6, B12 deficiencies should undergo regular checks to assess the effectiveness of treatment and adjust doses as necessary[64]. (C, NIVE).

C8.9: Improvement of symptoms and long-term safety profile are key criteria for adjusting the dose and route of administration of neurotrophic B vitamins, both for loading and maintenance doses. (Unanimity).

Key criteria for adjusting the dose of neurotrophic B vitamins, both for loading and maintenance doses, are improvement in symptoms and long-term safety profile [8]. (C, NIVE).

There is no need to adjust the dose of vitamin B1 in renal or hepatic insufficiency[69], nor are dose adjustments of vitamin B12 required in patients with renal or hepatic insufficiency. The estimated average requirement (EAR) [70] in pregnant women should be increased by 0.2 µg/day to cover fetal demands.

C8.10: At high doses, the efficacy of the oral route, if intact, is similar to that of the IM route for the administration of vitamin B12. (Unanimity).

This is widely reported in the literature [13,20,38,39,71,72] (71 and 72 RCT, 20 RSM, 38 SRMA, 39 SC, 13 CPG; NIE), with a high degree of evidence.

C8.11: Sublingual, intranasal, or subcutaneous routes may have some advantages, but more studies are needed to obtain better evidence of this. (Unanimity).

They may offer advantages in terms of immediacy of bloodstream delivery, convenience, and apparent safety, but there is a lack of literature support regarding their efficacy, and studies are limited [68].

C9.- Can the stability of vitamins B1, B6, B12 in injectable presentations change?

Knowing well the susceptibility of B vitamins in their injectable form to degrade during their storage or service life, especially if vitamin B12 is mixed with B1 and B6 [73], the following three recommendations have been stated:

C9.1: Vitamin B12 is susceptible to photolytic, hydrolytic, oxidative, and thermal degradation. (Unanimity).

C9.2: When vitamin B12 is mixed with B1 and B6 in injectable form, it denatures. (Unanimity). C9.3: Injectable presentations must implement measures such as double-chamber galenic technologies that guarantee the separation of vitamin B12 from the other two vitamins B1 and B6. (Unanimity).

DISCUSSION

Given the limited efficacy of available means for managing deficiencies of vitamins B1, B6, B12, and PN, the optimization of the tools used remains an area of significant unmet medical need. In this regard, an attempt has been made to reach a consensus on various key points of the topic by bringing together a series of international Latin American experts for a global update while keeping regional particularities in mind, which may influence situations and actions in the field under consideration. This does not mean that the content of the consensus cannot be perfectly applicable in other regions.

Up to now, there is a lack of agreement regarding the role of B neurotrophic vitamins in the world of PN, the categorization of their deficiencies, the cutoff points defining these categories, how to diagnose and monitor these states, which patients require supplementation and treatment, and when and at what doses, duration, molecular form, and route of administration they should be given. Recently, other consensuses [8,9] or expert opinions [67] have been conducted and published on B neurotrophic vitamins and peripheral neuropathies, supporting views and recommendations similar to those expressed here. The work of Pinzon et al. [8] gathered 8 experts from Hong Kong, India, Indonesia, Malaysia, the Philippines, South Africa, Thailand, and the United Arab Emirates.

ORIGINAL PAPER

They propose 7 basic recommendations on general points and criteria, without specifying indications or how to act in PN conditions. On the other hand, Ziegler et al. [9] developed a consensus on diabetic neuropathy, among 15 experts representing the European Union, the United Kingdom, Eastern Europe, Russia, the Middle East, Asia, and the United States. Latin America is excluded from both works. The questionnaire of this latter work is very comprehensive (179 questions) but somewhat cumbersome. The arguments on which the 60 recommendations extracted, five aimed at the diagnosis and treatment of ND in times of COVID, are based are presented collaterally and not sufficiently explained. Finally, the work of Calderón et al. [67], although extremely useful and providing timely data and reasons, is not a true consensus in its development. However, no inconsistencies or glaring differences are observed between these studies and the current consensus.

As limitations, it should be noted the partial or total lack of scientific evidence in many of the points of this topic, both due to the few or no studies carried out on the specific issue and due to the lack of generalizable results from high-quality studies. Another limitation is the great heterogeneity exhibited in the results of certain systematic reviews. Additionally, there are statistical aspects related to the sensitivity and specificity of the different available tests for the analytical demonstration of deficiencies, with reference cutoff points not universally agreed upon, and clinical-biochemical scenarios whose interpretation and linkage with neurological, cardiovascular, renal outcomes, etc., among others, are the object of evidence construction that must underlie the topic and that underlies terms that are confusing and need to be defined and thoroughly explained.

Finally, given the breadth of the topic, there are points left for discussion beyond the established scope for consensus.

CONCLUSION

Nine questions considered fundamental were addressed at the beginning of the consensus process. In these nine instances, a series of issues were discussed and developed, which were considered worthy of analysis, thus resulting in the expression of a consensus comprising a total of 41 of these points and the respective detailed recommendations for screening, diagnosis, and management of deficiencies of vitamins B, B6, B12 in relation to PN in clinical practice.

ORIGINAL PAPER

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ORIGINAL PAPER

REFERENCES

1.Stein J, Geisel J, Obeid R. Association between neuropathy and B-vitamins: A systematic review and meta-analysis. Eur J Neurol. 2021 Jun;28(6):2054-2064. doi: 10.1111/ene.14786.

2.Longa López JC, Dinamarca-Montecinos JL, Mejía-Rojas K, Bernaola Cuadros AC, Ampuero Bárcena JB, Palacio-Sánchez L, Fernandez-Fairen M. Vitaminas B1, B6, B12 y Neuropatías Periféricas. Revisión sistemática de la literatura. Rev Fac Med Hum. 2024; en prensa.

3.Ang CD, Alviar MJ, Dans AL, Bautista-Velez GG, Villaruz-Sulit MV, Tan JJ, Co HU, Bautista MR, Roxas AA. Vitamin B for treating peripheral neuropathy. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD004573. doi: 10.1002/14651858.CD004573.pub3.

4.Chapman LE, Darling AL, Brown JE. Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes Metab. 2016 Nov;42(5):316-327. doi: 10.1016/j.diabet.2016.03.008.

5.Julian T, Syeed R, Glascow N, Angelopoulou E, Zis P. B12 as a Treatment for Peripheral Neuropathic Pain: A Systematic Review. Nutrients. 2020 Jul 25;12(8):2221. doi: 10.3390/nu12082221.

6. Liew J, Barlow A, Lim L-L, Suastika K, Yasahardja Y, Chan SP, Soh A, Li LS, Tan AT; 2244-PUB: Role of B Vitamins (B1, B6, B12) in Managing Diabetic Peripheral Neuropathy (DPN): A Systematic Review. Diabetes June 2019;68(Suppl.1):2244–PUB. https://doi.org/10.2337/db19-2244-PUB.

7. Sun Y, Lai MS, Lu CJ. Effectiveness of vitamin B12 on diabetic neuropathy: systematic review of clinical controlled trials. Acta Neurol Taiwan. 2005 Jun;14(2):48-54. PMID: 16008162.

8. Pinzon RT, Schellack N, Matawaran BJ, Tsang MW, Deerochanawong C, Hiew FL, Nafach J, Khadilkar S. Clinical Recommendations for the use of Neurotrophic B vitamins (B1, B6, B12) for the Management for Peripheral Neuropathy: Consensus from a Multidisciplinary Expert Panel. J Assoc Physicians India. 2023;71(7):93-98. doi: 10.59556/japi.71.0290.

9. Ziegler D, Tesfaye S, Spallone V, Gurieva I, Al Kaabi J, Mankovsky B, Martinka E, Radulian G, Nguyen KT, Stirban AO, Tankova T, Varkonyi T, Freeman R, Kempler P, Boulton AJ. Screening, diagnosis and management of diabetic sensorimotor polyneuropathy in clinical practice: International expert consensus recommendations. Diabetes Res Clin Pract. 2022;186:109063. doi: 10.1016/j.diabres.2021.109063.

10. van Tulder M, Becker A, Bekkering T, Breen A, del Real MT, Hutchinson A, Koes B, Laerum E, Malmivaara A; COST B13 Working Group on Guidelines for the Management of Acute Low Back Pain in Primary Care. Chapter 3. European guidelines for the management of acute nonspecific low back pain in primary care. Eur Spine J. 2006 Mar;15 Suppl 2(Suppl 2):S169-91. doi: 10.1007/s00586-006-1071-2.

11. Aguayo-Albasini JL, Flores-Pastor B, Soria-Aledo V. Sistema GRADE: clasificación de la calidad de la evidencia y graduación de la fuerza de la recomendación. Cir Esp. 2014 Febrero;92(2):82-88. doi: 10.1016/j.ciresp.2013.08.002.

12. Cats-Baril W, Gehrke T, Huff K, Kendoff D, Maltenfort M, Parvizi J. International consensus on periprosthetic joint infection: description of the consensus process. Clin Orthop Relat Res. 2013 Dec;471(12):4065-75. doi: 10.1007/s11999-013-3329-4.

13. Devalia V, Hamilton MS, Molloy AM; British Committee for Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol. 2014 Aug;166(4):496-513. doi: 10.1111/bjh.12959.

14. Carmel R. Cobalamin (vitamin B12). In: Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, eds. Modern Nutrition in Health and Disease. 11th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2014:369-389.

15. Leishear K, Boudreau RM, Studenski SA, Ferrucci L, Rosano C, de Rekeneire N, Houston DK, Kritchevsky SB, Schwartz AV, Vinik AI, Hogervorst E, Yaffe K, Harris TB, Newman AB, Strotmeyer ES; Health, Aging and Body Composition Study. Relationship between vitamin B12 and sensory and motor peripheral nerve function in older adults. J Am Geriatr Soc. 2012 Jun;60(6):1057-63. doi: 10.1111/j.1532-5415.2012.03998.x.

16. Vargas-Uricoechea H, Nogueira JP, Pinzón-Fernández MV, Agredo-Delgado V, Vargas-Sierra HD. Population Status of Vitamin B12 Values in the General Population and in Individuals with Type 2 Diabetes, in Southwestern Colombia. Nutrients. 2023; 15(10):2357. https://doi.org/10.3390/nu15102357.

17. Dinamarca-Montecinos JL, Vásquez-Leiva A. Are older adults with hip fractures a specific risk group for vitamin B12 deficiency? JCSM Clinical Reports 2022;7:44-52. doi: 0.1002/crt2.48.

18. Langan RC, Goodbred AJ. Vitamin B12 Deficiency: Recognition and Management. Am Fam Physician. 2017 Sep 15;96(6):384-389. PMID: 28925645.

19. Hannibal L, Lysne V, Bjørke-Monsen AL, Behringer S, Grünert SC, Spiekerkoetter U, Jacobsen DW, Blom HJ. Biomarkers and Algorithms for the Diagnosis of Vitamin B12 Deficiency. Front Mol Biosci. 2016 Jun 27;3:27. doi: 10.3389/fmolb.2016.00027.

20. Wang H, Li L, Qin LL, Song Y, Vidal-Alaball J, Liu TH. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database Syst Rev. 2018 Mar 15;3(3):CD004655. doi: 10.1002/14651858.CD004655.pub3.

21. Vinik A. Diabetic sensory and motor neuropathy. N Enlg J Med. 2016; 374:1455-1464. doi; 10.1056/NEJMcp1503948.

22. Vollbracht C, Gündling PW, Kraft K, Friesecke I. Blood concentrations of vitamins B1, B6, B12, C and D and folate in palliative care patients: Results of a cross-sectional study. J Int Med Res. 2019 Dec;47(12):6192-6205. doi: 10.1177/0300060519875370.

23. Solomon LR. Functional cobalamin (vitamin B12) deficiency: role of advanced age and disorders associated with increased oxidative stress. Eur J Clin Nutr. 2015 Jun;69(6):687-92. doi: 10.1038/ejcn.2014.272.

24. Qureshi SA, Ainsworth A, Winocour PH. Metformin therapy and assessment for vitamin B12 deficiency: is it necessary? Practical Diabetes 2011;28(7): 302-304. doi: 10.1002/pdi.1619.

25. de Jager J, Kooy A, Lehert P, Wulffelé MG, van der Kolk J, Bets D, Verburg J, Donker AJ, Stehouwer CD. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ. 2010 May 20;340:c2181. doi: 10.1136/bmj.c2181.

26. Shivaprasad C, Gautham K, Ramdas B, Gopaldatta KS, Nishchitha K. Metformin Usage Index and assessment of vitamin B12 deficiency among metformin and non-metformin users with type 2 diabetes mellitus. Acta Diabetol. 2020 Sep;57(9):1073-1080. doi: 10.1007/s00592-020-01526-4.

27. Mumtaz H, Ghafoor B, Saghir H, Tariq M, Dahar K, Ali SH, Waheed ST, Syed AA. Association of Vitamin B12 deficiency with long-term PPIs use: A cohort study. Ann Med Surg (Lond). 2022 Sep 26;82:104762. doi: 10.1016/j.amsu.2022.104762.

28. McCaddon A. Vitamin B12 in neurology and ageing; clinical and genetic aspects. Biochimie 2013; 95: 1066-1076. doi: 10.1016/j.biochi.2012.11.017.

29. Vinik AI, Strotmeyer ES. Diabetic Neuropathy. In Pathy's Principles and Practice of Geriatric Medicine. Sinclair AJ, Morley JE, Vellas B, eds.; JohnWiley & Sons, Ltd.: Chichester, UK, 2012; pp. 751–767. ISBN 978-1-119-95293-0.

30. Kibirige D, Mwebaze R. Vitamin B12 deficiency among patients with diabetes mellitus: is routine screening and supplementation justified? J Diabetes Metab Disord. 2013 May 7;12(1):17. doi: 10.1186/2251-6581-12-17.

31. Al Mansoori A, Shakoor H, Ali HI, Feehan J, Al Dhaheri AS, Cheikh Ismail L, Bosevski M, Apostolopoulos V, Stojanovska L. The Effects of Bariatric Surgery on Vitamin B Status and Mental Health. Nutrients. 2021 Apr 20;13(4):1383. doi: 10.3390/nu13041383.

32. Riccò M, Rapacchi C, Romboli A, Vezzosi L, Rubichi F, Petracca GL, Ferrari S, Valente M, Tartamella F, Marchesi F. Peripheral neuropathies after bariatric surgery. Preliminary results from a single-centre prospective study in Northern Italy. Acta Biomed. 2019 Sep 6;90(3):259-265. doi: 10.23750/abm.v90i3.7601.

33. Russell JW, Zilliox LA. Diabetic neuropathies. Continuum (Minneap Minn). 2014 Oct;20(5 Peripheral Nervous System Disorders):1226-1140. doi: 10.1212/01.CON.0000455884.29545.d2.

34. Shipton MJ, Thachil J. Vitamin B12 deficiency - A 21st century perspective. Clin Med (Lond). 2015 Apr;15(2):145-50. doi: 10.7861/clinmedicine.15-2-145.

35. Ankar A, Kumar A. Vitamin B12 Deficiency. [Updated 2022 Oct 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441923/.

36. Castelli MC, Friedman K, Sherry J, Brazzillo K, Genoble L, Bhargava P, Riley MG. Comparing the efficacy and tolerability of a new daily oral vitamin B12 formulation and intermittent intramuscular vitamin B12 in normalizing low cobalamin levels: a randomized, open-label, parallel-group study. Clin Ther. 2011 Mar;33(3):358-371.e2. doi: 10.1016/j.clinthera.2011.03.003.

37. Didangelos T, Karlafti E, Kotzakioulafi E, Margariti E, Giannoulaki P, Batanis G, Tesfaye S, Kantartzis K. Vitamin B12 Supplementation in Diabetic Neuropathy: A 1-Year, Randomized, Double-Blind, Placebo-controlled Trial. Nutrients. 2021 Jan 27;13(2):395. doi: 10.3390/nu13020395.

38. Butler CC, Vidal-Alaball J, Cannings-John R, McCaddon A, Hood K, Papaioannou A, Mcdowell I, Goringe A. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency: a systematic review of randomized controlled trials. Fam Pract. 2006 Jun;23(3):279-85. doi: 10.1093/fampra/cml008.

39. Andrès E, Kurtz JE, Perrin AE, Maloisel F, Demangeat C, Goichot B, Schlienger JL. Oral cobalamin therapy for the treatment of patients with food-cobalamin malabsorption. Am J Med. 2001 Aug;111(2):126-9. doi: 10.1016/s0002-9343(01)00792-6.

40. Hin H, Clarke R, Sherliker P, Atoyebi W, Emmens K, Birks J, Schneede J, Ueland PM, Nexo E, Scott J, Molloy A, Donaghy M, Frost C, Evans JG. Clinical relevance of low serum vitamin B12 concentrations in older people: the Banbury B12 study. Age Ageing. 2006 Jul;35(4):416-22. doi: 10.1093/ageing/afl033.

41. NICE. Guideline Vitamin B12 deficiency in over 16s: diagnosis and management. July 2023. https://www.nice.org.uk/guidance/GID-NG10176/documents/draft-guideline.

42. Sathienluckana T, Palapinyo S, Yotsombut K, Wanothayaroj E, Sithinamsuwan P, Suksomboon N. Expert consensus guidelines for community pharmacists in the management of diabetic peripheral neuropathy with a combination of neurotropic B vitamins. J Pharm Policy Pract. 2024 Feb 7;17(1):2306866. doi: 10.1080/20523211.2024.2306866.

43. Gu Y, Dennis SM. Are falls prevention programs effective at reducing the risk factors for falls in people with type-2 diabetes mellitus and peripheral neuropathy: A systematic review with narrative synthesis. J Diabetes Complications. 2017 Feb;31(2):504-516. doi: 10.1016/j.jdiacomp.2016.10.004.

44. Orlando G, Balducci S, Boulton AJM, Degens H, Reeves ND. Neuromuscular dysfunction and exercise training in people with diabetic peripheral neuropathy: A narrative review. Diabetes Res Clin Pract. 2022 Jan;183:109183. doi: 10.1016/j.diabres.2021.109183.

45. Dixit S, Maiya AG, Shastry BA. Effect of aerobic exercise on peripheral nerve functions of population with diabetic peripheral neuropathy in type 2 diabetes: a single blind, parallel group randomized controlled trial. J Diabetes Complications. 2014 May-Jun;28(3):332-9. doi: 10.1016/j.jdiacomp.2013.12.006.

46. Seyedizadeh SH, Cheragh-Birjandi S, Hamedi Nia MR. The Effects of Combined Exercise Training (Resistance-Aerobic) on Serum Kinesin and Physical Function in Type 2 Diabetes Patients with Diabetic Peripheral Neuropathy (Randomized Controlled Trials). J Diabetes Res. 2020 Mar 6;2020:6978128. doi: 10.1155/2020/6978128.

47. Calderon-Ospina CA, Nava-Mesa MO. B Vitamins in the nervous system: Current knowledge of the biochemical modes of action and synergies of thiamine, pyridoxine, and cobalamin. CNS Neurosci Ther. 2020;26:5-13. doi: 10.1111/cns.13207.

48. Jaya MK, Dwicandra NM. Effectivity analysis of neuroprotector (vitamin B complex and mecobalamin) as neuropathic pain supportive therapy in elderly with type 2 diabetes mellitus. Asian J Pharm Clin Res. 2017;10:320-323. doi: 10.22159/ajpcr.2017.v10i12.21845.

49. Karedath J, Batool S, Arshad A, Khalique S, Raja S, Lal B, Anirudh Chunchu V, Hirani S. The Impact of Vitamin B12 Supplementation on Clinical Outcomes in Patients With Diabetic Neuropathy: A Meta-Analysis of Randomized Controlled Trials. Cureus. 2022 Nov 22;14(11):e31783. doi: 10.7759/cureus.31783.

50. Fonseca VA, Lavery LA, Thethi TK, Daoud Y, DeSouza C, Ovalle F, Denham DS, Bottiglieri T, Sheehan P, Rosenstock J. Metanx in type 2 diabetes with peripheral neuropathy: a randomized trial. Am J Med. 2013 Feb;126(2):141-9. doi: 10.1016/j.amjmed.2012.06.022.

51. Liew J, Barlow A, Lim L-L, Suastika K, Yasahardja Y, Chan SP, Soh A, Li LS, Tan AT; 2244-PUB: Role of B Vitamins (B1, B6, B12) in Managing Diabetic Peripheral Neuropathy (DPN): A Systematic Review. Diabetes 1 June 2019; 68 (Supplement_1): 2244–PUB. https://doi.org/10.2337/db19-2244-PUB.

52. Hakim M, Kurniani N, Pinzon RT, Tugasworo D, Basuki M, Haddani H, et al. Management of peripheral neuropathy symptoms with a fixed dose combination of high-dose vitamin B1, B6 and B12: A 12-week prospective noninterventional study in Indonesia. Asian J Med Sci. 2018; 9:32-40. doi: 10.3126/ajms.v9i1.18510.

53. Thornalley PJ, Babaei-Jadidi R, Al Ali H, Rabbani N, Antonysunil A, Larkin J, Ahmed A, Rayman G, Bodmer CW. High prevalence of low plasma thiamine concentration in diabetes linked to a marker of vascular disease. Diabetologia. 2007 Oct;50(10):2164-70. doi: 10.1007/s00125-007-0771-4.

54. Alvarez M, Sierra OR, Saavedra G, Moreno S. Vitamin B12 deficiency and diabetic neuropathy in patients taking metformin: a cross-sectional study. Endocr Connect. 2019 Oct 1;8(10):1324-1329. doi: 10.1530/EC-19-0382.

55. American Diabetes Association. 1. Improving Care and Promoting Health in Populations: Standards of Medical Care in Diabetes-2020. Diabetes Care 2020;43:S7-S13. doi: 10.2337/dc20-S001.

56. Serra MC, Kancherla V, Khakharia A, Allen LL, Phillips LS, Rhee MK, Wilson PWF, Vaughan CP. Long-term metformin treatment and risk of peripheral neuropathy in older Veterans. Diabetes Res Clin Pract. 2020 Dec;170:108486. doi: 10.1016/j.diabres.2020.108486.

57. Kakarlapudi Y, Kondabolu SK, Tehseen Z, Khemani V, J SK, Nousherwani MD, Saleem F, Abdelhameed AN. Effect of Metformin on Vitamin B12 Deficiency in Patients With Type 2 Diabetes Mellitus and Factors Associated With It: A Meta-Analysis. Cureus. 2022 Dec 7;14(12):e32277. doi: 10.7759/cureus.32277.

58. Niafar M, Hai F, Porhomayon J, Nader ND. The role of metformin on vitamin B12 deficiency: a meta-analysis review. Intern Emerg Med. 2015 Feb;10(1):93-102. doi: 10.1007/s11739-014-1157-5.

59. Reinstatler L, Qi YP, Williamson RS, Garn JV, Oakley GP Jr. Association of biochemical B_{12} deficiency with metformin therapy and vitamin B_{12} supplements: the National Health and Nutrition Examination Survey, 1999-2006. Diabetes Care. 2012 Feb;35(2):327-333. doi: 10.2337/dc11-1582.

60. Rodríguez-Gutiérrez R, Montes-Villarreal J, Rodríguez-Velver KV, González-Velázquez C, Salcido-Montenegro A, Elizondo-Plazas A, González-González JG. Metformin Use and Vitamin B12 Deficiency: Untangling the Association. Am J Med Sci. 2017 Aug;354(2):165-171. doi: 10.1016/j.amjms.2017.04.010.

61. Sánchez H, Masferrer D, Lera L, Arancibia E, Angel B, Albala C. Vitamin B12 deficiency associated with high doses of metformin in older people diabetic. Nutr Hosp. 2014;29:1394-1400.

62. Ts R, Ranganathan RS, Solai Raja M, Srivastav PSS. Prevalence of Vitamin B12 Deficiency in Type 2 Diabetes Mellitus Patients on Metformin Therapy. Cureus. 2023 Apr 12;15(4):e37466. doi: 10.7759/cureus.37466.

63. Shivaprasad C, Gautham K, Ramdas B, Gopaldatta KS, Nishchitha K. Metformin Usage Index and assessment of vitamin B12 deficiency among metformin and non-metformin users with type 2 diabetes mellitus. Acta Diabetol. 2020 Sep;57(9):1073-1080. doi: 10.1007/s00592-020-01526-4.

64. Calderón-Ospina CA, Franco-González H, Leal-Martínez F, Orozco-Vázquez H, Plascencia-Pérez S, Sánchez-Mijangos J. Uso clínico de las vitaminas B neurotrópicas en enfermedades del sistema nervioso periférico en México y América Central. Med Int Mex. 2022;38:887-902. doi: 10.24245/mim.v38i4.5133.

65. Botas Velasco M, Cervell Rodríguez D, Rodríguez Montalbán AI, Vicente Jiménez S, Fernández de Valderrama Martínez I. Actualización en el diagnóstico, tratamiento y prevención de la neuropatía diabética periférica. Angiología. 2017;69(3):174-181.

66. Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, Malik RA, Maser RE, Sosenko JM, Ziegler D; American Diabetes Association. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care. 2005 Apr;28(4):956-62. doi: 10.2337/diacare.28.4.956.

67. Calderón-Ospina CA, Palacios-Sánchez L, Nava-Mesa MO, Huertas-Quintero JA. Vitaminas B neurotrópicas y neuropatía periférica: estado del arte y acuerdo de expertos. Acta Neurol Colomb. 2023;39(4):1201. doi: 10.22379/anc.v39i4.1201.

68. Elangovan R, Baruteau J. Inherited and acquired vitamin B12 deficiencies: Which administration route to choose for supplementation? Front Pharmacol. 2022 Sep 29;13:972468. doi: 10.3389/fphar.2022.972468.

69. Allen LH, Miller JW, de Groot L, Rosenberg IH, Smith AD, Refsum H, Raiten DJ. Biomarkers of Nutrition for Development (BOND): Vitamin B-12 Review. J Nutr. 2018 Dec 1;148(suppl_4):1995S-2027S. doi: 10.1093/jn/nxy201.

70. Chawla J, Kvarnberg D. Hydrosoluble vitamins. Handb Clin Neurol. 2014;120:891-914. doi: 10.1016/B978-0-7020-4087-0.00059-0.

71. Sanz-Cuesta T, González-Escobar P, Riesgo-Fuertes R, Garrido-Elustondo S, del Cura-González I, Martín-Fernán dez J, Escortell-Mayor E, Rodríguez-Salvanés F, García-Solano M, González-González R, Martín-de la Sierra-San Agustín MÁ, Olmedo-Lucerón C, Sevillano Palmero ML, Mateo-Ruiz C, Medina-Bustillo B, Valdivia-Pérez A, García-de Blas-González F, Mariño-Suárez JE, Rodríguez-Barrientos R, Ariza-Cardiel G, Cabello-Ballesteros LM, Polentinos-Castro E, Rico-Blázquez M, Rodríguez-Monje MT, Soto-Díaz S, Martín-Iglesias S, Rodríguez-González R, Bretón-Lesmes I, Vicente-Herrero M, Sánchez-Díaz J, Gómez-Gascón T, Drake-Canela M, Asúnsolo-del Barco Á; OB12 Group. Oral versus intramuscular administration of vitamin B12 for the treatment of patients with vitamin B12 deficiency: a pragmatic, randomised, multicentre, non-inferiority clinical trial undertaken in the primary healthcare setting (Project OB12). BMC Public Health. 2012 May 31;12:394. doi: 10.1186/1471-2458-12-394.

72. Schijns W, Homan J, van der Meer L, Janssen IM, van Laarhoven CJ, Berends FJ, Aarts EO. Efficacy of oral compared with intramuscular vitamin B-12 supplementation after Roux-en-Y gastric bypass: a randomized controlled trial. Am J Clin Nutr. 2018 Jul 1;108(1):6-12. doi: 10.1093/ajcn/nqy072.

73. Ahmad I, Hussain W. Stability of cyanocobalamin in parenteral preparations. Pak J Pharm Sci. 1993 Jan;6(1):53-9. PMID: 16414727.