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B vitamins and homocysteine as determinants of bone health: A literature review of human studies

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Abstract

Although there are several factors related to bone diseases such as physical activity, gender (oestrogen), race/ethnicity, smoking and alcohol habits, nutrition is a modifiable risk factor that could be employed to prevent or manage the onset of bone health diseases such as osteoporosis in humans. Aside from calcium and vitamin D, B vitamins are a group of water-soluble vitamins that play a vital role in cell metabolism. In this review, current evidence on B vitamins and bone health is assessed. Clinical trials (interventions) indicate that treatment with B vitamins impact the concentrations of total plasma/serum homocysteine concentrations (tHcy); however, most studies have reported the lack of an effect of low homocysteine concentrations on bone turnover markers, bone mineral density or fracture risks. Current studies have been inconsistent in their reports on the role of B vitamins and homocysteine in bone health. More data are therefore required to show the mechanism and effect of tHcy and B vitamins on bone mineral density, bone metabolism and fracture risk.

KEYWORDS

BMD, bone health, bone metabolism, B vitamins, homocysteine, osteoporosis

Key points

- B vitamins are important for the regeneration of tissues and organs.
- This review shows that B vitamins may contribute to increased osteogenesis.
- When administered in the normal range, the bioavailability of B vitamins may be beneficial.
- More interventions and longitudinal studies are needed for the effect of B vitamins and homocysteine.

INTRODUCTION

There is an exponential increase in the risk of osteoporosis and bone fractures with age after menopause in women. Furthermore, women aged 50 years and above are more prone to the risk of hip fractures.[1] Several factors are considered to be related to the risk of age-related bone disorders, such as gender, loss of oestrogen, ethnicity, sedentary lifestyle, excessive alcohol use, smoking and an unhealthy nutrient-deficient diet devoid of calcium and vitamin D. The role and impact of B vitamins has, however, emerged as an interesting diet-related nutrient that could affect bone metabolism through their singular actions and through modulation of homocysteine concentrations in the body.[2]

Homocysteine is an amino acid that is not supplied from the diet but is synthesised from methionine, an essential amino acid. Normal plasma blood sample

ranges of homocysteine concentrations for men and women are typically between 5 and 15 μmol L^{-1}, and hyperhomocysteine has been reported as concentrations exceeding 15 μmol L^{-1}.[3] It can be converted to cysteine and methionine by the combination B vitamins (such as folate, B_6 and B_{12}) and the enzyme methylenetetrahydrofolate reductase (MTHFR).[4] Homocysteine levels are often categorised into three medical groups for reference: moderate (16–30 μmol L^{-1}), intermediate (31–100 μmol L^{-1}) and severe (over 100 μmol L^{-1}).[5]

The conversion of homocysteine to methionine is called remethylation and this process requires vitamin B_{12} as a cofactor. Methionine can subsequently be regenerated to homocysteine by breaking down *S*-adenosylmethionine. During the transsulfuration reaction, cysteine is also generated from homocysteine with pyridoxal-5′-phosphate and cystathionine B-synthase acting as catalysts.[6] The elevation of homocysteine has, however, been suggested to be caused by disruptions to any one of these reactions and a common cause of hyperhomocysteinaemia is known to be the inadequacy of the enzyme MTHFR as a result of genetic defects.[7]

Thiamin (vitamin B_1) and in its active form thiamine pyrophosphate is an essential micronutrient that acts as a cofactor of key enzymes involved in the process of carbohydrate, lipid and amino acid metabolism, as well as in the synthesis of neurotransmitters. It cannot be made by the body, but is used by the body to metamorphise energy from food.[8]

Riboflavin (vitamin B_2), is a key component of coenzymes involved with the metabolic pathways in growth of cells, energy production, and the breakdown of fats, steroids and medications. Biologically active forms of riboflavin are flavin adenine dinucleotide and flavin mononucleotide. Because of ageing and reduced absorption efficiency in the elderly, they are more susceptible and vulnerable to vitamin B_2 deficiencies.[9]

Niacin, an essential human nutrient otherwise known as vitamin B_3 or nicotinic acid are substrates for both nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP). These coenzymes are known electron acceptors for fuel molecules in redox reactions. Niacin exerts antioxidant effects and is involved in conversion of nutrients to energy, DNA formation and repair, and cellular activities.[9,10]

Vitamin B_6 (pyridoxine) is important for many enzymatic functions (>100) and its role in neurotransmitters, cognitive function, the immune system and in cellular and amino acid metabolism is essential.[10] The bioactive form is known as pyridoxal-5′-phosphate and is also involved in the metabolism of glycogen and phospholipids.[9]

Folate (vitamin B_9) plays a critical role in the nucleotide synthesis, homocysteine metabolism and in DNA, RNA, protein, and phospholipid methylation. Folate and vitamin B_{12} play a vital role in the methylation pathway of methionine synthesis; therefore, their deficiencies cause megaloblastic changes to the bone marrow and tissues.[9]

Vitamin B_{12} is involved in DNA synthesis and normal haematological processes as well as in cognitive and neuro-psychiatric functions. In addition, folate′s role in amino acid metabolism responsible for the synthesis of DNA and RNA is essential for the body.[2] Because of the role that vitamins B_6, B_{12} and folate play in the biochemistry of homocysteine, as well as in drug-nutrient interactions in cases such as proton pump inhibitors (PPIs), a medicine sometimes used for the treatment of indigestion (e.g., omeprazole) can elevate homocysteine.[11,12] Causes of deficiencies of these vitamins include alcohol abuse, malabsorption in pernicious anaemia, atrophic gastritis and intestinal diseases (Crohn's disease and coeliac disease). Medications such as methotrexate and metformin could also result in B vitamin deficiency and can elevate homocysteine. Inadequate dietary intake in cases such as veganism and vegetarianism could also result in a low vitamin B_{12} status.

Elevated concentrations of homocysteine have been correlated with several conditions such as increased cerebrovascular, cardiovascular and thromboembolic diseases.[4,6,13] Cognitive ability decline, chronic kidney disease, Alzheimer's disease, hypothyroidism and schizophrenia have also been linked to high concentrations of homocysteine.[14–16] These studies have shown that lowering homocysteine concentrations can be beneficial in lowering the risk for cardiovascular and cerebrovascular disease. However, reports have been controversial. A study showed the beneficial effects of lower homocysteine concentrations in slowing down the acceleration rate of brain atrophy[14]; however, another meta-analysis by the American Heart Association showed that a lower homocysteine level does not positively impact coronary heart disease[17] or prevent stroke.[13]

In addition, hyperhomocysteinaemia has been linked to osteoporosis and increased hip fracture in women, most especially postmenopausal women. The pathophysiology is speculated to be the result of an alteration of the bone matrix when homocysteine interferes in the collagen cross-linking leading to increase in bone fragility.[18] Elevated homocysteine negatively influences the formation of bone matrix by the inhibition of collagen cross-linking enzyme lysyl oxidase (Lox), as well as a possible repression of its mRNA expression. Plasma total homocysteine concentration is influenced by B vitamins including riboflavin (vitamin B_2). Low concentrations of these vitamins cause elevated plasma total homocysteine, with the main nutritional determinant being low vitamin B_{12}, such that folate fortification is employed in most countries.[19] Folic acid fortification is, however not generally used because not all countries allow fortification of the food supply, which creates complications in the analysis of evidence and data in studies.

Pyridoxine (vitamin B_6) acts as an essential co-enzyme for lysyl oxidase, which is an enzyme necessary for collagen cross-linking. Pyridoxine is also known for physiological activities in hormone receptors because of its role in the regulation of steroid hormones such as oestrogen.[20] Apparently, the relationship between B vitamins and bone metabolism is multifactorial and interwoven with other metabolic pathways in the skeletal system.

Therefore, the primary objective of this scoping narrative/literature review is to provide an updated summary of available data on the correlation between B vitamins, homocysteine and bone health in observational studies (Tables 1 and 2), clinical trials and metanalyses (Table 3).

In September 2021, a search was carried out in the Massey University library Discover using PubMed, Google Scholar and Web of Science. The search words B vitamins, homocysteine and bone were used. Relevant papers were then used in the finalisation of the study (Table 4).

DISCUSSION

Most of the cross-sectional epidemiological studies on B vitamins (both in diet recall and blood samples) and bone health have largely been on cobalamin (vitamin B_{12}). Not many cross-sectional studies have been conducted on the other B vitamins.

THIAMIN

Two studies were conducted over two decades ago, with one of the studies reporting thiamin status in orthopaedic patients and indicating a deficiency of thiamin in patients with femoral neck fracture.[67] The other study reported a high proportion of falls that may be a result of moderate and severe thiamin deficiency in aged hospitalised patients.[68]

RIBOFLAVIN

Three cross-sectional studies were conducted on vitamin B_2 (riboflavin) and bone health. One of the studies reported a positive correlation between vitamin B_2 intake and femoral neck BMD in *TT* genotype women.[39] *MTHFR* genotype was associated with femoral neck and lumbar spine BMD indicating a reduced activity of the *MTHFR* enzyme in the *TT* genotype as a result of the loss of B_2 cofactor.[10] One of the other two studies found a positive association between vitamin B_2 and lumbar spine BMD,[40] whereas the third study found no association with vitamin B_2 and bone density.[38] In longitudinal studies, three studies conducted showed a positive relationship between vitamin B_2 and BMD; in Scottish women with *MTHFR TT* genotype[48] and in Dutch participants.[49,51]

NIACIN

Likewise, in a cross-sectional study conducted in New Zealand postmenopausal women, vitamin B_3 was positively associated with spine, femoral neck, hip and whole-body BMD.[40] Similarly, premenopausal intake of niacin (vitamin B_3) in a Japanese women was positively correlated with BMD.[69] However, in the Singaporean Chinese Health Study, dietary intake of vitamin B_1, B_2 and B_3 was not associated with risk of fracture in the men or women.[52]

PYRIDOXINE

Three out of five cross-sectional studies that measured the correlation between pyridoxine (vitamin B_6) and bone mass and/or fracture risk found a significant association. The Danish osteoporosis prevention study showed a positive association between vitamin B_6 and BMD[39]; similarly, in German men and women, a positive association was found between serum vitamin B_6 and trabecular number in subjects.[28] An inverse association was also found in Chinese women residents between vitamin B_6 and osteoporosis risk, whereas no association was observed in men.[34] Two studies, however, found no association between vitamin B_6 and BMD; this may be a result of the small sample size and/or study design. More relevant prospective studies are therefore needed to validate the results.

In the Rotterdam study, a positive association was observed between vitamin B_6 and femoral neck BMD and an inverse relationship was observed with vitamin B_6 and fracture risk.[49] Similarly, the Framingham Osteoporosis study reported an inverse association between vitamin B_6 and bone loss/hip fracture risk.[46] The Singaporean Chinese Health Study observed a significant dose-dependent inverse relationship between dietary vitamin B_6 intake and risk of hip fracture among women and not with men; the women were also further reported to have a history of diabetes.[52] Similarly, a small-sampled cross-sectional study reported that lower serum vitamin B_6, folate and vitamin B_{12} concentrations were significantly associated with lower serum concentrations of osteocalcin (OC), a bone turnover marker. Lower vitamin B_6 and folate concentrations were associated with lower trabecular thickness and trabecular area but there was no association between B vitamins and BMD or tartrate-resistant acid phosphatase (TRAP).[28]

TABLE 1 Observational studies on the association between B vitamins and bone health determinants and fracture risks

Reference	Sample size and subjects	Exposures and outcomes	Main findings
Studies using blood (serum or plasma) samples			
Cagnacci et al.[21]	161 Italian postmenopausal women	Serum folate, vitamin B_{12} and total serum homocysteine/ BMD	Folate was positively related to BMD ($r = 0.254$, $p < 0.011$) but not vitamin B_{12} and homocysteine
Dhonukshe-Rutten et al.[22]	194 free-living Dutch frail elderly aged ≥ 70 years	Serum or plasma vitamin B_{12}/BMC and BMD	BMC and BMD were explained positively by plasma vitamin B_{12} in women ($R^2 = 1.3\%–3.1\%$). The risk of osteoporosis was more profound in women with marginal or deficient vitamin B_{12} status compared to women with a normal status
Golbahar et al.[23]	271 Iranian postmenopausal women with mean age of 60.8 years	Plasma total homocysteine, plasma folate and vitamin B_{12}; MTHFR C667T polymorphism/ femur and lumbar spine BMD	Lumbar spine BMD positively associated with plasma folate ($r = 0.14$, $p = 0.02$), no correlation observed between MTHFR, vitamin B_{12} and femur and lumbar spine BMD. Negative correlation for the logarithm of plasma total homocysteine and femoral neck ($r = -0.18$, $p = 0.003$) and lumbar spine BMD ($r = -0.16$, $p = 0.01$)
Golbahar et al.[24]	366 Iranian postmenopausal women with mean age of 60.8 years	RBC 5-MTHFR and plasma 5-MTHFR/BMD	RBC 5-MTHF was more positively correlated with BMD at the lumbar spine ($r = 0.21$, $p = 0.001$) and femoral neck ($r = 0.19$, $p = 0.004$) than was plasma 5-MTHF (lumbar spine; $r = 0.14$, $p = 0.03$ and femoral neck; $r = 0.17$, $p = 0.006$)
Morris et al.[25]	1500 White American men and women aged > 55 years	Serum and RBC folate, serum vitamin B_{12} and homocysteine/ BMD; osteoporosis prevalence risk factor	Serum and RBC folate were not related to BMD or osteoporosis. Vitamin B_{12} was positively associated ($p = 0.01$) with BMD when $B_{12} < 220$ (pmol L^{-1}). Significant risk of osteoporosis reported in the lowest quartile compared to the highest quartile. Individuals with serum Hcy ≥ 20 μmol L^{-1} had significantly lower BMD than subjects with serum Hcy < 10 μmol L^{-1} Prevalence of osteoporosis marginally increased ($p = 0.049$) among participants in the lowest serum vitamin B_{12} quartile category
Baines et al.[26]	328 British postmenopausal women	Serum folate, vitamin B_6, B_{12} and MTHFR genotypes, and plasma	Folate was significantly positively associated with BMD ($r = 0.132$, $p = 0.025$, log folate) but not vitamins B_6, B_{12}. Also, total Hcy appeared to be related to BMD

TABLE 1 (Continued)

Reference	Sample size and subjects	Exposures and outcomes	Main findings
		homocysteine/ BMD	($r = -0.130$, $p = 0.033$, log total Hcy)
Bozkurt et al.[27]	178 Turkish postmenopausal women with mean age 53.8 ± 7.1 years (range: 38–75 years)	Serum folate, B_{12} and homocysteine/ BMD	High Hcy and low vitamin B_{12} levels were associated with the risk of osteoporosis. Vitamin B_{12} <quintile value ($p < 0.05$) and the Hcy concentrations >median value ($p < 0.05$) were the significant variables to predict osteoporosis in both the femur and the lumbar vertebra. No association was found between folate and BMD (femoral neck and lumbar spine)
Holstein et al.[28]	94 German men and women aged 52–83 years	Serum folate, B_6 and B_{12}/BMD, trabecular thickness, number and area; BTMs, OC and TRAP	Significant lower trabecular thickness and trabecular area in subjects with low serum folate and vitamin B_6 concentrations ($p < 0.05$). Osteocalcin concentrations was significantly lowered in subjects with a low serum B vitamin concentration ($p < 0.05$)
Halıloglu et al.[29]	120 Turkish postmenopausal women	Serum folate, vitamin B_{12} and homocysteine/ BMD, BTM (BAP and CTx)	Serum Hcy concentrations were significantly higher in osteoporotic women after adjusting for confounders (adjusted OR = 38.95 [1.474–1029.88] $p = 0.02$). Serum homocysteine was positively related with BTM (CTx and BAP concentrations) $\beta = 0.239$, $p = 0.026$; $\beta = 0.451$, $p = 0.001$. No association between folate and vitamin B_{12} and BMD or BTM
Rumbak et al.[30]	131 Croatian women aged 45–65 years	Plasma homocysteine, serum and RBC folate, and vitamin B_{12}/BMD	No relationship was found for homocysteine, folate or B_{12} and BMD
Bailey et al.[31]	2806 US women aged ≥ 50 years	Plasma total Hcy, methylmalonic acid, vitamin B_{12} and serum/red blood cell folate/ total-body and lumbar spine BMD, BTM (BAP and uNTx)	High concentrations of MMA and total Hcy were related to increased lumbar osteoporosis risk. Total Hcy was negatively related, serum folate was positively associated, and MMA and vitamin B_{12} were not significantly related with lumbar and total-body BMD
Tariq et al.[32]	156 postmenopausal women aged 50–70 years	Serum 25(OH)D, vitamin B_{12}, tHCY and BMD	Significant negative correlation of homocysteine with vitamin D and B_{12} in postmenopausal non-osteoporotic ($r = -0.383$, $p = 0.005$) and homocysteine with vitamin B_{12} in postmenopausal osteoporotic women ($\rho = -0.376$, $p < 0.001$)

(Continues)

TABLE 1 (Continued)

Reference	Sample size and subjects	Exposures and outcomes	Main findings
Beyazit and Pek[33]	184 Turkish postmenopausal women with average age 57.5 ± 10.6 years	Serum vitamin B_{12}, folate, uric acid and inflammation markers/BMD	No association was found between concentrations of serum vitamin B_{12}, folate and inflammatory markers with femur neck and lumbar spine BMD measurements. Higher tertiles of uric acid was observed with higher BMD values. There was a correlation between femaoral neck BMD and uric acid ($p < 0.001$) and BMI ($p = 0.003$)
Wang et al.[34]	1829 residents (men ≥ 50 years and women ≥ 45 years) of Shanghai, China	Serum vitamin B_6/ lumbar spine BMD, BTM (N-terminal propeptide of type I collagen, β-C-terminal telopeptide of type I collagen and osteocalcin)	Osteoporosis risk was 61% higher only in women with serum vitamin B_6 concentrations of $< 19.2\,\mu g\,L^{-1}$ than those with $> 26.9\,\mu g\,L^{-1}$ (OR = 1.61, 95% CI = 1.00–2.58). Serum vitamin B_6 concentration was significantly negatively correlated to concentrations of all bone turnover markers in the osteoporotic women. No association was observed in men
Kalimeri et al.[35]	93 healthy Chinese-Singaporean postmenopausal women aged between 55 and 70 years old	Fasting plasma insulin, glucose, folate, and vitamin B_{12}/area BMD (aBMD) and volumetric BMD (vBMD)	Folate concentrations were significantly higher among the normal BMD group compared to the osteoporosis group ($p = 0.04$). The aBMD and vBMD were positively associated with folate concentrations, whereas composite strength indices were positively associated with vitamin B_{12} concentrations ($p < 0.05$)
Liu et al.[36]	3529 members of 2 cohorts (ages 35–90 years; mean, 51 years)	Plasma vitamin B_6, B_{12}, folate and methylmalonic acid (MMA), a biomarker for vitamin B_{12}/ vBMD by DXA and QCT	There was an association between rs2274976 and vitamin B_{12} and rs34671784 and MMA $< 210\,nmol\,L^{-1}$ and lumbar spine BMD. An association was also found between rs6586281 and vitamin $B_{12} \geq 258\,pmol\,L^{-1}$ and femoral neck BMD
Saiedullah et al.[37]	77 postmenopausal women (age > 45 years)	Serum vitamin B_{12}, BMD and T-scores	The log of vitamin B_{12} was positively associated with BMD (0.119 [$p = 0.018$], 0.085 [$p = 0.140$], 0.011 [$p = 0.012$]) and T-score (1.028 [$p = 0.022$], 0.698 [$p = 0.064$], 0.940 [$p = 0.015$]) at lumbar spine, right and left femoral neck. As can be noted, the right femoral neck is not significant
Studies using blood samples and dietary intakes			
Clarke et al.[38]	110 treated celiac disease patients; mean age men 53.0 (12.3) and women 52.0 (12.7)	Dietary B vitamin intakes and Plasma vitamin B_2, B_6, B_{12} and homocysteine, and	Serum vitamin B_{12} (but no other B vitamin biomarker) was a significant determinant of BMD at the femoral neck ($\beta = 0.416$,

TABLE 1 (Continued)

Reference	Sample size and subjects	Exposures and outcomes	Main findings
		serum 25-hydroxyvitamin D and BMD	$p = 0.011$) and total hip ($\beta = 0.327$, $p = 0.049$) in men only
Studies using dietary intakes			
Abrahamsen et al.[39]	1700 Danish postmenopausal women	Dietary intake of vitamin B_2, B_6, folate, and B_{12}/BMD; fracture risk	Vitamin B_2 intake was significantly positively correlated with femoral neck BMD (*TT* genotype women) ($p < 0.05$). MTHFR genotype was associated with femoral neck and lumbar spine BMD in the lowest quartile of vitamin B_2 intake and similar threshold were observed for folate, vitamin B_6 and B_{12}
Ilesanmi-Oyelere et al[40]	101 New Zealand postmenopausal women aged between 54 and 81 years	Dietary vitamin B_2 and B_3/BMD	Positive association was found between intake of vitamin B_2 and spine BMD ($r = 0.232$, $p = 0.020$) as well as B_3 and lumbar spine ($r = 0.256$, $p < 0.01$), femoral neck ($r = 0.305$, $p < 0.01$), hip ($r = 0.257$, $p < 0.01$) and whole-body BMD ($r = 0.299$, $p < 0.01$)

Abbreviations: BAP, bone alkaline phosphatase; BMC, bone mineral content; BMD, bone mineral density; BTM, bone turnover markers; CI, confidence interval; CTx, C-terminal telopeptide; DXA, dual-energy X-ray absorptiometry; HCY, homocysteine; MMA, methylmalonic acid; MTHFR, methylenetetrahydrofolate reductase; OC, osteocalcin; OR, odds ratio; QCT, quantitative computed tomography; RBC, red blood cell; TRAP, tartrate-resistant acid phosphatase; uNTX, urinary N-telopeptide.

FOLATE

A clinical trial reported by Herrmann et al.[56] showed that a combination of vitamin B_6, B_{12} and folate (vitamin B_9) supplementation increased lumbar spine BMD, reduced HCY and decreased OC and P1NP only in hyperhomocysteinaemic patients. This may be as a result of the apparent effect and role of homocysteine on bone density and quality. Removal of tHcy from the circulation can either be by remethylation, which is catalysed by MTHFR, or by transulfuration, catalysed by β-cystathionine synthase, which requires vitamin B_6 and both enzymes are regulated by *S*-adenosyl methionine and could result in the elevation of homocysteine if impaired because of their dependency on each other.[48]

Some years later, another randomised clinical trial led by Herrmann et al.[59] also reported a combination of vitamin D, folate, vitamin B_{12}, B_6 and calcium carbonate increased 25(OH)D and lowered parathormone, bone alkaline phosphatase (BAP), OC and TRAP. Furthermore, the nurses' health study, however, reported that a high intake of vitamin B_6 (≥35 mg day^{-1}) was associated with increased risk of hip fracture in postmenopausal women.[53] Similar observation of a high dose of vitamin B_6 being somewhat associated with risk of hip fracture was also reported in a clinical trial by Garcia Lopez et al.[64] However, no association was found on the effect of B vitamins (vitamin B_{12} and folate) in reducing fracture risk or bone metabolism rates measured using bone biomarkers (CTX and P1NP) in an ancillary study of the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS).[63] However, a significant interaction was found between vitamin B_6 treatment and fracture risk.

Observational study findings and reports on the effect of folate on BMD and risk of fractures have been inconsistent. Some epidemiological studies have reported a significant association between increased folate intake and/or level and increase in BMD/BTM[21,23,26,28,31,35,39,47,50] or reduced fracture risk.[44,45,54] Meanwhile, others have reported no associations.[25,29,30,55] More studies are required to evaluate the effect of folate on bone parameters especially conducted at different stages of the life span.

COBALAMIN

Vitamin B_{12} and bone health have been well researched in various community settings and ethnic groups, either singly or with other B vitamins. In this review, 17 cross-sectional studies reported on association of vitamin B_{12} and bone mass.[21–23,25–33,35–39] Of these, eight studies found a significant association between vitamin B_{12} and BMD.[22,25,27,35–39] There were 12 reporting longitudinal studies for vitamin B_{12} and bone parameters,[41–50,52,53] with three of these studies reporting a relationship

TABLE 2 Longitudinal studies on the association between B vitamins and bone health determinants and fracture risks

Reference	Sample size and subjects	Exposures and outcomes	Main findings
Studies using blood (serum or plasma) samples			
Stone et al.[41]	83 White American women aged ≥ 65 years/3.5 and 5.9 years follow-up	Serum vitamin B_{12}/hip and calcaneal BMD measures; BTM (BAP and osteocalcin)	Women with serum vitamin B_{12} concentrations ≤ 280 pg mL^{-1} experienced more hip bone loss than those with B_{12} > 280 pg mL^{-1}. No relationship was found between vitamin B_{12} and BTM or calcaneal BMD.
Dhonukshe-Rutten et al.[42]	615 men and 652 women with a mean age of 76 ± 6.6 (SD) years/3 years follow-up	Plasma Hcy, serum vitamin B_{12} and the combined effect/BUA, BTM (OC and DPD/Cr) and fracture risk	Women with vitamin B_{12} concentrations < 200 pM and Hcy concentrations > 15 μM had lower BUA, higher DPD/Cr and higher OC concentrations. With high Hcy and/or low vitamin B_{12} concentrations, the risk of fracture was 3.8 for men and 2.8 for women. Both vitamin B_{12} and Hcy was associated with bone health ($p < 0.05$)
Tucker et al[43]	2576 White American men and women aged 30–87 years/cross-sectional analysis	Plasma vitamin B_{12}/BMD at all sites	Both men and women with vitamin B_{12} concentrations <148 pM had lower than average BMD than those with vitamin B_{12} above this cut-off mark. These were significant for men at the hip and women at the spine ($p < 0.05$)
Ravaglia et al.[44]	702 Italians aged 65–94 years/4 years follow-up	Serum folate, vitamin B_{12} and plasma total Hcy/fracture risks	Hyperhomocysteinaemia (plasma total homocysteine [total Hcy] > 15 μmoL) was 1.58 (95% CI = 0.71–3.53) and low folate concentrations was related to increased risk of fractures. No association for serum vitamin B_{12}
Gjesdal et al.[45]	4766 Norwegian men and women aged 65–67 years/12.6 years follow-up	Plasma total Hcy, folate, and vitamin B_{12} and MTHFR 677 C→T and 1298 C→T polymorphisms/hip fracture	Dose–response analyses showed a positive association between total Hcy and risk of fracture in both sexes and a negative association between folate and risk of fracture in women. Adjusted hazard ratio at 95% confidence interval for fracture in subjects with high (≥15 μM) compared to low concentrations (<9.0 μM) of total Hcy was 2.42 (1.43–4.09) among women and 1.37 (0.63–2.98) among men. No significant association between vitamin B_{12} concentrations of MTHFR genotype and hip fracture risk
McLean et al.[46]	1002 White American men and women with mean aged 75 years/4 years follow-up	Plasma folate, vitamin B_{12}, vitamin B_6 and homocysteine/BMD, fracture risk	An inverse association was observed between vitamin B_6 and bone loss (p for trend 0.01). Vitamin B_6 and B_{12} were inversely related to hip fracture risk even after adjusting for BMD and homocysteine (all p for trend < 0.05)
Cagnacci et al.[47]	161 healthy postmenopausal women mean aged 54 years/5 years follow-up	Serum folate, vitamin B_{12} and homocysteine/BMD	Follow-up assessments at baseline and 5-year follow-up showed a significant relationship between serum folate and annual change of lumbar spine BMD, that is, folate concentrations (the coefficient of regression [CR] = 2.040; 95% CI = 0.483–3.596; $p = 0.011$) and the initial BMD values (CR = −0.060; 95% CI = −0.117 to −0.003; $p = 0.040$). No significant relation between the change of vertebral BMD and homocysteine or vitamin B_{12} was found

TABLE 2 (Continued)

Reference	Sample size and subjects	Exposures and outcomes	Main findings
Studies using dietary intakes			
Macdonald et al.[48]	1241 Scottish women aged 45–54 years/6.6 years follow-up	Dietary intake of vitamin B_2, B_6, folate and B_{12}/BMD, BMD change; fPYD/Cr and fDPD/Cr (nmol/mmol) and serum P1NP	Intake of vitamin B_2 was significantly positively associated with MTHFR *TT* genotype, and BMD ($p = 0.01$ for baseline FN BMD, $p = 0.02$ for follow-up FN BMD). No association was observed between MTHFR (*CC* or *CT*) genotype or other B vitamins and BMD
Yazdanpanah et al.[49]	5304 Dutch men and women aged ≥ 55 years/ ≥ 6–7 years follow-up	Dietary intake of vitamin B_2, B_6, folate and B_{12}/BMD and fracture risks	A positive relationship was observed between vitamin B_2, B_6 and femoral neck BMD and an inverse relationship between B-6 and fracture risks ($p < 0.05$). However, no association was found between folate, B_{12} and bone
Rejnmark et al.[50]	1869 Danish perimenopausal women aged 43–58 years/ 10 years follow-up	Dietary and supplemented intake of vitamin B_2, B_{12}, and folate/BMD, fracture risk	Diet and supplement intake of folate was positively correlated with femoral neck BMD at year 5 ($p < 0.05$). No associations were found between intake of vitamin B_2 or B_{12} and BMD or fracture risk
Yazdanpanah et al.[51]	5035 Dutch men and women aged ≥ 55 years/ ≥ 6–7 years follow-up	Dietary intake of vitamin B_2 and folate/BMD, fracture risk	A small significant positive association was found between dietary pyridoxine ($\beta = 0.09$, $p = 1 \times 10^{-8}$) and riboflavin intake ($\beta = 0.06$, $p = 0.002$) with baseline femoral neck BMD. Lowest quartile of vitamin B_2 intake in female 677-T homozygotes had 1.8 times higher risk for incident osteoporotic fractures and 2.6 times higher risk for fragility fractures compared to the 677-CC genotype. In the lowest quartile of B_2 intake, T-homozygous individuals (men and women combined) had higher Hcy concentrations compared to C-homozygotes. No association was found for dietary folate
Dai et al.[52]	63,154 Singaporean Chinese men and women aged 45–74 years/5 years follow-up	Dietary intake of vitamin B_1, B_2, B_3, B_6, B_{12} and folate/ hip fracture risk	A significant inverse relationship between dietary B_6 intake and hip fracture risk was observed among women (p for trend = 0.002) but not among men. 22% reduction in hip fracture risk was observed with the highest quartile intake of B_6. No association was observed with the other B vitamins
Meyer et al.[53]	75,864 postmenopausal women	Dietary and plasma vitamin B_6 and B_{12}, hip fracture	High intake of both vitamin B_6 (≥35 mg day^{-1}), ($p = 0.06$ for linear trend) and B_{12} (≥30 μg day^{-1}), ($p = 0.02$ for linear trend) were associated with increased fracture risk

Abbreviations: BAP, bone alkaline phosphatase; BMD, bone mineral density; BTM, bone turnover marker; BUA, broadband ultrasound attenuation; Cr, creatinine; DPD, deoxypyridinoline; HCY, homocysteine; MTHFR, methylenetetrahydrofolate reductase; OC, osteocalcin; PYD, pyridinoline; P1NP, procollagen-1 N-terminal peptide.

between vitamin B_{12} and BMD,[41,43,48] one study on bone turnover markers[42] and another one on hip fracture.[46] In total, nine intervention studies were reviewed for vitamin B_{12} and bone,[56–64] with three of these studies reporting a significant effect of vitamin B_{12} on bone with respect to supporting the protective role of vitamin B_{12}; one finding was noted in hyperhomocysteinaemic patients,[56] another study reported an effect on bone turnover markers[59] and another study reported an effect on fracture risk in persons aged ≥80 years.[62] Even though not many intervention study reports showed a significant effect, supplementation with B vitamins reduced tHCY

TABLE 3 Randomised clinical trials on B vitamins and bone health outcomes

Reference	Sample size and subjects	Treatment (T) and control (C)	Outcomes	Main findings
Sato et al.[54]	628 aged ≥ 65 years stroke patients with residual hemiplegia; follow-up for 1 year + /2 years	T: Daily oral treatment with 5 mg of folate and 1500 μg of mecobalamin for 2 years. C: double placebo	Plasma homocysteine and incidence of hip fracture	Treatment group had decreased plasma homocysteine concentrations and placebo group had higher homocysteine after 2 years ($p < 0.001$). Treatment group also had significantly reduced incidence of fracture than placebo group ($p < 0.001$). No difference was observed in BMD
Herrmann et al.[55]	61 healthy individuals (mean age: 58+/−8 years); 8 weeks follow-up	T: 0.4, 1 or 5 mg of folate daily C: Placebo	Fasting serum HCY, folate, vitamin B_{12} and BTM-osteocalcin (OC), procollagen type I N-terminal propeptide (PINP) and C-terminal telopeptides of human collagen type I (CTx-I)	No effect was found for folate supplementation on bone turnover markers
Herrmann et al.[56]	47 osteoporotic subjects (age 55–82 years); 4, 8 and 12 months follow-up	T: 2.5 mg folate, 0.5 mg vitamin B_{12} and 25 mg vitamin B_6 C: Placebo	BMD, urinary DPD and plasma TRAP, CTx, OC and PINP	B vitamin supplementation had no effect on BMD, TRAP, CTx, OC and P1NP. However, B vitamin supplementation significantly reduced HCY, it also increased lumbar spine BMD and decreased OC and P1NP in hyperhomocysteinaemic subjects
Green et al.[57]	276 Healthy older persons aged ≥ 65 years; follow-up for 2 years	T: Daily supplement of folate (1 mg), vitamin B_{12} (500 μg), and vitamin B_6 (10 mg) C: Placebo	Plasma homocysteine, serum bone-specific alkaline phosphatase, bone-derived collagen fragments (β-CTX)	Folate, vitamin B_6 and B_{12} supplementation lowered plasma homocysteine (95% CI: 3.9, 6.6 μmol L^{-1}; $p < 0.001$) but had no effect on bone turnover markers
Shahab-Ferdows et al.[58]	132 non-pregnant and non-lactating women aged 20–59 years; 3 months follow-up	T: 1 mg of vitamin B_{12} i.m. followed by 500 μg/day oral vitamin B_{12} supplements C: Placebo	Serum B_{12}, folate, holotranscobalamin (holoTC), total homocysteine, MMA; BTM: BAP	Vitamin B_{12} supplementation increased holoTC ($r = 0.7$; $p < 0.001$), serum vitamin B_{12} and lowered MMA ($r = -0.28$, $p < 0.0007$) and total Hcy concentrations ($r = -0.20$, $p < 0.01$). No effect on BAP was found
Herrmann et al.[59]	93 healthy subjects; age > 54 years; 6 and 12 months follow-up	T: Daily vitamin D_3 (1200 IU), folic acid (0.5 mg), vitamin B_{12} (0.5 mg), vitamin B_6 (50 mg), and calcium carbonate (456 mg) (group A) or only vitamin D_3 plus calcium carbonate (group B)	Parathormone, plasma 25-hydroxy vitamin D, bone alkaline phosphatase, sclerostin, TRAP, OC	One year supplementation of vitamin D_3 or D_3 and B increased plasma 25(OH)D, lowered parathormone and decreased BAP, OC and TRAP. Low tHCY had no additional effect on bone turnover
Keser et al.[60]	31 women aged 65–93 years with homocysteine concentrations >10 μmol L^{-1}; 4 months follow-up	T: Daily folic acid (800 μg) and vitamin B_{12} (1000 μg) C: Matching placebo	Serum homocysteine, alkaline phosphatase, and CTX-I	Homocysteine concentrations was lower in the treatment group compared to the placebo (10.6 vs 18.5 μmol L^{-1}, $p = 0.007$) but there was no difference in the alkaline phosphatase or CTX-I

TABLE 3 (Continued)

Reference	Sample size and subjects	Treatment (T) and control (C)	Outcomes	Main findings
Gommans et al.[61]	8164 Caucasian with recent stroke or transient ischaemic attack; median duration of 2.8 years therapy and 3.4 years follow-up	T: One tablet of folic acid 2 mg, vitamin B_6 25 mg, vitamin B_{12} 500 μg daily C: One tablet of placebo	Serum homocysteine, osteoporotic or osteoporotic hip fracture risks	There was no effect with daily treatment with B vitamins on osteoporotic fractures. Homocysteine concentrations was lower in the treatment group but did not predict fracture risks
van Wijngaarden et al.[62]	2919 individuals aged ≥ 65 years with elevated homocysteine concentrations (12–50 μmol L^{-1}); 2 years follow-up	T: Daily 500 μg vitamin B_{12} plus 400 μg folic acid plus 600 IU vitamin D_3 supplementation C: Placebo plus 600 IU vitamin D_3	Serum homocysteine, First time osteoporotic fracture	Homocysteine concentrations was lower in the treatment group, but fracture risk did not differ between groups. In persons aged ≥ 80 years, fracture risk was lower in the treatment group. However, incidence of cancer was higher in the treatment group than the placebo
Stone et al.[63]	8171 participants aged ≥ 40 years; 7.3 years treatment and follow-up	T: folic acid (2.5 mg day^{-1}), vitamin B_6 (50 mg day^{-1}), and vitamin B_{12} (1 mg day^{-1}) C: Placebo	Plasma concentrations of homocysteine and B vitamins, BTM-CTX-I and P1NP and fracture risks (wrist, hip and non-spine fractures)	No significant difference was found for any effect of supplementation with B vitamins in reducing fracture risks or bone metabolism rates
Garcia Lopez et al.[64]	6837 participants from 2 RCTs (mean age was 62.3 ± 11.0 years); 3.4 years follow-up for Norwegian Vitamin Trial (NORVIT) and 3.2 years for Western Norway B Vitamin Intervention Trial (WENBIT)	T[1]: folic acid (0.8 mg) plus vitamin B_{12} (0.4 mg) and vitamin B_6 (40 mg)[2]; folic acid (0.8 mg) plus vitamin B_{12} (0.4 mg)[3]; vitamin B_6 alone (40 mg) C: Placebo	Plasma tHCY and vitamin B_6, Serum folate and vitamin B_{12}. Hip fracture risks	Treatment with folate plus vitamin B_{12} was not associated with hip fracture risk however, treatment with high dose of vitamin B_6 was slightly associated with risk of hip fracture (HR = 1.42; 95% CI = 1.09–1.83).

Abbreviations: BAP, bone alkaline phosphatase; BMD, bone mineral density; BTM, bone turnover marker; CI, confidence interval; CTX-1, type I collagen cross-linked C-telopeptide; DPD, deoxypyridinoline; HCY, homocysteine; holoTC, holotranscobalamin; HR, hazard ratio; MMA, methylmalonic acid; OC, osteocalcin; P1NP, procollagen-1 N-terminal peptide; TRAP, tartrate-resistant acid phosphatase.

TABLE 4 Meta-analyses on B vitamins and bone health outcomes

Reference	Sample size and subjects	Treatment (T) and control (C)	Outcomes	Main findings
Van Wijngaarden et al.[65]	14 cross sectional studies, 13 prospective observational studies and 1 RCT	Folate, vitamin B_{12} and homocysteine	BMD and fracture risk	There was a 4% decrease in fracture risk per 50 pmol L^{-1} increase in vitamin B_{12} concentrations, which was borderline significant. There was also a 4% increase in fracture risk per μmol L^{-1} increase in homocysteine concentration. No conclusion for folate as a result of too few studies
Ruan et al.[66]	8 RCTs	B vitamins and homocysteine	BTM and fracture risk	No risk-reducing effect of daily supplementation with B vitamins on bone turnover markers and osteoporotic fracture

Abbreviations: BMD, bone mineral density; BTM, bone turnover marker; RCT, randomised controlled trial.

concentrations in the subjects. This was evident in eight of the studies[54,56–62] showing high dependency of the metabolism of homocysteine on vitamin B_{12}, folic acid and vitamin B_6. Included among the factors that raise concentrations of homocysteine are a poor diet and lifestyle (high consumption of coffee, alcohol, and smoking), prescription medications (such asPPIs), poor thyroid function, diabetes, and rheumatoid arthritis.

Two systematic meta-analyses have been conducted on B vitamins and its effect on BMD, BTM and fracture risks. One of the meta-analyses reviewed 14 cross-sectional and 13 longitudinal studies and found a 4% decrease in fracture risk per 50 pmol L^{-1} increase in vitamin B_{12} concentrations, which was borderline significant; no significant effect was found on the relationship between vitamin B_{12} and BMD. The other study found no risk reducing effect of daily supplementation of B vitamins on BTM and fracture risks. However, taken together, these results show a possible modest effect of B vitamins on bone quality, although more clinical studies are required to validate this effect.

CONCLUSIONS

Based on the current available data, there are effects of vitamin B_6, folate and vitamin B_{12} on bone metabolism and bone physiology. However, more longitudinal studies and clinical intervention studies are required for both the dietary effects and supplementation effects of B vitamins on bone density and turnover. This is particularly important for the B vitamins that are less studied.

AUTHOR CONTRIBUTIONS

Bolaji L. Ilesanmi-Oyelere conducted the search and wrote the first draft. Marlena C. Kruger reviewed the manuscript. Both authors read and approved the final version of the manuscript submitted for publication.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no datasets were generated or analysed during the present study.

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