

Update on Safety Profiles of Vitamins B1, B6, and B12: A Narrative Review

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Abstract: The neurotropic B vitamins B1 (thiamine), B6 (pyridoxine), and B12 (cobalamin) are essential for proper functioning of the nervous system. Deficiencies may induce neurological disorders like peripheral neuropathy (PN) and mainly occur in vulnerable populations (eg, elderly, diabetics, alcoholics). As epidemiologic cohort studies raised safety concerns about vitamin B6/B12 intake being potentially associated with increased risks of hip fracture (HF) and lung cancer (LC), we explored these aspects and performed comprehensive literature searches. However, we suggest not to neglect actual high-risk factors (eg, smoking in LC, higher age in HF) by focusing on individual nutrients, but to examine the complex interaction of numerous factors involved in disease development. Because it warrants continued consideration, we also provide an update on neurotoxicity associated with vitamin B6. We consider that neurological side effects due to vitamin B6 intake are rare and only occur with high daily doses and/or longer treatment duration. The benefit-risk ratio of high-dose treatment with neurotropic B vitamins in indications like PN is therefore considered advantageous, particularly if dosing recommendations are followed and serum levels monitored.

Keywords: neurotropic B vitamins, safety, thiamine, pyridoxine, cobalamin, neurotoxicity, hip fracture, lung cancer

Introduction

Neurotropic B vitamins are essential for proper functioning of the nervous system.¹⁻³ Deficiencies possibly leading to neurological disturbances, such as peripheral neuropathy (PN), may be due to an unbalanced diet (decreased availability) but mainly occur in certain vulnerable populations (eg, elderly, diabetics, alcoholics, dialysis patients, patients with gastrointestinal diseases) due to impaired absorption/utilization, accelerated usage, increased loss⁴⁻¹³ or increased hydrolysis during inflammatory diseases.¹⁴ In addition, deficits may be related to the chronic use of several widely used medications (eg, omeprazole, methotrexate, metformin).¹⁵⁻¹⁷ The use of B vitamins, particularly vitamins B1 (thiamine), B6 (pyridoxine), and B12 (cobalamin), for the treatment of PN, is well-established worldwide¹⁸⁻²⁴ and usually considered safe, even with high doses and in the long term.¹⁹

In rare cases, vitamin B12 administration can be associated with dermal adverse effects (eg, acne).²⁵ The risk appears to be higher with hydroxocobalamin than cyanocobalamin. So far, the European Food Safety Authority (EFSA) reported dermal reactions mainly with high parenteral doses (12x5 mg).²⁶ The authors of a recent case report series attributed acne eruption in one of their patients to oral

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vitamin B12 administration, but the patient took a multivitamin preparation containing vitamins B1, B2, B6, and B12 (no doses specified).²⁵ Acne due to vitamin B12 treatment usually resolves completely after treatment cessation.^{26–29} Apart from dermal reactions, cumulative adverse effects of vitamin B12 high-dose and long-term treatment are unknown. Several randomized placebo-controlled trials provide evidence on long-term use of high-dose vitamin B12 by oral route for up to 7 years without mentioning signs of overdosage or reporting side-effects different from placebo.^{30–32}

Low dose intake of neurotropic B vitamins according to Recommended Dietary Allowance (RDA) to prevent deficiencies in the healthy population is well-established and generally considered safe for long-term use;²⁵ there is rarely any new safety information available. However, over the past few years, some epidemiologic cohort studies raised new safety concerns about B vitamins (notably vitamins B6 and B12) being associated with an increased risk of hip fracture and lung cancer.^{33,34} In addition, neurological adverse effects (such as ataxia and sensory neuropathy) under long-term/high-dose treatment with vitamin B6 warrant continued consideration worthy of being updated, although they are well-described and usually reversible.^{1,25} Therefore, we aimed to explore and update these three aspects – neurotoxicity, hip fracture risk, and lung cancer risk – in the present narrative review with the help of comprehensive literature searches.

Methods

Literature Search and Selection Strategy

We performed systematic literature searches in PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>) and Cochrane (<https://www.cochrane.org/>) for English-language articles with available full text that had been published through October 2, 2019 (hip fracture, lung cancer) or October 30, 2019 (neurotoxicity). The search terms were combinations of “vitamin B1”, “thiamine”, “vitamin B6”, “pyridoxine”, “vitamin B12”, “cobalamin”, OR “B vitamins” AND “hip fracture” OR “lung cancer” as well as combinations of “vitamin B6” OR “pyridoxine” AND “neurotoxicity” OR “neurotoxic”. Additional articles were identified through manual searches in Google Scholar and the authors’ own files. Figure 1 shows the literature search and selection strategy. To receive a comprehensive overview, we did not filter for original research articles and also considered reviews, but did not include reviews in the overview

(Tables 1–3) that list selected original articles (randomized controlled trials [RCTs], cohort studies, case reports). In order to not miss any relevant, not properly indexed articles in PubMed, we also did not filter for “humans”, although we excluded original articles on animal research.

Current Evidence and Discussion

Vitamin B1 and Adverse Reactions

We were unable to identify any relevant articles for vitamin B1 (thiamine) regarding the selected safety aspects, and – to the best of our knowledge – there are no reports of adverse effects from oral thiamine consumption by food or supplements. Doses of thiamine >5 mg decline its absorption rate and the excess is excreted in the urine.²⁵ In contrast to the oral route, parenteral use has been associated with phlebitis and very rarely with hypersensitivity reactions such as pruritus, respiratory distress, nausea, abdominal pain, and even anaphylactic shock, which are mainly associated with the administration route (<2%).^{35–37}

Vitamin B6 and Neurotoxicity

The neurotoxic effect of ultrahigh-dose vitamin B6 (1,000–7,000 mg/kg) has been known since the 1940s from animal experiments.²⁵ As reviewed by Rao et al,³⁸ toxic exposure to vitamin B6 induces primary injury of nerve cell bodies (neuronopathy), possibly followed by necrosis as well as axonal and myelin degeneration. If the injury is not too advanced, the nerves can regenerate after treatment cessation, resulting in clinical improvement or resolution of symptoms.³⁸ Relevant original articles on neurotoxicity of vitamin B6 in humans obtained by our searches included seven case reports/series, one prospective study, and one case-control study (Table 1).^{39–47} In half of them, neurotoxic side-effects of vitamin B6 were mostly due to very high doses and/or long-term treatment and resolved after treatment cessation.^{39–41} Specifically, reported clinical neuropathy cases occurred in a timeframe of 2–24 months depending on the administered dose: after 12 months or longer with doses of ≤2,000 mg/day, and after less than 12 months with doses >2,000 mg/day.^{39–46} The first clinical assessment study of pyridoxine-induced neurotoxicity in humans by Schaumburg et al⁴⁷ included seven patients with severe sensory neuropathy in the extremities after taking 2,000–6,000 mg/day pyridoxine for 2–40 months. Four of these individuals were not able to walk. All symptoms,

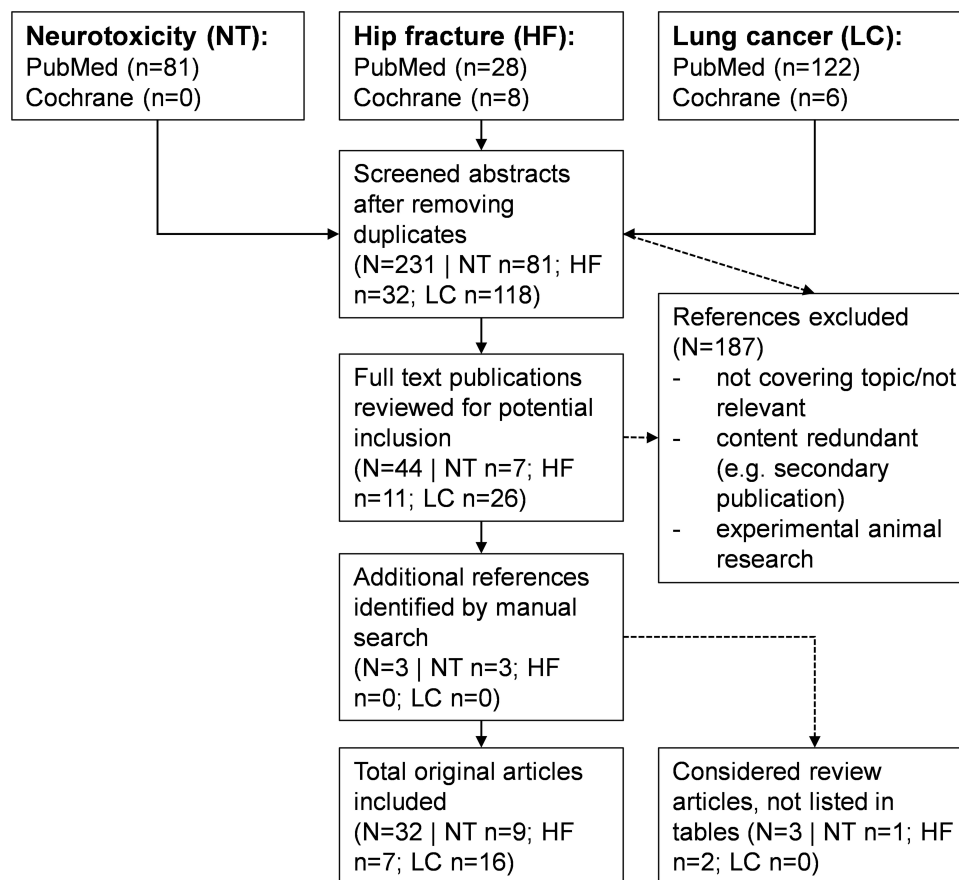


Figure 1 Literature search and selection strategy for the following adverse events possibly associated with the use of B vitamins: neurotoxicity (NT), hip fracture (HF), and lung cancer (LC). n=size number.

assessed through objective neurological diagnosis, improved after medication discontinuation.⁴⁷ Another case series report by Parry and Bredesen⁴⁶ studied 16 patients with neuropathy (all assessed by history and examination, seven electrophysiologically confirmed diagnoses, two sural nerve biopsies) after taking 100–5,000 mg/day pyridoxine for up to 72 months. Patients with doses ≤ 500 mg/day showed neuropathy after 23 months on average, while those taking 5,000 mg/day developed symptoms on average after around 3 months. In contrast, none of the patients taking 50 mg/day for <6 months presented with neuropathy, but when the intake exceeded 6 months, 20% developed symptoms.⁴⁶ These results indicate an association between neuropathy and dose/duration of vitamin B6 use, suggesting that 50 mg/day for <6 months is safe. As here, in the publications describing cases with persisting symptoms after vitamin B6 discontinuation (Table 1),^{42–45} it was unclear whether the neurological symptoms were only attributable to vitamin B6 treatment or

were favored by underlying diseases or co-medication. The study from Dalton and Dalton⁴¹ deserves special attention because it is usually cited when the potential neurotoxicity of low doses such as 50 mg is discussed.²⁵ However, the study design has often been criticized, for example by the Food and Nutrition Board of the Institute of Medicine (IOM), because neurological symptoms were not adequately detailed and actual doses may have been underestimated due to parallel intake of vitamin supplements; thus, the study appears unsuitable for determining the upper limit.³⁵

Van Hunsel et al⁴² described 90 assumed adverse drug reactions (ADRs) in the form of neuropathy reported to the Netherlands Pharmacovigilance Center between 1991 and 2017 that had been attributed to the intake of vitamin B6 supplements. In the description of selected cases, they also mentioned very few permanent cases. However, the causality between vitamin B6 intake and the occurrence of ADRs was not always clear, and important details on many cases were missing (eg, exact vitamin B6 amount,

Table 1 Characteristics of Included Studies and Case Reports on Neurotoxicity of Vitamin B6

Reference	Study Type and Country	Sample Size	Main Findings	Comment
Echaniz-Laguna et al, 2018 ³⁹	Case report, France	N=1 patient with homocystinuria	Patient treated with vitamin B6 1,250–1,750 mg/day for 20 years developed progressive sensory neuropathy with ataxia and impaired sensation in the extremities; reduction of vitamin B6 dosage to 500 mg/day led to disappearance of symptoms	Very high-dose long-term treatment led to symptoms that were still reversible
van Hunsel et al, 2018 ⁴²	Case series, Netherlands	N=90 ADR reports on products containing vitamin B6 with at least one ADR being “peripheral neuropathy”	Amount of vitamin B6 varied between 1.4 and 100 mg per tablet. The serum vitamin B6 level was only known in 36 cases (mean: 907 nmol/L); causality assessment showed it is plausible for the vitamin B6 supplements to have caused complaints such as neuropathies, especially with higher dosages and prolonged use, but dosages <50 mg/day also cannot be excluded	Case series has several limitations (see Vitamin B6 and neurotoxicity)
Kulkantrakorn, 2014 ⁴³	Case series, Thailand	N=3 patients with chronic underlying diseases (lacunar infarction, DM, etc.)	Patients consumed a vitamin B6 dose of 600 mg/day for 3–10 years; blood levels of PLP were 67–105 times upper normal; signs of polyneuropathy and sensory ataxia; patients showed no significant improvement of neuropathy and gait 2 years after vitamin discontinuation	High-dose long-term treatment; authors do not exclude other causes of neuropathy, but considered statin therapy and diabetes less likely as significant factors in two of the patients due to short duration of low-dose statin therapy and only 1–2 years of DM (well controlled)
Mikalunas et al, 2001 ⁴⁴	Case series, US	N=6 patients on HPN	Patients received multivitamin solution (contained, among other vitamins, 4 mg B6); two of the patients (both with renal failure) had elevated vitamin B6 blood levels and possible neurotoxicity (peripheral neuropathy, involuntary movements); parenteral multivitamin administration was stopped in one and decreased to once weekly in the other; vitamin B6 levels fell to normal; no improvement in neurological symptoms	Comorbidities may have contributed to the neurological symptoms in these severely ill patients (excessive levels of water-soluble vitamins have been reported in patients with renal failure); periodic monitoring of serum levels is recommended
Berger et al, 1992 ⁴⁰	Prospective study, US	N=5 healthy volunteers	Volunteers received 1 or 3 g/day vitamin B6 over 1.5–7 months (until neuropathy symptoms occurred); high-dose subjects became symptomatic earlier than low-dose subjects; clear dose-dependent relationship; all symptoms gradually resolved after treatment discontinuation	Symptoms were reversible despite very high doses

(Continued)

Table I (Continued).

Reference	Study Type and Country	Sample Size	Main Findings	Comment
Albin et al, 1987 ⁴⁵	Case series, US	N=2 patients with mushroom intoxication	Couple with mushroom intoxication received an estimated total dose of 132 g/183 g iv vitamin B6 over 3 days; developed neurological symptoms of which some but not all improved after treatment cessation	Ultra-high doses considerably in excess even of those recommended to treat <i>Gyromitra esculenta</i> intoxication
Dalton and Dalton, 1987 ⁴¹	Case-control study, UK	N=172 women with PMS	All women took vitamin B6 (<50 to <500 mg/day) and had raised serum levels; 103 women developed neurological symptoms that resolved after withdrawal; cases had taken vitamin B6 for a significantly longer period than controls (2.9±1.9 vs 1.6±2.1 years) but mean doses were comparable	Results of the study are considered unreliable and invalid by IOM ³⁵
Parry and Bredesen, 1985 ⁴⁶	Case series	N=16 patients with neuropathy (all assessed by examination, 7 by electrophysiological confirmation and 2 had sural nerve biopsy)	62.5% of the patients developed large fiber sensory neuronopathy; 6.4% had motor failure and 31.3% showed small fiber involvement. Two patients had a coasting phenomenon. Symptoms and clinical improvement were shown in 11 patients, several (not specified) months after cessation of pyridoxine medication	Small sample size; real pyridoxine dose intake not clear due to lack of information on any other vitamin supplement or medication taking during the studied time
Schaumburg et al, 1983 ⁴⁷	Case series	N=7 patients (5 women, 2 men)	Severe sensory neuropathy patients (showing progressive paresthesia of both hands and feet, marked sensory ataxia, absent tendon reflexes and flexor plantar responses) with high doses of vitamin B6 (2,000–6,000 mg/day) and long-time intakes (2–40 months) showed symptom improvement after cessation of medication	Small sample size; unclear if symptoms were attributed only to vitamin B6 intake or to any other medication

Abbreviations: ADR, adverse drug reaction; DM, diabetes mellitus; HPN, home parenteral nutrition; IOM, Institute of Medicine; iv, intravenous; PLP, pyridoxal 5' phosphate; PMS, premenstrual syndrome; UK, United Kingdom; US, United States.

exact product composition, actual intake, serum levels, neuropathy-triggering predisposing factors, clinical examinations). Moreover, due to missing data on the number of ADRs in relation to the number of supplement users, the authors could not assess the actual risk of adverse effects at the dose considered the maximal acceptable intake (25 mg).⁴²

We conclude that neurological side-effects due to vitamin B6 are rare, habitually reversible, and usually occur

after taking high daily doses (>500 mg/day) and/or longer treatment (>6 months).

Vitamin B6 and/or B12 and Risk of Hip Fracture

For several years, it has been suggested that high homocysteine (Hcy) levels are associated with lower bone mineral density (BMD), thereby increasing fracture risk.^{48,49} It is also known that B vitamins such as B12

Table 2 Characteristics of Included Studies on an Association Between Vitamin B6 and/or B12 Treatment and Hip Fracture Risk

Reference	Study Type and Country	Sample Size	Main Findings	Comment
Meyer et al, 2019 ³³	Prospective cohort study, US	N=75,864 postmenopausal women	Both vitamin B6 and B12 intake were associated with increased fracture risk	Study has several limitations (see Vitamin B6 and /or B12 and risk of hip fracture)
Garcia Lopez et al, 2017 ⁵⁰	Secondary analysis of combined data from two RCTs (NORVIT, WENBIT), Norway	N=6,837 patients with ischemic heart disease	Slightly increased risk of hip fracture for treatment with vitamin B6 alone	Study has limitations since both RCTs originally were not designed or powered to study hip fractures; baseline data on BMD, bone markers, falls, etc. missing
Dai et al, 2013 ⁵²	Prospective population-based cohort study, Singapore	N=63,257 participants from Singapore Chinese Health Study	Statistically significant inverse relationship between dietary vitamin B6 intake and hip fracture risk in women but not men; hip fracture risk reduced by 22% for women in highest intake quartile compared to women in lowest intake quartile; no relation for other B vitamins of interest	Dietary intake of B vitamins was recorded using a food-frequency questionnaire; diet assessment only at study recruitment
McLean et al, 2008 ⁵³	Longitudinal follow-up study, US	N=1,002 participants from Framingham Study	Vitamins B12 and B6 were inversely associated with hip fracture risk; low status of vitamin B12 and vitamin B6 may be independent risk factors for hip fracture	Results may only be valid for older white men and women; only plasma concentrations of B vitamins were available, which may not provide optimum assessment of vitamin status
Gjesdal et al, 2007 ⁵⁴	Prospective cohort study, Norway	N=4,766 participants from Hordaland Homocysteine Study	Hcy seemed to be a predictor of hip fracture among elderly men and women while folate was a predictor among women only; vitamin B12 did not predict hip fracture	Plasma samples for folate and vitamin B12 determination had been stored for up to 10 years before analysis, which may have weakened an association
Morris et al, 2005 ⁵⁵	Prospective cohort study, US	N=1,550 participants from NHANES III	Higher serum vitamin B12 was related to higher BMD; subjects with high serum Hcy had significantly lower BMD than subjects with low serum Hcy	Results may only be valid for elderly
Lumbers et al, 2001 ⁵⁶	Case-control study, UK	N=75 older female hospital patients admitted for emergency surgery of fractured femur neck and N=50 age-matched independent-living females	Fracture patients had lower intakes of vitamin B6 and other nutrients	Small sample size

Abbreviations: BMD, bone mineral density; Hcy, homocysteine; NHANES, National Health and Nutrition Examination Survey; NORVIT, Norwegian Vitamin Trial; RCTs, randomized controlled trials; UK, United Kingdom; US, United States; WENBIT, Western Norway B Vitamin Intervention Trial.

Table 3 Characteristics of Included Studies on an Association Between Vitamin B6 and/or B12 Treatment and Lung Cancer Risk

Reference	Study Type and Country	Sample Size	Main Findings	Comment
Takata et al, 2019 ⁸⁰	Prospective cohort study, US	N=1,064 lung cancer cases among 68,236 participants	Neither the use of folic acid-containing supplements nor food intake of vitamin B6, vitamin B12 and riboflavin were associated with lung cancer risk	Study was designed to assess folic acid from food or supplements; vitamin B6 and B12 intake from supplements was not assessed
Fanidi et al, 2019 ⁵⁹	Case-control study nested within LC3 study, international	N=5,183 case-control pairs Genetic data from N=29,266 cases and N=56,450 controls from the TRICL-ILCCO study	Circulating vitamin B12 was positively associated with overall lung cancer risk in a dose-response fashion; findings support the hypothesis that high vitamin B12 status increases the risk of lung cancer	Study has several weaknesses: secondary analysis of data from 20 cohorts that were not designed to study such association; reference groups of the different cohorts were the ones with the lowest levels of circulating vitamin B12; B12 not measured but "estimated" in the TRICL-ILCCO study
Zuo et al, 2019 ⁸¹	Case control study nested within LC3, international	N=5,232 case-control pairs	Increased vitamin B6 catabolism related to inflammation and immune activation is associated with a higher risk of developing lung cancer	Conclusions are based on measurements at a single time point (regression dilution bias possible)
Yang et al, 2018 ⁶⁷	Meta-analysis of 14 case-control studies/nested case-control studies, international	N=8,097 lung cancer patients and N=10,008 healthy controls	Serum folate and vitamin B6 might be protective factors against lung carcinogenesis and Hcy could contribute to lung cancer risk	Included cohorts were designed for such analysis; blood samples were used instead of intake estimates; three studies with reliable evidence, 11 studies with less certain evidence
Zuo et al, 2018 ⁸²	Nested case-control study, Europe	N=892 incident lung cancer cases and N=1,748 controls from the EPIC study cohort	Increased vitamin B6 catabolism is independently associated with a higher risk of future lung cancer	Conclusions are based on measurements at a single time point (regression dilution bias possible); median time between blood draw and lung cancer diagnoses was 5.2 years
Fanidi et al, 2018 ⁶⁴	Nested case-control study, international	N=5,364 incident case-control pairs (NCI cohorts)	Participants with higher circulating concentrations of vitamin B6 and folate had a modestly decreased risk of lung cancer risk overall	Conclusions are based on measurements at a single time point (regression dilution bias possible); median time between blood draw and lung cancer diagnoses was 6.3 years
Brasky et al, 2017 ³⁴	Prospective cohort study, US	N=77,118 participants (VITAL cohort)	Use of vitamin B6 and B12 from individual supplement sources, but not from multivitamins, was associated with a 30–40% increase in lung cancer risk among men; no association in women	Study has several limitations (see Vitamin B6 and /or B12 and risk of lung cancer)
Zuo et al, 2015 ⁸³	Prospective cohort study, Norway	N=6,539 participants (Hordaland Health Study)	Associations of vitamin B6 with cancer may be related to increased catabolism of vitamin B6 captured by plasma PAa, in particular for lung cancer where inflammation may be largely involved in carcinogenesis; the active B6 vitamer PLP was not significantly associated with overall cancer risk	Study investigated certain types of cancer (including but not limited to lung cancer); findings based on relatively small case numbers per cancer type; included a comprehensive panel of vitamin B6 markers
Tastekin et al, 2015 ⁸⁴	Case-control study, Turkey	N=40 males with lung cancer, N=40 healthy controls	Plasma folate levels significantly lower in lung cancer cases compared with controls ($P<0.001$) but no significant difference with regard to B12 levels	Small sample size

(Continued)

Table 3 (Continued).

Reference	Study Type and Country	Sample Size	Main Findings	Comment
Baltar et al, 2013 ⁸⁵	Nested case-control study, Europe	N=891 cases; N=1,747 controls (EPIC cohort)	Structural equation modeling (including vitamins B2, B6, folate, B12) indicated roles of methionine-Hcy metabolism and immune activation in lung cancer risk; of the measured B vitamins, only folate and B6 were significantly ($P<0.01$) lower in cases than controls; tobacco smoking remained exposure with strongest impact on lung cancer risk	Authors emphasize that complex pathways (OCM, folate cycle, and immune system) rather than activities of single vitamins or nutrients should be considered in lung cancer carcinogenesis
Takata et al, 2012 ⁸⁶	Prospective cohort study, China	N=74,941 women (Shanghai Women's Health Study)	Dietary riboflavin intake was inversely associated with lung cancer risk while intakes of other B vitamins (eg, B6, B12) were not associated	Large study of female never-smokers with lung cancer; population had lower intakes than other populations; intakes of B6 and B12 only estimated; no information on serum levels
Bassett et al, 2012 ⁸⁷	Prospective cohort study, Australia	N=41,514 people (Melbourne Collaborative Cohort Study)	Little evidence of an association between intake of B vitamins or methionine and lung cancer risk; weak inverse association between riboflavin and lung cancer risk in current smokers needs further investigation	Information on intake (self-reporting questionnaire) and potential confounding variables was only collected at baseline; no information on serum levels
Johansson et al, 2010 ⁶⁵	Case-control study, Europe	N=899 lung cancer cases; N=1,770 controls (EPIC)	Serum levels of vitamin B6 and methionine were inversely associated with risk of lung cancer	Measurements of serum levels only at baseline (regression dilution bias possible)
Ebbing et al, 2009 ⁸⁸	Combined data from two RCTs (NORVIT, WENBIT), Norway	N=6,837 participants with ischemic heart disease	While treatment with vitamin B6 alone was not associated with any significant effects, treatment with folic acid plus vitamin B12 was associated with increased cancer outcomes and all-cause mortality	Study has limitations since both RCTs originally were not designed or powered to study lung cancer risk; authors point out that observed associations were confined only to serum folate, suggesting that the adverse effects were mediated by folate, not by vitamin B12
Tsao et al, 2007 ⁸⁹	Case-control study, China	N=27 patients and N=23 controls	RBC levels of vitamins B2 and B6 were reduced in NSCLC patients	Small sample size
Hartman et al, 2001 ⁶⁶	Nested case-control study, Finland	N=300 male case-control pairs	No significant associations were seen between serum folate, vitamin B12 or Hcy and lung cancer risk; significantly lower risk of lung cancer among men who had higher serum vitamin B6 levels	Correlations between dietary intake and serum markers of B vitamins were not strong; many males had inadequate serum levels of folate and B6

Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; Hcy, homocysteine; LC3, Lung Cancer Cohort Consortium; NCI, National Cancer Institute; NORVIT, Norwegian Vitamin Trial; NSCLC, non-small cell lung cancer; OCM, one-carbon metabolism; PAr, 4-pyridoxic acid/(pyridoxal 1 pyridoxal 5'-phosphate) ratio; PLP, pyridoxal 5' phosphate; RBC, red blood cell; RCTs, randomized controlled trials; TRICL-ILCCO, Transdisciplinary Research Into Cancer of the Lung-International Lung Cancer Consortium; US, United States; VITAL, vitamins and Lifestyle; WENBIT, Western Norway B Vitamin Intervention Trial.

and B6 have a major impact on the Hcy metabolism as coenzymes³ and lower Hcy levels,^{48,49} leading to the logical assumption that sufficiently high vitamin B6/B12 levels could theoretically help protect against low BMD or fractures.⁴⁸ Although most research primarily sought to define a positive effect of B vitamins, a few recent articles

propose an alternative assumption.^{33,50} Our literature searches revealed seven relevant studies on vitamin B6 and/or B12 and the risk of hip fracture: four cohort studies, one longitudinal follow-up study, one case-control study, and one secondary analysis of data from two RCTs (Table 2).^{33,50-56}

The recent prospective cohort study by Meyer et al³³ claimed that a combined high intake of vitamin B6 (≥ 35 mg/day) and B12 (≥ 20 μ g/day) in postmenopausal women is associated with an increased hip fracture risk and suggests that vitamin supplements should be used cautiously. A possible biological explanation is that high pyridoxine doses might increase the risk of falling due to neurological symptoms, including reversible neuropathy, ataxia, and decreased muscle tone, as mentioned before. Another explanation may be related to accelerated bone loss induced by vitamin B6 by counteracting the modulating influence of estrogens on steroid receptors.⁵¹ However, current use of vitamin B6 was not associated with an increased fracture risk at any of the evaluated doses in the study (relative risk [RR]=1.12 (95% confidence interval [CI]=0.95–1.31)),³³ suggesting that the slightly increased fracture risk is rather related to chronic (>2 years) than to current pyridoxine use. However, this study³³ also has numerous limitations, including the design as a cohort study, self-reporting of participants, high age of the study population, high confounding bias, etc. In addition, information is available only on vitamin intakes but not on blood/serum levels.³³ Information on reasons for supplement intake is also lacking.³³ As most supplements contain multivitamins, supplementation of vitamin B6 and/or B12 is likely to be taken with vitamin D and calcium.⁴⁸ We assume that multivitamin supplements are predominantly prescribed to or voluntarily used by elderly at risk of fractures, which means that supplement usage is normally driven by being at risk. We also believe that many other factors (eg, age, body mass index, physical activity, osteoporosis) may have contributed to the incidence of hip fractures and that the data are insufficient to provide evidence for a correlation of vitamin B6 intake and hip fracture risk. Most articles identified by us (Table 2) do not confirm this correlation, and several studies even found correlations between a higher vitamin B6 and/or B12 status and a lower risk of hip fracture and/or higher BMD.^{52–56} In agreement with a recent report of combined data from two RCTs,⁵⁰ Meyer et al³³ also found no association between vitamin B12 and an increased fracture risk (RR=1.25; 95% CI=0.98–1.58).

In summary, it cannot be assumed that the risk of hip fractures increases with vitamin B6/B12 intake levels per se but that it is rather modulated by a complex interplay of many factors such as calcium or D vitamin or metabolic and pharmacological factors. It would be

a mistake in our opinion to change intake recommendations for (possibly otherwise required) higher vitamin B6/B12 doses based on conclusions that do not take sufficient account of the complex processes.

Vitamin B6 and/or B12 and Risk of Lung Cancer

The idea that B vitamins—in one way or another—play a role in carcinogenesis is not new. Indeed, in a population-based cohort study, higher plasma levels of cobalamin were associated with higher risk of cancer.⁵⁷ Due to their antioxidant properties and their substantial participation in one-carbon metabolism (OCM) and, thus, the regulation of DNA methylation, an impact is almost undeniable (reviewed in Gruber⁵⁸). However, when discussing whether B vitamins have cancer-protective or risk-increasing effects, it should be highlighted that OCM and other metabolic cycles involved in carcinogenesis are highly complex processes depending on a variety of inter-related factors.⁵⁸ Nevertheless, several recent epidemiological studies do claim an association between lung cancer risk and B vitamins.^{34,59} In total, we identified nine case-control studies, four cohort studies, one meta-analysis of 14 case-control studies, and one analysis of combined data from two RCTs (Table 3) dealing with vitamin B6 and/or B12 and lung cancer.

One of the few studies proposing an association between B vitamins and lung cancer risk was published by Brasky et al³⁴ in 2017. The Vitamins and Lifestyle (VITAL) cohort included 77,118 subjects aged 50–76 from the US and examined the association between the long-term use of supplemental B vitamins and lung cancer risk.³⁴ In the 6-year follow-up on average, 808 lung cancer cases occurred. The 10-year average daily doses from individual and multivitamin supplements as well as mixtures were retrospectively documented at baseline by self-assessment questionnaires. When trying to establish associations, the authors found the long-term use of high-dose vitamin B6 (defined as >20 mg/day) or B12 (defined as >55 μ g/day) from individual supplement sources, but not multivitamins, to be associated with a 30–40% increase in lung cancer risk among male smokers.³⁴ However, in our opinion, the study does not prove causality between B vitamin intake and lung cancer risk and has significant limitations, as already pointed out by Obeid and Pietrzik.⁶⁰ When reviewing patient characteristics of the VITAL study, 42% of lung cancer cases were ≥ 70 years, while

only 19% of controls belonged to this age group.³⁴ The percentage of smokers was almost four times higher for cases than controls.³⁴ This imbalance was even more evident for smoking duration: 71% of lung cancer cases had smoked for >35 years vs 16% of controls. Likewise, 70% of cases and only 19% of controls had smoked >25 pack-years of cigarettes.³⁴ Finally, the history of COPD was 5-times more frequent in cases than controls,³⁴ and it is well known that this condition increases the risk of lung cancer – especially squamous cell carcinoma – by the factor five.^{61,62} Because these determinants of lung cancer, such as advanced age, cigarette smoking, and COPD history, were much more prevalent in cases than controls,³⁴ it is much more likely that the authors estimated the effect of these well-known risk factors instead of the effect of B vitamins on this outcome.^{34,60}

Without measuring serum levels over time, Brasky et al³⁴ started from the premise that a self-reported intake above the RDA reflects disturbed vitamin homeostasis, but self-reported intakes should not be taken as surrogate markers for vitamin levels. As mentioned before, age, smoking status, smoking duration, smoking intensity, COPD history, and some genetic variants are well-known lung cancer risk factors.⁶³ The fact that these factors were also associated with vitamin usage raises the suspicion that the association between vitamin intake and cancer was due to confounding, despite the authors' attempts to compensate for it through adjustment for known or suspected risk factors. Like Obeid and Pietrzik,⁶⁰ we consider a reverse causality more likely; ie, knowing to have an increased risk (which every smoker does) can trigger healthier behaviors in other areas of life, including taking vitamin supplements. Therefore, we do not believe that the VITAL study uncovered a causal relationship between supplement intake and lung cancer. Apart from our own assumptions, many studies contradict the findings from a scientific point (Table 3). For example, several authors reported inverse relationships between vitamin B6 levels and lung cancer risk,^{64–66} and Yang et al⁶⁷ even consider a possible protective effect of vitamin B6 in a systematic review and meta-analysis, including 14 studies and >8,000 patients. This protective effect of vitamin B6 has also been described in gastrointestinal cancer, pancreatic cancer, and breast cancer.^{68–70}

Taken together, the current evidence from (almost exclusively epidemiological) studies on a relationship between vitamin B6 and/or B12 intake and lung cancer risk is not conclusive.^{34,–59,–64–67,80–89} The results of

Brasky et al³⁴ regarding vitamins B6 and B12 should be interpreted with caution. The potential role of B vitamins in lung cancer carcinogenesis should be regarded in a bigger context and consider the complex interaction in OCM, folate cycle, etc., which we believe requires further intense research. However, the focus should still be on the actual high-risk factors such as smoking, which increase the risk many times.⁶³

Additional Considerations: General Morbi-Mortality

Although the combination of vitamin B6 and B12 plus vitamin B9 (folic acid) has been suggested to prevent cardiovascular events (considering the relationship between Hcy levels and vascular risk),^{71,72} high doses of vitamin B6 (25 mg/day), vitamin B12 (1 mg/day), and vitamin B9 (2.5 mg/day) resulted in reduced glomerular filtration rates and increased vascular events in a placebo-controlled trial in patients with diabetic nephropathy.⁷³ Correspondingly, higher vitamin B12 plasma levels were associated with a higher mortality risk in a cohort of hemodialysis patients.⁷⁴ The same study found low serum folate levels to be related with the same higher risk of all-cause mortality,⁷⁴ showing that overall evidence remains controversial and no final recommendation can be established. However, we suggest that levels of B vitamins should be anyway continuously monitored to reach adequate levels in patients with chronic kidney disease requiring supplements. Unlike patients with nephropathy, the frequency of adverse events in patients with cardiovascular disease using B vitamin supplements is similar to placebo.⁷⁵

Interestingly, serum vitamin B12 levels may be increased in patients with heart failure, regardless of vitamin supplementation.⁷⁶ This increase may be attributed to a subclinical liver dysfunction (cardiohepatic syndrome) which leads to the release of vitamin B12 from damaged liver cells and – paradoxically – produces clinical signs of vitamin B12 deficiency.⁷⁶

Finally, some studies reported an association between higher plasma vitamin B12 levels and mortality in elderly⁷⁷ and hospitalized patients (without vitamin B12 intake).⁷⁸ A recent longitudinal cohort study also showed this association in a general population of apparent non-users of vitamin B12 supplements,⁷⁹ but the authors did not establish a causal relationship due to residual confounding factors.⁷⁹

Limitations

This review has several limitations. First, we have limited this review and the corresponding literature searches to various current safety aspects (ie, neurotoxicity, risk of hip fracture, and risk of lung cancer) and have not fully captured the entire evidence of the past decades in other areas. Our literature searches may therefore have been biased by our prior knowledge of the particularly highlighted epidemiologic cohort studies. Second, we assume that, despite the widespread use of B vitamins, the scientific literature does not fully reflect clinical reality. For example, underreporting of safety issues is a common problem, particularly in countries with less well-established health systems.⁹⁰

Conclusion

The high-dose use of neurotropic B vitamins as medicinal products has proven useful in specific indications such as PN. We consider vitamin B1 as generally safe, with adverse reactions being limited to parenteral administration. If dosage recommendations especially for vitamin B6 are followed, we also consider the benefit–risk ratio to be advantageous. Ideally, treatment duration should be <6 months and serum levels monitored during treatment. This not only helps to avoid the rare cases of vitamin B6 overdose with potential neurological side-effects, but also to prevent possible undersupply, which can still occur with malabsorption despite high doses. Taking low doses of neurotropic B vitamins to prevent deficiencies in the otherwise healthy population is also well-established and can be considered safe overall. In our opinion, a causal relationship between the vitamin B6 and/or B12 intake and an increased hip fracture or lung cancer risk cannot be considered at present. We rather propose not to focus on individual nutrients, but to examine the complex interplay of the innumerable involved metabolic processes in detail and to expand the basic research on the development of these diseases on a biochemical level. Considering the predominantly renal excretion of these vitamins and a potentially increased risk of adverse outcomes in patients with diabetic nephropathy, we recommend monitoring B vitamin levels in this patient group.

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Author Contributions

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

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