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META-ANALYSIS

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Effect of B Vitamin (Folate, B6, and B12) Supplementation on Osteoporotic Fracture and Bone Turnover Markers: A Meta-Analysis

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Background: B vitamins (including folate, B6, and B12) supplementation can effectively and easily modify high plasma homocysteine (Hcy). However, the role of Hcy in the pathogenesis of osteoporotic fracture and bone turnover is still controversial. This meta-analysis aimed to assess the impact of B vitamin supplementation on occurrence of any osteoporotic fracture and bone turnover by pooling the results of previous studies.

Material/Methods: Relevant randomized controlled trials (RCTs) were searched in databases. Data integration and analysis were done by using Review Manager 5.3 (the Cochrane Collaboration). The risk ratio (RR) and corresponding 95% confidence intervals (CI) of fracture (intervention *vs.* control) were estimated. Changes in bone turnover indicators (continuous data), weighted mean difference (WMD), and corresponding 95% (CI) were pooled for estimation.

Results: Based on the results of 4 RCTs, this meta-analysis failed to identify a risk-reducing effect of daily supplementation of B vitamins on osteoporotic fracture in patients with vascular disease and with relatively normal plasma Hcy. In addition, we also did not find any positive effects of B vitamin supplementation on bone turnover.

Conclusions: B vitamin supplementation might not be effective in preventing fracture and improving bone turnover. However, the possible benefits in selective populations, such as populations with very high plasma Hcy and from regions without B vitamin fortification should be explored in the future.

MeSH Keywords: **Fractures, Bone • Homocysteine • Meta-Analysis as Topic • Vitamin B Complex**

Abbreviations: **Hcy** – homocysteine; **WMD** – weighted mean difference; **BMD** – bone mineral density; **ALP** – alkaline phosphatase; **CTX** – cross-linked C-telopeptide

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Background

Osteoporosis is a metabolic skeletal disorder characterized as decreased bone strength and significantly increased risk of fracture [1]. The most common osteoporotic fracture sites include hip, spine, and wrist. Particularly, spine and hip fractures are associated with poor outcomes, which usually require hospitalization and surgery [2,3]. In addition, these fractures also significantly increase the risk of disability, morbidity, and mortality [4]. Therefore, simple interventions that can delay the onset of osteoporosis or lower the risk of osteoporotic fracture are needed.

Plasma homocysteine (Hcy), which is formed by the demethylation of dietary methionine, has been postulated as a novel and potential risk factor of osteoporotic fractures [5]. High plasma total homocysteine levels are associated with accelerated bone loss in men and premenopausal women [6]. A large prospective study found that the population group with the highest quartile of tHcy had 2 times higher risk of fracture [7]. A recent meta-analysis based on 14 863 patients also confirmed that all fracture risk of the highest Hcy quartile group compared with the lowest quartile group was 1.59 (95% CI 1.30–1.96) [8]. Although several studies have been performed to explore the relationship between Hcy and osteoporosis, it is still not clear whether the association is causal, confounded, or biased due to reverse causality [9,10].

B vitamin (including folate, B6, and B12) supplementation can effectively and easily modify high plasma Hcy [11,12]. Therefore, it is possible to determine whether tHcy is a causal risk factor of bone fracture and how it affect bone metabolism in terms of bone turnover markers through comparing B-vitamins *vs.* placebo in randomized controlled studies (RCTs). In fact, several relevant RCTs were performed, but the results are conflicting. Due to uncertainties about the role of Hcy in pathogenesis of osteoporotic fracture and bone turnover, this meta-analysis aimed to assess the effect of B vitamin supplementation (folate, B6, and B12) on occurrence of any osteoporotic fractures and bone turnover by pooling results of previous studies.

Material and Methods

Searching and screening of studies

Studies were searched in Embase, PubMed, and ClinicalTrial.gov databases. To search for qualified studies, the following searching and screening criteria was used: ("homocysteine") AND ("B vitamin" OR "folate" OR "B12" OR "B6") AND ("osteoporosis" OR "osteoporotic" OR "fracture" OR "bone turnover") AND ("randomized controlled trial" OR "RCT" OR "controlled trials"). To avoid missing any qualified studies, we performed a manual search of reference lists of included trials and relevant reviews. Trials were included regardless of publication status and language.

Inclusion and exclusion criteria

The trials included in this meta-analysis had to qualify simultaneously for the following criteria: (1) randomized controlled trials; and (2) studies comparing effect of B vitamin supplementation *vs.* placebo on fracture risk or bone turnover indicators. Studies meeting any the following criteria were excluded: (1) case report, animal study, or review; (2) studies with detailed outcome data (RR of fracture or changes of bone turnover) not extractable.

Data extraction

Two authors independently performed data extraction and data analysis. A third author was responsible for cross-checking the data. Disagreements were solved by discussion and consensus. Generally, the following information and data were extracted from the included trials: the family name of the first author, year of publication, features of patients included, number of participants, average age, sex, total plasma Hcy concentration at baseline, treatment (B vitamins used for supplementation and control), the period of intervention, outcome indicators measured, and whether there was significant Hcy reduction caused by the intervention. If the outcomes were reported with different units, unit conversion was performed before pooling the data.

Qualities assessment of trials included

Quality assessment of the trials was performed according to the recommendation of the Cochrane Handbook for Systematic Reviews of Interventions. Generally, 6 items were used to assess the bias of the RCTs: adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, free of selective reporting, and free of other bias. The bias risk was reported as low risk of bias or high risk of bias.

Statistical analysis

Data integration and analysis were performed using Review Manager 5.3 (the Cochrane Collaboration). The risk ratio (RR) and corresponding 95% confidence intervals (CI) of fracture (intervention *vs.* control) were pooled for overall estimation. As to the changes of bone turnover indicators (continuous data), weighted mean difference (WMD) and corresponding 95% (CI) were pooled for overall estimation. Chi-square based Q test and I^2 value were used to assess between study heterogeneity, which were also used to determine the methods used for making estimation. A random effect model (DerSimonian

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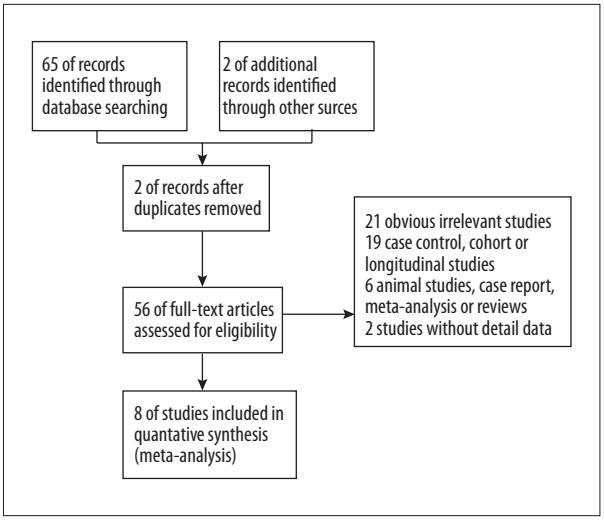

Figure 1. The searching and screening process.

and Laird method) was used when p <0.1 in Q test or I^2 >50%, which indicate significant heterogeneity. Otherwise, the fixed effect model based on Mantel-Haenszel method was applied. If unacceptable high heterogeneity was observed, the sources of heterogeneity were further explored. If significant clinical heterogeneity, subgroup analysis will be performed. p<0.5 in Z test is considered as statistically significant.

Results

Studies included in this meta-analysis

Based on searching in the database by using the preset selection criteria, eight RCTs involving 26,707 participants were finally included in this meta-analysis. The overall searching and screening process is described in Figure 1. Quality assessment of the studies is summarized in Figure 2. Generally, the quality of the 8 RCTs was high. Only 2 studies did not have blind design [13,14]. The key characteristics of the trials were summarized in Table 1. Four RCTs assessed the effect of B vitamin supplementation on fracture risk [15–18] and 4 RCTs assessed the change of bone formation markers after B vitamin supplementation [13,14,19,20]. All of the studies reported significantly lowered plasma Hcy in the intervention group than in the control group.

B vitamin supplementation had no effect on fracture risk

Four studies [15–18] involving 26 378 participants assessed B vitamin supplementation on fracture risk. Among them, 2 studies [16,18] gave patients a combination of folate, B6, and B12 and 2 studies [15,17] used a combination of folate and B6. Significant heterogeneity was observed when directly pooling the results of the 4 studies (I^2=78%) (Figure 3). Excluding Sato et al. study significantly reduced the heterogeneity. In fact, compared with the remaining 3 studies, Sato et al. study population was highly selected and characterized as severe disability, unusually high fracture rate in controls (10 times higher than the national average of Japan), and very high Hcy concentrations (mean 19.9 μmol/L) [21]. Therefore, subgroup analysis was performed by stratifying plasma Hcy. Plasma Hcy>15μmol/L is usually considered as the boundary of high plasma Hcy [22]. Thus, stratification is based on this standard. Only Sato et al. reported significantly reduced fracture risk (RR: 0.25, 95%CI 0.12–0.53, p=0.0003) (Figure 3). The remaining 3 studies with 25 750 participants found no significant association between B vitamin supplementation and fracture risk (RR: 1.00, 95%CI 0.89–1.13, p=1.00) (Figure 3).

B vitamin supplementation had no effect on bone turnover markers

Four RCTs with 329 participants assessed the change of bone formation markers after B vitamin supplementation [13,14,19,20]. One study [13] gave patients folate, B6, and B12 simultaneously, 1 study [19] used both folate and VB12, 1 study [14] provided VB6 and VB12, and 1 study [20] only provided folate. Although the combination of B vitamins varied in different studies, all of them reported that the intervention significantly reduced plasma Hcy. Bone formation marker (ALP) and resorption markers (CTX) were used to assess the effect of B vitamin supplementation on bone turnover. Generally, compared with placebo, supplementation of B vitamins had no significant effect on ALP (WMD: –0.96, 95%CI: –4.10 to 2.18, p=0.55, I^2=0%) (Figure 4A) and CTX (WMD: –0.01, 95%CI: –0.06 to 0.07, p=0.87, I^2=0%) (Figure 4B). Salari et al. [20] study measured urine CTX instead of serum CTX and their results also showed that folate supplementation could not change urine CTX (supplementation *vs.* placebo, p=0.285).

Discussion

Homocystinuria, a disease characterized as high plasma homocysteine, usually contributes to distributed bone collagen profiles due to attachment of Hcy [23], leading to altered bone collagen fibers and fragile bones. Several epidemiological studies observed that increased plasma homocysteine concentration was associated with a higher incidence of osteoporotic fractures [6,24]. Several observational studies found that high plasma total Hcy level is a potential risk factor of osteoporotic fractures. The underlying mechanisms between plasma Hcy levels and fractures are uncertain. The potential mechanisms include the regulative role of Hcy on bone tissue quality through altering the properties of collagen crosslink [25], affecting bone resorption by stimulating osteoclast formation and activity [26], and inducing mitochondrial dysfunction [27].

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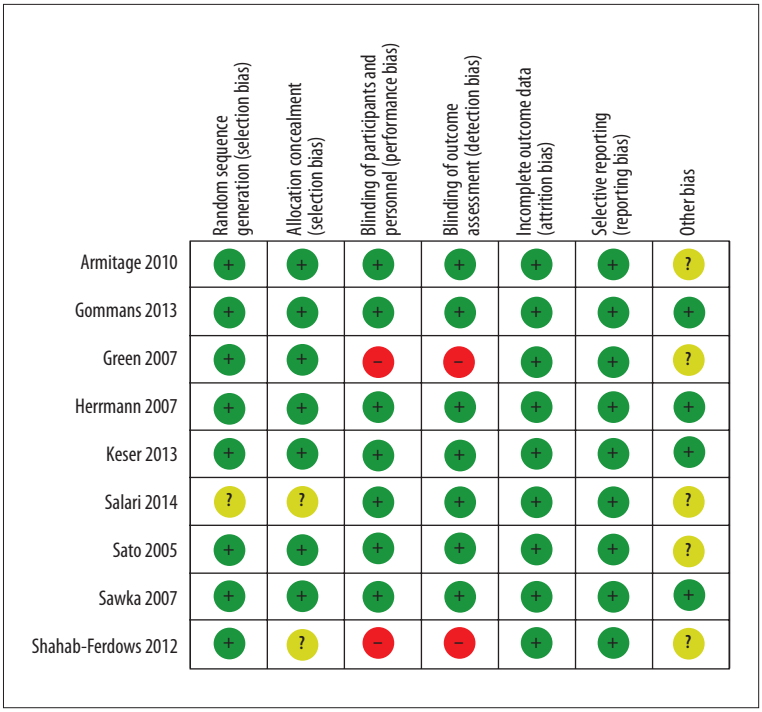

Figure 2. Quality assessment of RCTs included.

Table 1. Key characteristics of the RCTs included.

Study	Participants	No. participants	Age (mean)	Women (%)	Treatment		Baseline Hcy (μmol) (I/C)	Intervention period	Outcome measured	Significant Hcy reduction by intervention?
		I/C	I/C	I/C	I	C				
Green 2007	Age ≥65 y	68/67	74.1/74.6	60%/43%	1 mg folate + 10 mg VB6 + 0.5 mg VB12 daily	Placebo	19.7/19.3	24 months	Plasma Hcy; Serum ALP; Serum-CTX	Yes
Keser 2013	Women, age ≥65 y	17/14	75.4/75.1	100%/100%	0.8 mg folate + 1 mg VB12 daily	Placebo	13.7/16.0	4 months	Plasma Hcy; Serum ALP; Serum-CTX	Yes
Salari 2014	Postmenopausal osteoporotic women	17/14	63.8/64.2	100%/100%	1 mg folate daily	Placebo	11.7/14.1	6 months	Plasma Hcy; osteocalcin; Serum ALP; urine-CTX	Yes
Shahab-Ferdows 2012	Nonpregnant and nonlactating women	70/62	39.3/35.5	N.A.	1 mg VB6 + 0.5 mg VB12 daily	Placebo	11.3/10.4	3 month	Plasma Hcy; Serum ALP	Yes
Sato 2005	Ischemic stroke	314/314	71.6/71.2	54%/54%	5 mg folate + 1.5 mg VB12 daily	Placebo	19.9/19.9	24 months	Plasma Hcy; RR of fracture	Yes
Sawka 2007	Vascular disease or diabetes	2758/2764	68.8/68.9	29%/28%	2.5 mg folate + 50 mg VB6 + 1 mg VB12 daily	Placebo	12.2/12.2	60 months	Plasma Hcy; RR of fracture	Yes
Armitage 2010	Myocardial infarction	6033/6031	64/64	17%/17%	2 mg folate + 1 mg VB12 daily	Placebo	13.5/13.5	60 months	Plasma Hcy; RR of fracture	Yes
Gommans 2013	Stroke or TIA	4089/4075	62.5/62.6	36%/36%	2 mg folate + 25 mg VB6 + 0.5 mg VB12 daily	Placebo	14.4/14.2	3.4 years	Plasma Hcy; RR of fracture	Yes

Hcy – homocysteine; TIA – transient ischemic attack; ALP – alkaline phosphatase; CTX – β cross laps; VB6 – vitamin B6; VB12 – vitamin B12; I – intervention; C – control; RR – risk ratio; N.A. – not available.

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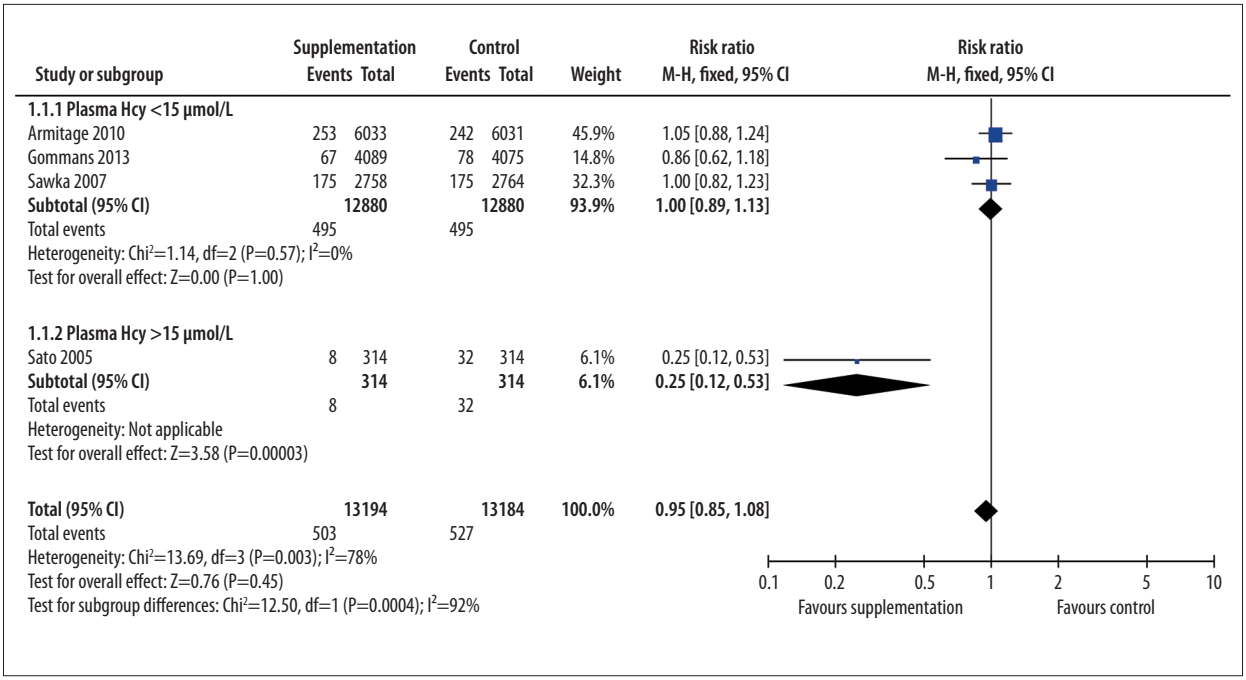

Figure 3. Meta-analysis of the effect of B vitamin supplementation on fracture risk.

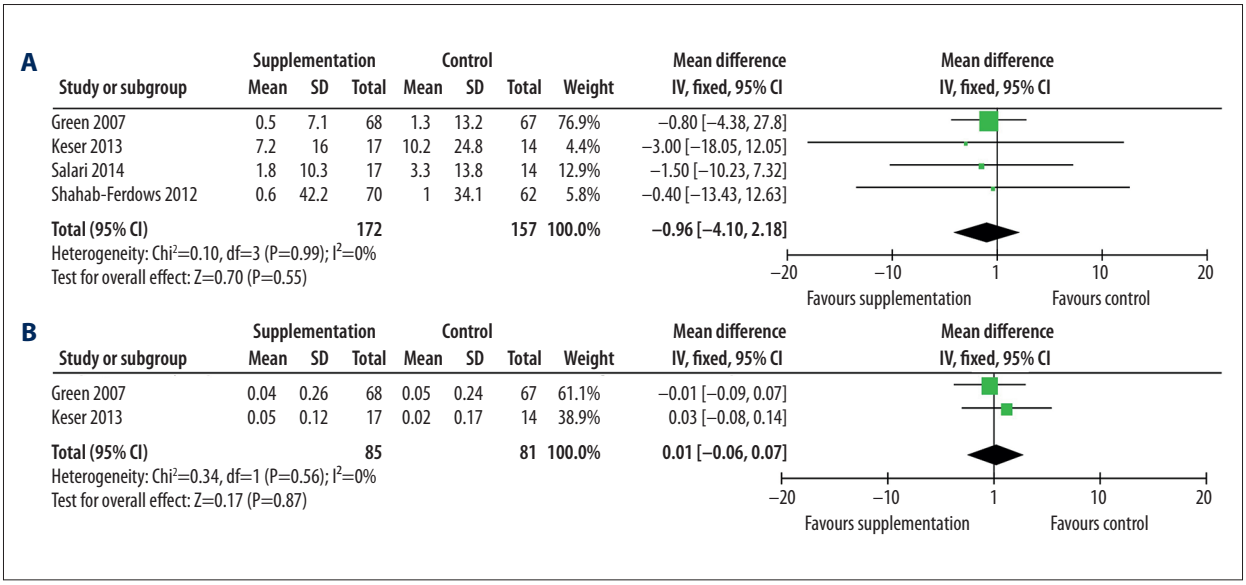

Figure 4. Meta-analysis of the effect of B vitamin supplementation on bone turnover. (**A**) Bone formation marker (ALP). (**B**) Resorption markers (CTX).

B vitamins play quite important roles in Hcy metabolism. The effect of B vitamins supplementation on Hcy lowering has been well recognized. Folic acid supplementation could lower approximately 25% of plasma homocysteine, while vitamins B12 and B6 also have additional homocysteine-lowering effects [28,29]. However, it is not clear if Hcy-lowering therapy by folic acid, vitamins B6, or B12 supplementation is helpful in reducing the risk of fracture. In fact, Hcy is considered as a risk factor of cardiovascular and cerebrovascular risks and several RCTs were performed to assess the effect of lowering Hcy on stroke risk [15–18]. Considering the putative important role of Hcy in osteoporosis, these RCTs also explored the effect of B vitamin supplementation on the risk of fracture. However, due to lower occurrence rate and small number of fracture events, some of the trials were without sufficient statistical power to detect the potential beneficial effect [18]. Therefore, it was necessary to make a meta-analysis by pooling previous studies and to make an integrated estimation.

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Based on results of 4 RCTs, this meta-analysis failed to identify any risk-reducing effect of daily supplementation of B vitamins on osteoporotic fracture in patients with vascular disease and with relatively normal plasma Hcy.

Although previous *in vitro* and *in vivo* studies observed a stimulatory effect of mildly elevated homocysteine on osteoclastic activity and a positive correlation between plasma Hcy and markers of bone resorption [30–32], few studies have examined the association between bone turnover markers and homocysteine-lowering intervention. The individual RCTs lack statistical power due to the small number of participants in experimental and control groups. Based on pooling the results of the 4 RCTs, this meta-analysis did not find any positive effect of B vitamin supplementation on bone turnover.

Although the number of studies included is relatively small, the sample size of the included studies, especially those that assessed B vitamin supplementation on fracture risks, is large. Thus, the statistical power of the findings is strong. However, the present study also has several limitations. Firstly, the baseline of the patients included varied significantly in some studies. For example, the mean baseline folate level of the participants in the HOPE2 study [16] was approximately 5 times higher than the participants in Sato's study in Japan [15]. Therefore, it might be possible that B vitamin supplementation might not generate additional benefits for the patients who already have high serum B vitamin level. Among the 4 RCTs that assessed B vitamin supplementation and fractures, only Sato's study observed a risk-reduction effect. In fact, the study population was highly selected and characterized as very high plasma Hcy level, severe disability, and an unusually (10-fold) high fracture risk rate of the control cases compared to the average Japanese population of the same age [21]. However, a recent meta-analysis observed that fortification with certain B vitamins, such as folate, exert protective effects on Hcy-related cerebrovascular risks and additional supplementation thus had no additive effect [33]. Therefore, we cannot exclude the possibility that B vitamin supplementation might have some protective effects on bone health due to the homocysteine-lowering effects in countries without folate fortification, such as Japan.

Conclusions

This meta-analysis failed to identify any risk-reducing effect of daily supplementation with B vitamins (single or combined use of folate, B6, and B12) on osteoporotic fracture in patients with vascular disease and with relatively normal plasma Hcy. In addition, we also did not observe any positive effects of B vitamin supplementation on bone turnover. However, the possible benefits in certain populations, such as populations with very high plasma Hcy and from regions without B vitamin fortification, should be explored in the future.

Conflict of interest

The authors had no conflict of interest.

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