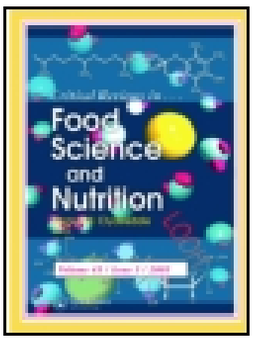

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REVIEW

Efficacy of vitamin D fortified foods on bone mineral density and serum bone biomarkers: A systematic review and meta-analysis of interventional studies

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ABSTRACT

Vitamin D fortified foods (VDFs) were taken into consideration due to the high prevalence of osteoporosis worldwide. However, the efficacy of VDFs on bone health has not been fully examined. The current meta-analysis was conducted in order to summarize the impacts of VDFs on serum 25-hydroxyvitamin D (25(OH)D), bone mineral density (BMD), and bone turnover markers (BTM). A systematic search up to October 2017 was done via PubMed and Scopus search engines. To pool mean differences, random-effects model (the DerSimonian-Laird estimator) was used. Heterogeneity among studies was examined by Cochrane Q test. 20 trials involving 1786 subjects were included in this meta-analysis. Based on random effect model, there were significant effects of VDFs on serum 25(OH)D (MD:16.94 nmol/L 95% CI: 13.38, 20.50; $p < 0.001$, $I^2 = 99.0\%$), BMD (MD: 0.03 gr/cm^2; 95% CI: (0.02, 0.05); $p < 0.001$, $I^2 = 58.8\%$) and paratormone hormone (PTH; MD:−9.22; 95% CI: (−14.97, −3.46); $p = 0.002$, $I^2 = 98.8\%$). VDFs may increase serum 25(OH)D and BMD while decrease serum PTH levels. We did not find any beneficial effect of VDFs on BTM.

KEYWORDS

Vitamin D-fortified food; bone mineral density; bone turnover markers; 25(OH)D

Introduction

Osteoporosis is defined as a chronic progressive skeletal disorder characterized by both loss of bone density and degradation of bone tissue. It leads to bone fragility and increased risk of fracture (Consensus 1993). Nearly half of the elderly over the age of 50 in the United States are at risk of fractures due to osteoporosis (US Department of Health and Human Services 2004). Besides, due to growing the elderly population and the fact that age is a major risk factor for osteoporosis, it is estimated that the economic burden of osteoporosis increases sharply by 2025 (Burge et al. 2007). Bone remodeling is a dynamic process of formation and resorption of bone which is somewhat reflected by bone formation markers like alkaline phosphatase (ALP), osteocalcin (OC), and procollagen type I N-terminal peptide (P1NP) and bone resorption markers including C-terminal telopeptide (CTX) and N-terminal telopeptide of type I collagen.

Bone mass accumulation is influenced by genetics, ethnicity, age and lifestyle factors including exercise, smoking, alcohol and diet (Cooper et al. 2006; Park et al. 2012). Among lifestyle factors, nutrition is responsible for 20–30% of bone mass variation (Nguyen et al. 1998) and the role of protein, calcium, and vitamin D in bone health is dominant (Lowe et al. 2011). Ninety-nine percent of total body calcium is stored in the bone (Barzel and Massey 1998) and 80–90% of bone mineral content are formed of calcium and phosphorous (Boskey 2006). Vitamin D, another important nutrient in bone, has fully been studied in relation to bone metabolism. Vitamin D play a crucial role in the musculoskeletal system and modulating bone turnover and mineralization in bone (Wintermeyer et al. 2016; Lips and van Schoor 2011). Exposure to ultraviolet B waves of sunlight is responsible for about 80–95% of the vitamin D and its circulating metabolite in blood (Adams et al. 1982). The amount of absorbed sunlight rays by the skin varies dependent on environmental and cultural factors (Gartner and Greer 2003). Consequently, regarding to the reduction of vitamin D intake from sunlight and the low levels of vitamin D in food, supplementation and fortification have been considered as possible ways to achieve normal serum levels of vitamin D. Due to coverage of population, cost and compliance, supplementation is not a reliable solution for vitamin D deficiency problem (Neuhouser 2003). Moreover, because of low cost and high efficacy of vitamin D fortified foods (VDFs) in increasing serum 25(OH)D, recently receiving vitamin D from fortified foods has been taken into consideration (Black et al. 2012a). To the best of our knowledge, there is no comprehensive review on the efficacy of VDFs

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on bone biomarkers. Therefore, the present study has been conducted to examine the efficacy of VDFs on bone biomarkers using meta-analysis of interventional studies.

Methods

This systematic review was written and reported based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Moher et al. 2009).

Search strategy

A systematic search via PubMed and Scopus search engines was done up to October 2017. Both Medical Subject Headings (MeSh) and text words were used (Supplemental file 1). Reference lists of articles were reviewed to avoid missing any citations. There was no limitation for time and language of the articles. Literature searches were downloaded into EndNote (version X7, for Windows, Thomson Reuters, Philadelphia, PA, USA) to merge obtained citations from two databases and to facilitate the screening process.

Eligibility criteria and study selection

The first screening of literature was done based on the title and abstract and with consideration of the following inclusion criteria: (i) interventional studies (ii) any VDFs with or without calcium (iii) reporting our desired outcomes including: any fractures, bone mineral density (BMD) of femoral neck or lumbar spine, hormonal markers of serum 25(OH)D and paratormone hormone (PTH), and bone turnover markers (BTM) like OC, ALP, P1NP, and CTX. Literature excluded if they met the following criteria: (i) reviews, cellular and molecular studies, animal studies, crossover studies, and case reports (ii) conference papers, letters, notes, books, and editorials (iii), non-English studies (iv), studies with population that affect the vitamin D metabolisms like pregnant women, hypo-and hyperthyroidism, hypo-and hyperparathyroidism, renal diseases, and cirrhosis. Moreover, studies with irrelevant content and those that are unavailable were all excluded. All of the literatures were checked double times for titles and abstracts by two independent researchers (HT and HE) to ensure no study was missed. Any disagreements between reviewers were discussed and resolved by the third reviewers (SS-b).

Data extraction and synthesis

Extracted information for each study included: study first author, country, year, journal, study population, age, and sex and data related to serum 25(OH) D, PTH, OC, ALP, P1NP, and CTX, type of fortified food, dose and duration of intervention, baseline and final values of outcome for intervention and placebo groups and their standard deviation. For the following studies: Bonjour et al. (2012), Daly et al. (2006), and Kukuljan et al. (2011) studies, the final values were calculated according to the change reported from baselines. In single arm studies by Suzuki et al. (2014), and Bonjour et al. (2009), and two arm studies by Costan, Vulpoi, and Mocanu (2014), and Palacios et al. (Palacios et al. 2005), the baseline values of intervention groups were used as the final values of the control group. Tenta et al. (2011) conducted their 30-month study in two phases with two different doses. These phases were considered as two different studies and final values of first phase were used for the second phase. In another 5-arm study by Neyestani et al. (2014) there were two groups of VDFs in milk or orange juice and both of them included in current meta-analysis as a separate study and were compared with placebo group.

Study quality assessment

To assess the quality of included studies, we used 5-score Jadad scale which includes randomization (2 point), double blinding (2 point), and explanation of cause of withdrawals and dropouts (1point).

Statistical analysis

All statistical analysis was conducted using version 14 STATA software (StataCorp, College Station, Texas, USA). Mean differences (MD) for serum 25(OH)D, BMD, PTH, OC, ALP, CTX, and P1NP were separately calculated in order to determine the overall effect size of included studies. The I^2 statistic and the Cochrane's Q test of heterogeneity was used to evaluate between-study heterogeneity. According to Cochrane criteria, I^2 statistic of 0–40% indicates low heterogeneity and negligible, 30–60% reflects moderate heterogeneity, 50–90% reflects substantial heterogeneity, and 75–100% reflects considerable heterogeneity (Higgins 2011). The fixed-effect model was used when I^2 was below 50% and the random-effects model in the cases of I^2 was above 50% were selected for meta-analysis. Funnel plots asymmetry and Egger's test were used to identify publication bias.

Sub-group analysis

To examine the source of heterogeneity, we did sub-group analysis for sex, age, study population, fortification dose of vitamin D, calcium dose, trial duration, food, measurement site of BMD, and quality of studies. Age was divided into two groups of above and less than 35 years, and sex was categorized into three groups: female, male, and both sexes. The study population was classified into two groups of apparently healthy and patient. Vitamin D and calcium dose of fortification categorized into 4 and 3 category including: $\leq$ 400, 400–1000, 1000–4000, and $>$ 4000 IU/day for vitamin D and $\leq$ 500, 500–1000, and $>$ 1000 mg/d for Ca, respectively. The study period is divided into three categories of $\leq$ 3, 3–6, and $>$ 6. Type of food fortified includes dairy and non-dairy. Also, site of BMD measurement consists of hip and spine. Study quality was categorized into 2 categories of low ($<$ 2) and high ($>$ 3) quality.

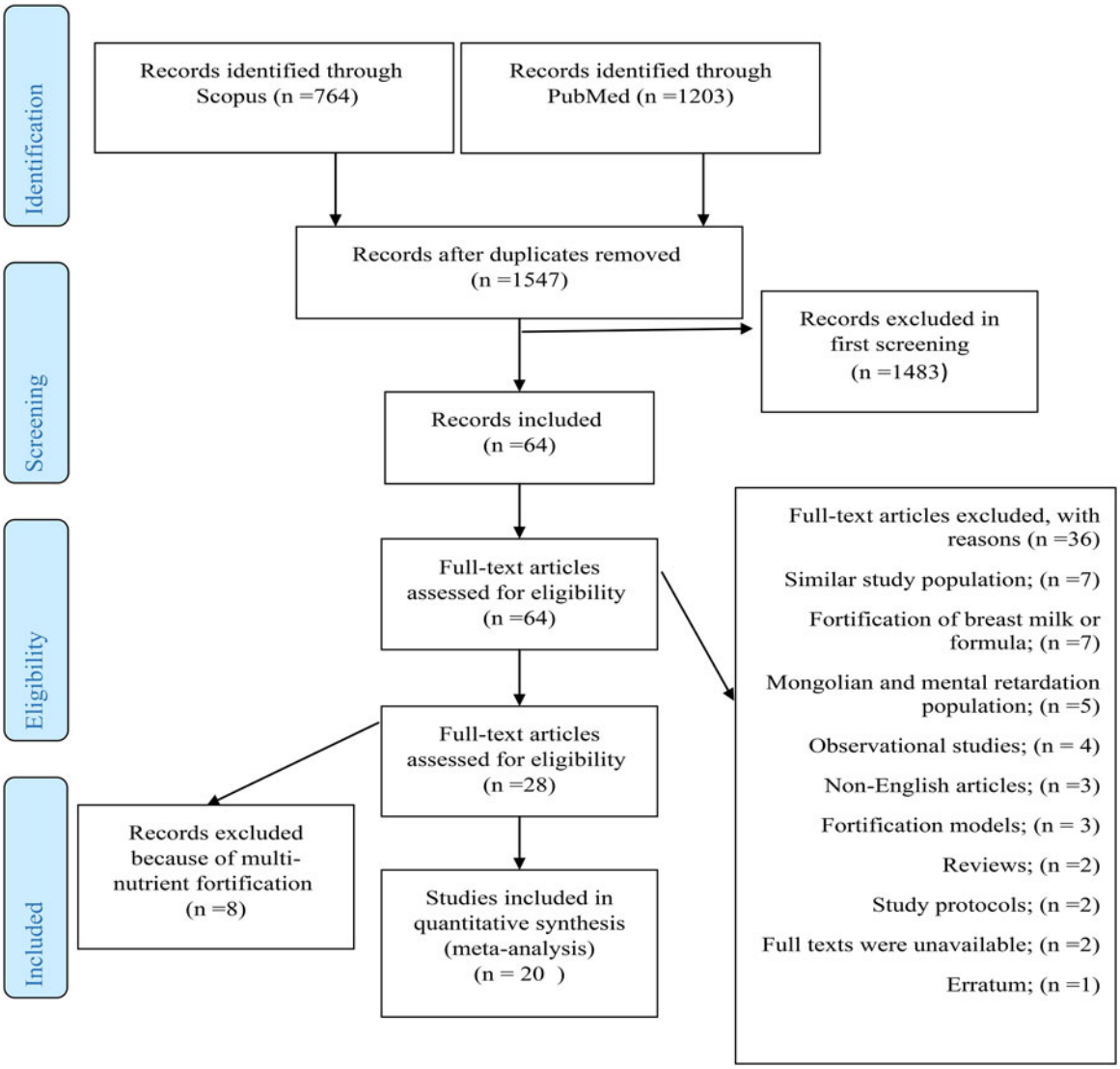

Figure 1. Inclusion process.

Results

Search results

The PRISMA flow chart displays the inclusion process (Figure 1).The comprehensive search identified 1967 references. Of which, 1203 and 764 papers were in PubMed and Scopus, respectively. In total, 1547 articles remained following duplicate removal (420 articles) that changed to 64 records after screening of titles and abstracts. After full text screening based on the screening form that provided for this review, 34 papers were excluded due to the following reasons: (i) seven were the several reports of the same papers (ii) in seven papers fortification of breast milk or formula had been done, (iii) five studies had been conducted in Mongolian and mental retardation population, (iv) four were observational studies, (v) three were non-English, (vi) three were fortification models, (vii) two were reviews, (viii) two were study protocols, (ix) the full texts were unavailable for three papers which one of them achieved after writing letter to author (x) one was erratum. Of 28 remaining papers, we only considered the VDF with or without calcium fortification. Of them, 8 studies were multi nutrient fortifications which were excluded. Finally, 20 articles were entered in the meta-analysis: 14 of them (Bonjour et al. 2009; Bonjour et al. 2012; Costan, Vulpoi, and Mocanu 2014; Daly et al. 2006; Kukuljan et al. 2011; Palacios et al. 2005; Suzuki et al. 2014; Tenta et al. 2011; Bonjour et al. 2015; Bonjour et al. 2013; Jafari et al. 2016; Manios et al. 2009; Neyestani et al. 2015; Neyestani et al. 2014) reported serum vitamin D (19 intervention arms), 8 (10 intervention arms) ALP (Bonjour et al. 2013; Bonjour et al. 2009; Bonjour et al. 2012; Jafari et al. 2016; Neyestani et al. 2014; Palacios et al. 2005; Suzuki et al. 2014; Zhu et al. 2005), 6 (15 intervention arms) BMD (Costan, Vulpoi, and Mocanu 2014; Daly et al. 2006; Moschonis et al. 2011; Moschonis et al. 2010; Moschonis and Manios 2006; Zhang et al. 2016), 15 (19 intervention arms) PTH (Bonjour et al. 2009; Bonjour et al. 2012; Costan, Vulpoi, and Mocanu 2014; Daly et al. 2006; Kukuljan et al. 2011; Suzuki et al. 2014; Neyestani et al. 2014; Tenta et al. 2011; Bonjour et al. 2015; Bonjour et al. 2013; Jafari et al. 2016; Manios et al. 2009; Neyestani et al. 2015; Mocanu et al. 2009; Zhu et al. 2005), 7 (9 intervention arms) OC (Bonjour et al. 2009; Bonjour et al. 2012; Manios et al. 2009;

Table 1. Characteristics of included studies ($n = 20$).

First author (Year)	Country	Gender	Mean age	Study population	Intervention group sample size	Food	Dose (IU/Day)	Duration (Month)	Jadad scale score
Jafari et al. (2016)	Iran	F	56.5	Diabetic postmenopausal women	30	Yogurt	2000	2.8	5
Zhang et al. (2016)	China		26.9	Postpartum lactating women	50/50/50	Milk/ yogurt	200	12	5
Bonjour et al. (2015)	England	F	73.4	Community dwelling home resident	24	Yogurt	400	2.8	5
Neyestani et al. (2015)	Iran	M/F	50.7	Diabetic	30/30	Yogurt drink	1000	3	5
Costan, Vulpoi, and Mocanu (2014)	Romania	M/F	70.7	Elderly with or without vertebral fractures	20/20	Bun	5000	12	1
Neyestani et al. (2014)	Iran	M/F	11	Healthy children	80/83	Milk/Juice	100	2.8	5
Suzuki et al. (2014)	Japan	F	18.5	Female college students	49	Milk	80	1.8	1
Bonjour et al. (2013)	French	F	85.5	Nursing homes resident	29	Yogurt	400	1.8	5
Bonjour et al. (2012)	French	F	56.6	Postmenopausal women	36	Cheese	100	1.4	1
Kukuljan et al. (2011)	Australia	M	60.8	Community dwelling home resident	45	Milk	800	18	3
Moschonis et al. (2011)	Greece	F	62.4	Postmenopausal women	26	Yogurt	400	12	2
Tenta et al. (2011)	Greece	F	60.9	Postmenopausal women	20/20	Milk/yogurt	300	30	3
Moschonis et al. (2010)	Greece	F	60	Postmenopausal women	35	Milk/yogurt	900	18	3
Bonjour et al. (2009)	French	F	84·8	Nursing homes resident	35	Cheese	100	1	1
Mocanu et al. (2009)	Romania	M/F	71	Elderly	40	Bun	5000	12	1
Manios et al. (2009)	Greece	F	60.9	Postmenopausal women	39	Milk/yogurt	300	5	3
Daly et al. (2006)	Australia	M	61.9	Healthy men	76	Milk	800	24	4
Moschonis and Manios al. (2006)	Greece	F	60.5	Postmenopausal women	39	Milk/yogurt	300	12	3
Palacios et al. (2005)	Spain	F	62.4	Postmenopausal women	34/35	Milk	228	6	4
Zhu et al. (2005)	China	F	11	Urban girls	210	Milk	133	24	2

Neyestani et al. 2014; Neyestani et al. 2015; Zhu et al. 2005; Mocanu et al. 2009), 3 (3 intervention arms) P1NP (Bonjour et al. 2013; Bonjour et al. 2009; Bonjour et al. 2012) and 6 (6 intervention arms) CTX (Bonjour et al. 2015; Bonjour et al. 2013; Bonjour et al. 2009; Bonjour et al. 2012; Manios et al. 2009; Mocanu et al. 2009).

Systematic review

Table 1 shows the characteristics of included studies. The current systematic review is made up of 20 articles with 1786 subjects (1090 in intervention groups) and dated from 2005 to 2016. The included studies were conducted in England (Bonjour et al. 2015), French (Bonjour et al. 2013; Bonjour et al. 2009; Bonjour et al. 2012), Greece (Manios et al. 2009; Moschonis et al. 2011; Moschonis et al. 2010; Moschonis and Manios 2006; Tenta et al. 2011), Spain (Palacios et al. 2005), Romania (Costan, Vulpoi, and Mocanu 2014; Mocanu et al. 2009), Australia (Daly et al. 2006; Kukuljan et al. 2011), Iran (Jafari et al. 2016; Neyestani et al. 2014; Neyestani et al. 2015), Japan (Suzuki et al. 2014), and China (Zhang et al. 2016; Zhu et al. 2005) with the range sample size from 40 to 429. All studies were done on women except two were conducted on men (Daly et al. 2006; Kukuljan et al. 2011) and four on both genders (Neyestani et al. 2014; Neyestani et al. 2015; Costan, Vulpoi, and Mocanu 2014; Mocanu et al. 2009). 16 studies were conducted on the elderly (one on healthy men (Daly et al. 2006), seven on postmenopausal women (Bonjour et al. 2012; Manios et al. 2009; Moschonis et al. 2011; Moschonis et al. 2010; Moschonis and Manios 2006; Palacios et al. 2005; Tenta et al. 2011), two on diabetic postmenopausal women and diabetic men (Jafari et al. 2016; Neyestani et al. 2015), two on nursing homes resident (Bonjour et al. 2013; Bonjour et al. 2009), two community dwelling home resident (Bonjour et al. 2015; Kukuljan et al. 2011), and two on the elderly with or without vertebral fractures (Bonjour et al. 2015; Costan, Vulpoi, and Mocanu 2014), two studies on the youth (female college students (Suzuki et al. 2014) and postpartum lactating women (Zhang et al. 2016)), and two on children (healthy (Neyestani et al. 2014) and urban girls (Zhu et al. 2005)). Study dose varied between 80 and 5000 IU vitamin D and study duration varied between 1 to 24 months. Fortified foods were included dairy products (milk (Daly et al. 2006; Kukuljan et al. 2011; Neyestani et al. 2014; Palacios et al. 2005; Suzuki et al. 2014; Zhu et al. 2005), yogurt (Bonjour et al. 2015; Bonjour et al. 2013; Jafari et al. 2016; Moschonis et al. 2011), yogurt drink (Neyestani et al. 2015), cheese (Bonjour et al. 2009; Bonjour et al. 2012) and combination of milk with yogurt (Manios et al. 2009; Moschonis et al. 2011; Moschonis et al. 2010; Tenta et al. 2011; Zhang et al. 2016), juices (orange juice (Neyestani et al. 2014)), or bread (bun (Costan, Vulpoi, and Mocanu 2014; Mocanu et al. 2009)).

Meta-analysis

VDFs and serum 25(OH) D

Fourteen studies (Bonjour et al. 2009; Bonjour et al. 2012; Costan, Vulpoi, and Mocanu 2014; Daly et al. 2006; Kukuljan et al. 2011; Neyestani et al. 2014; Palacios et al. 2005; Suzuki et al. 2014; Tenta et al. 2011; Bonjour et al. 2015; Bonjour et al. 2013; Jafari et al. 2016; Manios et al. 2009; Neyestani et al. 2015) were included in the meta-analysis. The meta-analysis showed that the vitamin D fortification increased serum 25(OH) D levels significantly in the intervention group in comparison with the placebo. The overall pooled MD for the effect of VDFs on serum 25(OH) D based on random effect model was 16.94 (95% CI: 13.38 nmol/L, 20.50; $p < 0.001$) and ($I^2 = 99.0\%$;

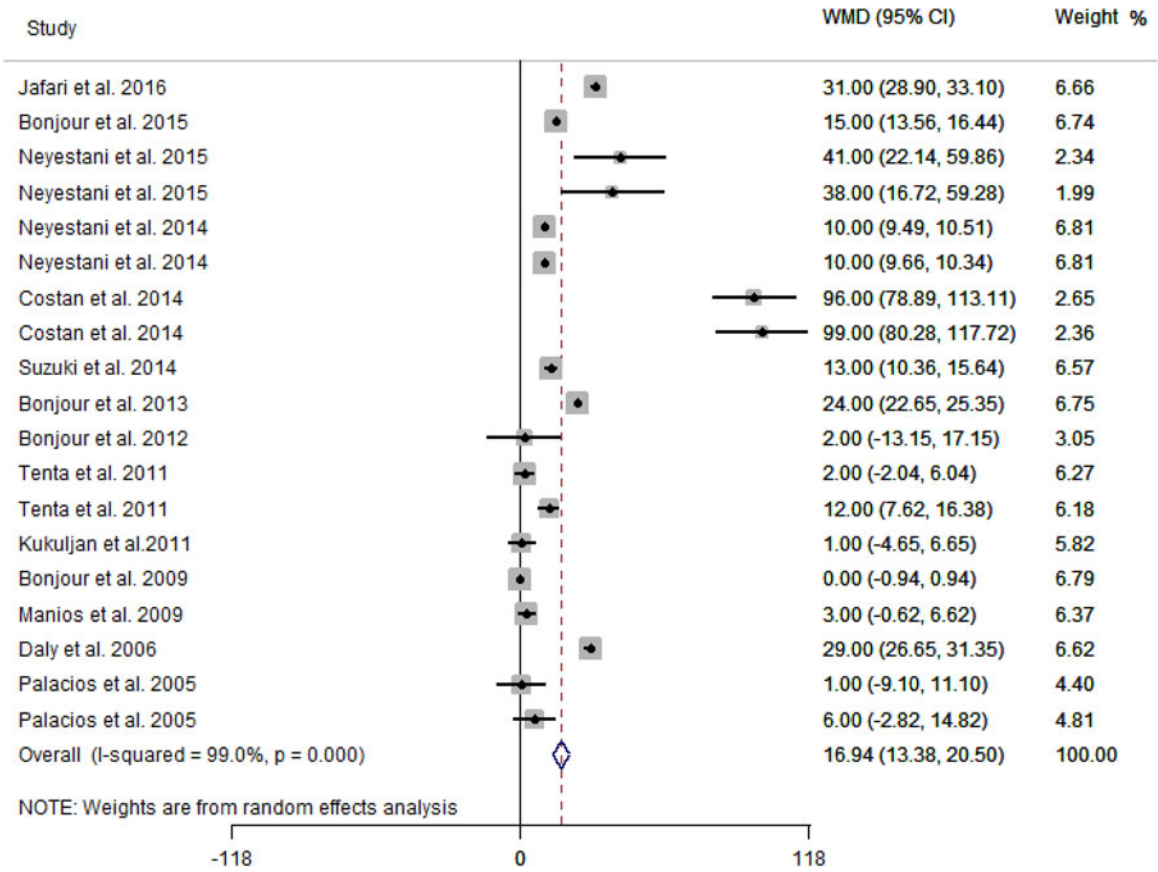

Figure 2. Forest plot for the association of VDFs and serum 25(OH)D (nmol/L).

$p < 0.001$) (Figure 2). Sub-group analysis revealed that population ($I^2 = 99.0\%$; $p = 0.000$), fortification dose of vitamin D ($I^2 = 99.0\%$; $p < 0.001$), and trial duration ($I^2 = 99.0\%$; $p < 0.001$) were sources of heterogeneity in which 25(OH) D increased more in those studies treated patients with dose of more than 4000 IU/day and for more than 3 months and less than 6 months (Supplemental file 2).

VDFs and BMD

The impact of vitamin D fortification on hip and spine BMD was reported in 6 trials (Costan, Vulpoi, and Mocanu 2014; Daly et al. 2006; Moschonis et al. 2011; Moschonis et al. 2010; Moschonis and Manios 2006; Zhang et al. 2016) including 15 interventional groups. The overall pooled MD suggested that BMD had significant increase following receiving VDFs (MD: 0.03 gr/cm^2, 95% CI: (0.02, 0.05); $p < 0.001$) and ($I^2 = 58.8\%$; $p = 0.002$) (Figure 3). Sub-group analysis was conducted based on sex, age, fortification dose of vitamin D, Ca dose, type of fortified food, measured BMD area, and quality of articles and all were indicated as source of heterogeneity. VDFs interventions improved BMD in studies conducted on both sex ($I^2 = 58.8\%$; $p = 0.002$), age of $<$ 35 ($I^2 = 58.8\%$; $p = 0.002$), vitamin D dose of higher than 400 IU/d ($I^2 = 58.8\%$; $p = 0.002$) and Ca dose of higher than 1000 mg/d ($I^2 = 58.8\%$; $p = 0.002$). Moreover, vitamin D fortification via non-dairy food ($I^2 = 58.8\%$; $p = 0.002$) were more effective at spine site area ($I^2 = 58.8\%$; $p = 0.002$) and in low quality studies ($I^2 = 58.8\%$; $p = 0.002$).

VDFs and serum PTH

Combining findings from 15 studies, we found a significant reduction in PTH (MD:−9.22 μg/L; 95% CI: (−1 4.97, −3.46); $p = 0.002$) with significant heterogeneity ($I^2 = 98.8\%$; $p < 0.001$). Sub-group analysis showed that the dose of vitamin D fortification was a potential source of heterogeneity. Serum PTH had more reduction in dose of >4000 IU/day of vitamin D ($I^2 = 58.8\%$; $p = 0.002$) compared with doses of $\leq$ 400, 400–1000, and 1000–4000 (Figure 4).

VDFs and serum OC

Nine intervention arms from seven papers (Bonjour et al. 2009; Manios et al. 2009; Mocanu et al. 2009; Neyestani et al. 2014; Neyestani et al. 2015; Zhu et al. 2005; Bonjour et al. 2012) were included in the meta-analysis. Our findings revealed no significant increase in serum OC (MD: 4.097 μg/L; 95% CI: (−7.20, 15.39); $p = 0.477$). Sub-group analysis specified age, study population, fortification dose of vitamin D, and trial duration as sources of heterogeneity. VDFs showed greater increase of serum OC in trials in which participants had age of > 35 years ($I^2 = 99.8\%$; $p < 0.001$) compared with age of less than 35, patient population ($I^2 = 99.8\%$; $p < 0.001$) compared with apparently healthy subjects, fortification dose of higher than 400 IU/d of vitamin D ($I^2 = 99.8\%$; $p < 0.001$) compared with dose of $\leq$400 and trial duration of higher than 6 months ($I^2 = 99.8\%$; $p < 0.001$) compared with $\leq$3, and 3–6.

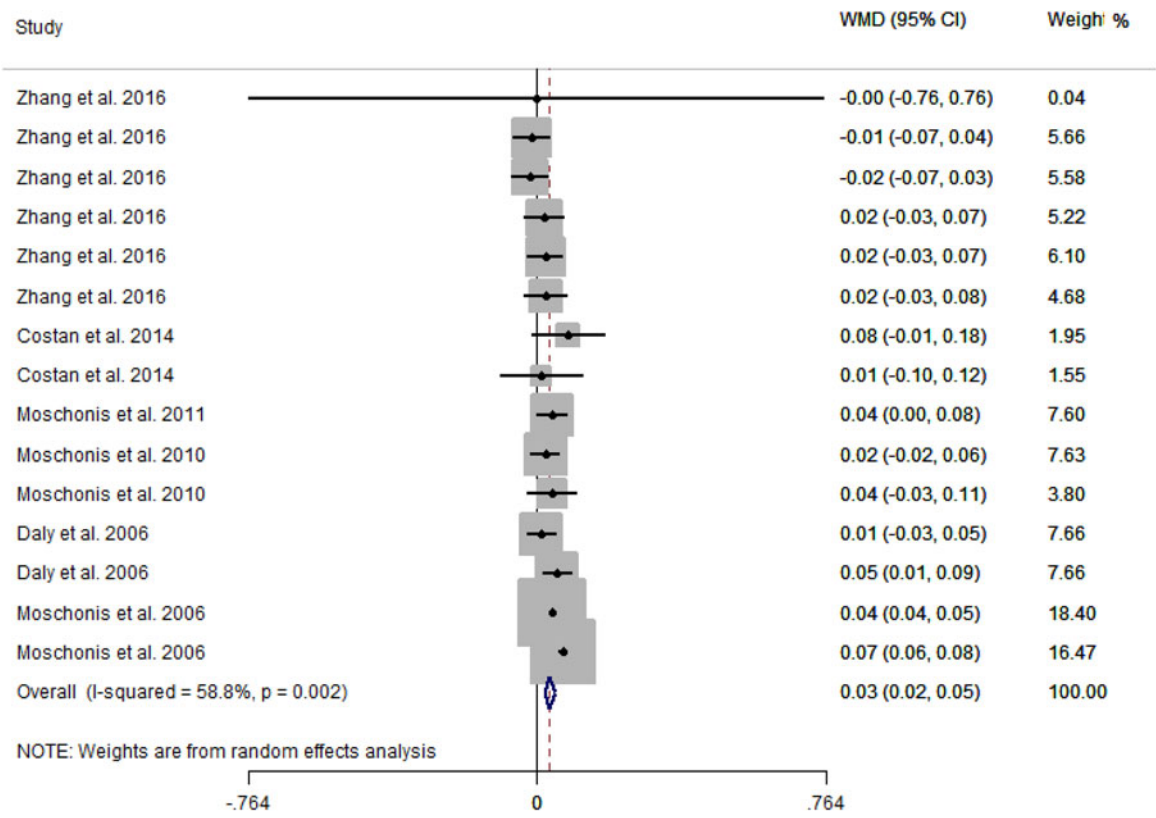

Figure 3. Forest plot for the association of VDFs and BMD (gr/cm^2).

VDFs and serum ALP

Eight (Bonjour et al. 2013; Bonjour et al. 2009; Bonjour et al. 2012; Jafari et al. 2016; Neyestani et al. 2014; Palacios et al. 2005; Suzuki et al. 2014; Zhu et al. 2005) studies comprising 10 intervention arms entered for the meta-analysis of ALP. A slight reduction was seen for the effect of VDFs on serum ALP, it was not significant though (MD:−3.434 µg/L; 95% CI: (−7.959, 1.090); $p = 0.137$, $I^2 = 97.1\%$; $p = 0.2$)). Sub-group analyses showed that none of the predefined criteria were probable sources of heterogeneity except trial duration and quality of studies. In fact ALP was reduced in studies with duration of more than 3 months ($I^2 = 97.1\%$; $p < 0.001$) compared with duration of less than 3 months, and in trials judged of lower quality (<2) ($I^2 = 97.1\%$; $p < 0.001$) than those judged of higher (>3)quality.

VDFs and serum CTX

Six studies (Bonjour et al. 2015; Bonjour et al. 2013; Bonjour et al. 2009; Bonjour et al. 2012; Manios et al. 2009; Mocanu et al. 2009) included in meta-analysis which four (Bonjour et al. 2015; Bonjour et al. 2013; Manios et al. 2009; Mocanu et al. 2009) of them were reported serum CTX in µg/L and 2 (Bonjour et al. 2009; Bonjour et al. 2012) in nmol/L. These two units are not comparable and there is no conversion equation available. Because of these, studies with different unites were analyzed separately. Pooled estimated of MDs for 4 studies in µg/L was −0.060 (95% CI: (−0.15, 0.03); $p = 0.218$) and ($I^2 = 96.5\%$; $p < 0.001$) and for 2 other studies in nmol/L was −0.307 (95% CI: (−1.07, 0.46); $p = 0.43$) and ($I^2 = 0.0\%$; $p = 0.86$).

VDFs and serum P1NP

Combining three (Bonjour et al. 2013; Bonjour et al. 2009; Bonjour et al. 2012) mean differences of three studies which reported P1NP, we found no significance change in serum P1NP using fixed model (MD: −1.13 ng/ml; 95% CI: (−13.76,11.48); $p = 0.86$) and ($I^2 = 37.3\%$; $p = 0.2$) and random model (MD:1.34; 95% CI: (−17.55, 20.23); $p = 0.88$) and ($I^2 = 37.3\%$; $p = 0.2$).

Publication bias assessment

Potential publication bias was evaluated by Egger's test. There was no evidence of publication bias for the serum 25(OH) D ($p = 0.189$), BMD ($p = 0.23$), PTH ($p = 0.577$), and ALP ($p = 0.856$). Funnel plot was depicted in Figure 5. A relative symmetry for included studies of serum 25(OH) D was seen.

Discussion

This meta-analysis demonstrated the beneficial effects of VDFs in improving serum 25(OH)D and BMD as well as serum PTH. Moreover, we found VDFs either with or without calcium intake reduced BTM like ALP, P1NP, and CTX but increased OC, such associations are not meaningful though. To the best of our knowledge, the current

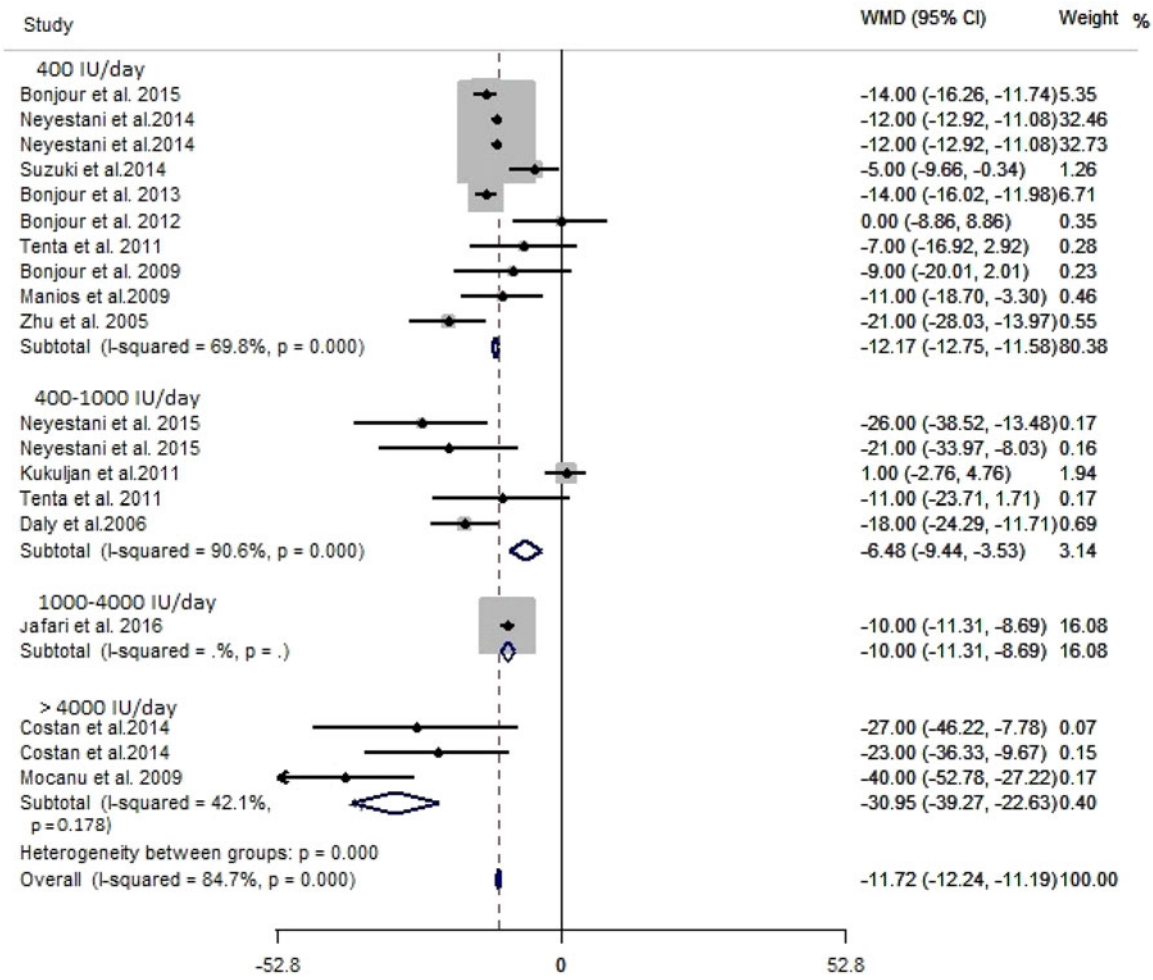

Figure 4. Forest plot for sub group analysis of the association of VDFs and PTH (μg/L).

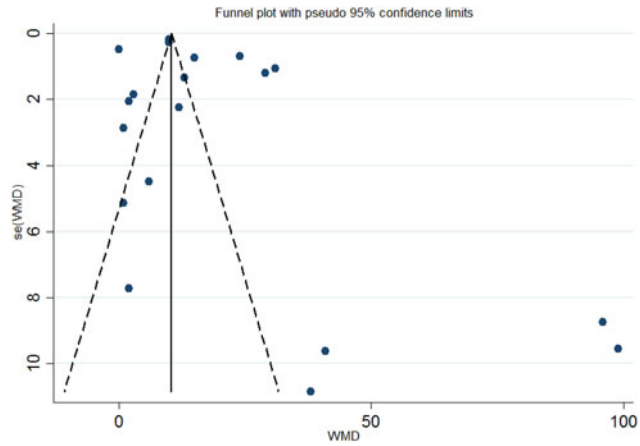

Figure 5. Funnel plot for included studies of serum 25(OH)D (nmol/L).

meta-analysis is the first study summarizing the effect of VDFs on BTM and BMD.

VDFs could increase serum 25(OH)D properly. This effect not only was seen in dairy products but also in non-dairy products such as juices and bread. Historically, many studies have examined the efficacy of supplementation and fortified foods with vitamin D on 25(OH)D. Most of them have shown the good efficacy of vitamin D fortification in foods (O'Mahony et al. 2011; O'Donnell et al. 2008; Black et al. 2012b; Ledger et al. 1994; Mocanu et al. 2009). However, a recently published 12-trial meta-analysis has been shown a highly significant reduction in serum 25(OH)D_3 following vitamin D_2 supplementation (Toyn et al. 2018). It may due to the vitamin D form of D_2 used in this review in comparison to D_3 reviewed in fortification models. Our meta-analysis shows greater efficacy of fortification in patients and with dose and duration of higher than 4000 IU and more than 3 months, respectively. These results can be a strong reason that the vitamin D cut off points proposed by the Endocrine Society of US and Institutes of Medicine (IOM), despite the many changes that have been made so far, are not well suited to raise serum vitamin D levels and to observe the health benefits of vitamin D (Pludowski et al. 2018).

Our study also showed VDFs reduced serum PTH level. Several studies are in line with our finding (Neyestani et al. 2014; Zhu et al. 2005) whereas some have not reported such effect (Bonjour et al. 2012; Kukuljan et al. 2011).Variation in serum PTH, as a BTM, are affected by several factors such as calcium and vitamin D supplementation, age, and etc. (Ledger et al. 1994; McKane et al. 1996). Aging results in elevated level of PTH. In parallel, serum BTM values progress with it. The consumption of VDFs or supplements can suppress serum PTH levels (Dawson-Hughes et al. 2005) as it was shown in the current meta-analysis. In

addition, our study showed that this decrease in serum PTH was observed in interventions with high doses vitamin D (greater than 4,000). As previously mentioned, cut offs for vitamin D levels required for bone health have changed several times so far, and maybe this study proves that higher levels of vitamin D are needed to see better effects on bone (Pludowski et al. 2018).

BMD measurement by dual X-ray absorptiometry (DXA) is the most accurate (more than 95%) method for diagnosis and management of osteoporosis but due to providing a static assessment of bone status, and depending on 2–3-year intervention period, BTM as a dynamic tool is used for estimating bone activity (Bonjour et al. 2009; Consensus 1993). Current meta-analysis revealed a significant increase in BMD of spine and hip following the consumption of VDFs compared with placebo. Since the trial period is often short and because to view the changes in BMD needs longer interventions, many interventions are not successful to conclude well (Aloia et al. 2005; Reid et al. 2017). Heterogeneity by sex, age, and study population, fortification dose of vitamin D, Ca dose, trial duration, food, and measured BMD area was explored by subgroup analysis for impact of VDFs on BMD. Several studies have shown ageing, sex (female gender) and menopause status may be important predictors of BMD (Bliuc et al. 2015; Pinheiro et al. 2010). In a meta-analysis of 17 RCTs, by Cranney et al. vitamin D supplementation doses above 700 IU along with calcium prevented bone loss compared with placebo (Cranney et al. 2008). This study showed the dose dependent effect of vitamin D on BMD via supplementation which applies to fortification too. An umbrella review of systematic reviews and meta-analyses of observational studies and randomized trials of health outcomes of vitamin D has marked the efficacy of vitamin D supplementation with calcium instead of vitamin D alone in improving bone density and decreasing fracture risk (Theodoratou et al. 2014).

Among bone formation markers, our study showed a non-significant increase in OC following the consumption of VDFs which is in line with Bonjour et al. (2009) and Neyestani et al. (2014) studies. OC is a non-collagenous protein synthetized by osteoblast during the mineralization of matrix and its rise shows bone formation (Power and Fottrell 1991), we did not see any significant relationships though.

Serum ALP in our study has shown a non-significant reduction. Changes in serum ALP should be explained by consideration of some factors like age, sex, circadian rhythm, puberty, estrogen deficiency which is seen in postmenopausal women, and also seasonal differences (Douglas et al. 1996; Khosla et al. 1997; Lindsay 1988; Wichers et al. 1999). Increase in BTM levels is seen during menopause (Khosla et al. 1997). Although the most populations of our study are postmenopausal elderly women, the observed reduction in serum levels of ALP has been observed using VDFs among non-elderly population (Neyestani et al. 2014; Suzuki et al. 2014; Zhu et al. 2005). Moreover, based on the phenomenon which is seen in children, supplementation or fortification with vitamin D and calcium may lower BTM like ALP in children (Heaney 1994; Zhu et al. 2005). Subgroup analysis based on age shows that the differences are visible, though they are not significant.

P1NP, another bone formation biomarker, is produced by collagen cleavage of osteoblasts during fibril formation (Banerjee et al. 2012). It showed a slight non-significant decline in serum P1NP level after consumption of VDFs compared to placebo. In line with our study, Schewetz et al. found no association between vitamin D supplementation and P1NP after 8-week supplementation with 2800 IU/day vitamin D (Schwetz et al. 2017), whereas in another study, serum P1NP decreased meaningfully after 9 month supplementation with 1000 IU/day (Nahas-Neto et al. 2018).

CTX fragments as bone resorption marker are released into circulation due to degradation of collagen during bone resorption (Risteli et al. 1993). Our finding revealed a non-significant reduction in serum CTX following the intake of VDFs. Previous studies applying vitamin D supplementation have shown consistent results. Ikedo et al. reported 1000 IU/day vitamin D supplementation along with low-fat milk (Ca 315 mg/day) for 6 months, could significantly reduce serum CTX (Ikedo et al. 2018). In another 9-month study, serum CTX decreased by 1000 IU/day vitamin D supplementation in comparison to control group (Nahas-Neto et al. 2018).

The main strength of this study is the consideration of several factors for heterogeneity analysis. One of the limitations of this study was lack of control groups in some studies. Moreover, number of pooled studies for CTX and P1NP were not enough to make a good judgment. Additionally, the included papers were highly heterogeneous due to differences in dose, duration and etc. These factors may affect the pooled effect.

Conclusions

The current meta-analysis combining all included vitamin D fortification trials suggests that VDFs specially along with calcium can successfully rise serum 25(OH)D and lower serum PTH levels and BMD loss. We did not find any beneficial effects of VDFs on BTM of OC, ALP, P1NP, and CTX.

Disclosure statement

Authors declared no personal or financial conflicts of interest.

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