Osteoporosis International (2019) 30:2183–2193
https://doi.org/10.1007/s00198-019-05102-7

REVIEW

Oral vitamin D_3 supplementation increases serum fibroblast growth factor 23 concentration in vitamin D-deficient patients: a systematic review and meta-analysis

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Received: 21 April 2019 / Accepted: 18 July 2019 / Published online: 1 August 2019

Abstract

Studies have suggested that vitamin D supplementation may increase serum fibroblast growth factor 23 (FGF23) among vitamin D-deficient patients although the results were inconsistent across the studies. This systematic review and meta-analysis was conducted to summarize all available data. A systematic review was conducted using MEDLINE and EMBASE database from inception to February 2019 to identify studies that provided oral vitamin D_3 supplement to vitamin D-deficient participants (25-hydroxyvitamin D < 20 ng/mL). Mean serum FGF23 concentration and standard deviation of participants at baseline and after vitamin D_3 supplementation were extracted to calculate standard mean difference (SMD). Pooled SMD was calculated by combining SMDs of each study using random effects model. Nine studies were eligible for the meta-analyses. Seven studies measured serum intact FGF23, and two studies measured serum C-terminal FGF23. The meta-analyses found that serum intact FGF23 increased significantly after oral vitamin D_3 supplementation in vitamin D-deficient participants with the pooled SMD of 0.36 (95%CI, 0.14, 0.57; $p = 0.001$; I^2 of 36%). Serum C-terminal FGF23 also increased after vitamin D_3 supplementation in vitamin D-deficient participants with the pooled SMD of 0.28 although without reaching statistical significance (95%CI, − 0.08, 0.65; $p = 0.13$; I^2 of 0%). Funnel plot of the meta-analysis of serum intact FGF23 did not provide a suggestive evidence for publication bias. Vitamin D supplementation leads to a significant increase in serum intact FGF23 among vitamin D-deficient patients. An increase in serum C-terminal FGF23 was also observed although the number of included studies was too small to demonstrate statistical significance. The present systematic review and meta-analysis revealed that serum intact FGF23 concentration increased significantly after oral vitamin D_3 supplementation in vitamin D-deficient participants. An increase in serum C-terminal FGF23 concentration was also observed although the number of included studies was too small to demonstrate statistical significance.

Keywords Fibroblast growth factor 23 · Meta-analysis · Vitamin D deficiency · Vitamin D_3 supplementation

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Introduction

Vitamin D is a steroid hormone responsible for maintaining calcium and phosphate homeostasis. Humans endogenously synthesize vitamin D in the skin upon exposure to ultraviolet B radiation and exogenously derive vitamin D from dietary sources and supplements. Once entering the circulation, vitamin D undergoes liver hydroxylation by 25-hydroxylase enzyme and turns into 25-hydroxyvitamin D (25(OH)D), which is generally measured for assessment of vitamin D status. 25(OH)D is then converted by 1α-hydroxylase enzyme in the kidney into the active from of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) that exerts physiological functions by promoting intestinal calcium and phosphate absorption, renal tubular reabsorption of calcium, and bone resorption and formation

[1]. Vitamin D deficiency, defined as serum 25(OH)D concentration of less than 20 ng/mL [2], can cause transient hypocalcemia as a result of impairment of intestinal calcium absorption. Decreased serum ionized calcium can subsequently lead to secondary hyperparathyroidism as a compensatory mechanism to maintain serum calcium concentration in a physiologically acceptable range [1, 3].

FGF23 is a phosphaturic hormone secreted by osteocytes. It inhibits renal tubular reabsorption of phosphate causing increased urinary phosphate excretion [4]. In addition, FGF23 suppresses the expression of 1α-hydroxylase enzyme in the kidney and induces the expression of 25-hydroxyvitamin D-24-hydroxylase enzyme, resulting in a decrease in conversion of 25(OH)D into $1,25(OH)_2D$ and an increase in catabolism of 25(OH)D and $1,25(OH)_2D$ into inactive carboxylic acids [5, 6]. Increased serum phosphate concentration is the known major physiologic regulator that stimulates FGF23 production by osteocyte [4, 6]. In addition, in vivo studies revealed that $1,25(OH)_2D$ and parathyroid hormone (PTH) can also directly stimulate synthesis of FGF23 in osteocyte [5, 7, 8]. High concentration of serum FGF23 can be observed as a physiologic reaction to impaired renal function when renal phosphate excretion is compromised [6, 9]. Serum FGF23 can also be pathologically elevated in rare inherited diseases such as X-linked hypophosphatemic rickets as well as acquired disorders such as tumor-induced osteomalacia [10].

Although studies on the vitamin D–PTH–FGF23 axis are rising in number, the effect of vitamin D supplementation on serum FGF23 concentration in individuals with vitamin D deficiency is still not known. Treatment of vitamin D deficiency is known to recover intestinal calcium and phosphate absorption, leading to resolution of secondary hyperparathyroidism and decreased urinary loss of phosphate [3]. However, the effects of vitamin D supplementation on serum FGF23 are inconsistent across studies [11–19]. The current systematic review and meta-analysis was conducted with the aim to gather all available data to better describe the effect of vitamin D_3 (cholecalciferol) supplementation on changes in serum FGF23 among vitamin D-deficient patients.

Methods

Search strategy

Three investigators (P.U., N.C., P.R.) independently searched for published studies indexed in MEDLINE and EMBASE from inception (1950 for MEDLINE and 1947 for EMBASE) to February 2019. Search terms derived from terms related to fibroblast growth factor 23 and vitamin D. The detailed search strategy is provided in the Supplemental Material 1. No language limitation was applied.

Inclusion criteria

Studies that were eligible to be included into the meta-analysis must be either prospective interventional single-arm study or randomized controlled study that gave oral vitamin D_3 supplement to participants with vitamin D deficiency (defined as serum 25(OH)D concentration of less than 20 ng/mL, using assay methodology that measures the total 25(OH)D [$25(OH)D_2$ and $25(OH)D_3$] [2]. Eligible studies must clearly define dosage and duration of vitamin D_3 supplementation and must also report mean concentration of serum intact and/or C-terminal FGF23 of participants and its standard deviation (SD) or standard error of the mean at baseline and after oral vitamin D_3 supplementation.

Study eligibility was independently determined by the two investigators (N.C. and P.R.). Different opinions were resolved by conference with the senior investigator (P.U.).

Data extraction

A standardized data collection form was used for extracting the following details: last name of the first author, country where the study was conducted, study design, year of publication, number of participants, recruitment of participants, dosage and duration of oral vitamin D_3 supplementation, average age of participants, percentage of female, baseline serum 25(OH)D concentration, serum FGF23 at baseline and after vitamin D_3 supplementation, and duration of serum FGF23 follow-up measurement.

Statistical analysis

Mean serum FGF23 and SD of participants before and after vitamin D_3 supplementation were extracted from each study and the standard mean difference (SMD) was calculated. Pooled SMD was then calculated by combining SMDs of each study using random-effects model. The heterogeneity of the SMDs across the included studies was quantified using the Q statistic, which is complimented with I^2 statistics. A value of I^2 of 0–25% indicates insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity, and 76–100% high heterogeneity [20]. Visual inspection of funnel plots was used to assess for the presence of publication bias. Data analysis was performed using Review Manager 5.3 software from the Cochrane Collaboration (London, UK).

Results

Search results

A total of 4404 articles were retrieved from MEDLINE and EMBASE databases in which duplicated articles were

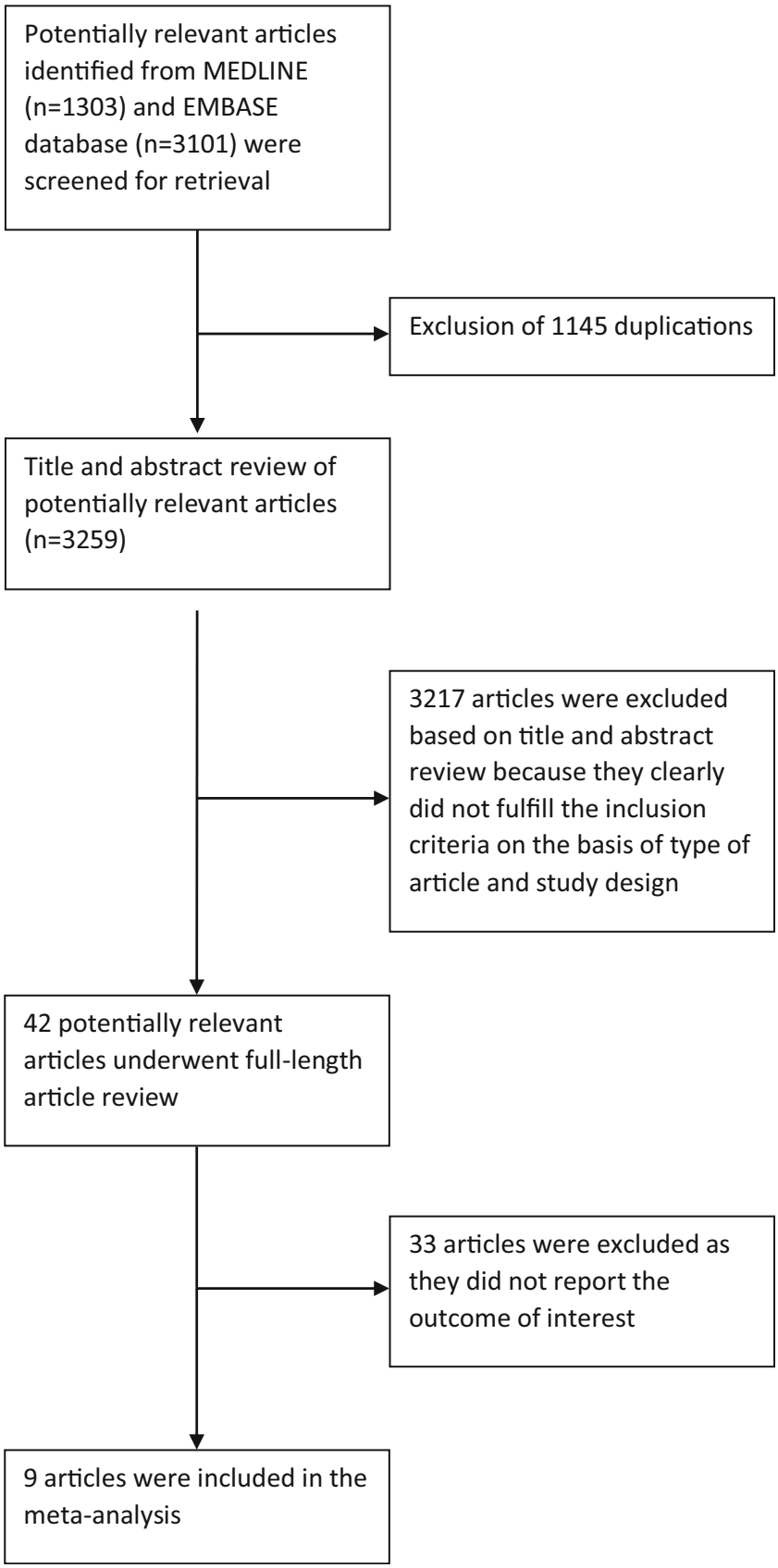

Fig. 1 Study identification and literature review process

Table 1 Characteristics of the included studies

Study	Study design	Recruitment of subjects	Intervention	Number of subjects in D_3 treatment arm	Female (%)	Age (SD) in years	Baseline 25(OH)D level (SD) in ng/mL	Assay of FGF23 measurement	Follow-up duration
Garcia-Lopes et al. 2012	Single arm prospective interventional study	Participants were stages 3 and 4 CKD adult patients aged > 18 years old from a single renal outpatient clinic of the Federal University of São Paulo, São Paulo, Brazil, who had serum 25(OH)D < 15 ng/mL. Participants must not have the following conditions: CKD stages 1, 2 or 5, serum ionized calcium > 1.40 mmol/L, intact PTH > 500 pg/mL, urinary protein > 3 g/24 h, liver disease, active malignancy, autoimmune or infectious disease, and use of any type of vitamin D compounds, calcium salts, corticosteroids or immunosuppressive drugs in the previous 3 months.	Oral weekly 50,000 IU of D_3 for 6 months	45	58	60.1 (15.6)	11.2 (2.5)	Enzyme-linked immunosorbent assay for intact FGF23	3 months
Nygaard et al. 2014	RCT	Participants were adults aged > 18 years old working at Roskilde University Hospital, Denmark who were diagnosed with vitamin D insufficiency (25(OH)D < 20 ng/mL ml). Participants must not have the following conditions: sarcoidosis, cancer within 5 years, pancreatitis, malabsorption, kidney stones, renal failure defined by serum Cr > 0.12 mmol/L, former admission due to alcohol related disease, taking medications influencing calcium balance (vitamin D analogues, anti-hypertensive, anti-diabetics, calcimimetics or intoxicating substances), pregnancy, unsafe contraception, nursing, plasma ionized calcium > 1.50 or known intolerance to D_3. Participants were recruited through posters and information meetings at Roskilde University Hospital during the winter of 2009 and 2010.	One group randomized to receive oral daily 3000 IU of D_3 for 16 weeks Another group randomized to receive placebo	22	48	42.8 (9.2)	12.3 (4.4)	Enzyme-linked immunosorbent assay for intact FGF23	16 weeks
Alshayeb et al. 2014	Single arm prospective interventional study	Participants were male aged > 18 years old who attended the outpatient clinics at the Veterans Affairs Medical Center in Memphis, TN, and were diagnosed	10,000 IU of oral D_3 once a week for 8 weeks	25 with normal renal function 27 with CKD 14 with ESRD	0	60.4 (6.6) in normal renal function group	12 (4.1) in normal renal function group	Enzyme-linked immunosorbent assay for intact FGF23	8 weeks

Table 1 (continued)

Study	Study design	Recruitment of subjects	Intervention	Number of subjects in D_3 treatment arm	Female (%)	Age (SD) in years	Baseline 25(OH)D level (SD) in ng/mL	Assay of FGF23 measurement	Follow-up duration
		with vitamin D deficiency (25(OH)D < 20 ng/mL). Participants must not have the following conditions: cirrhosis, sarcoidosis, lymphoma, malabsorption syndrome, solid organ transplant, primary hyperparathyroidism, use of medications known to alter vitamin D metabolism, including rifampin, corticosteroids, antiepileptics, and use of phosphate binders, active forms of vitamin D, and calcimimetics (except in ESRD patients)				66.4 (10.0) in CKD group 63.3 (15.2) in ESRD group	14.5 (4.4) in CKD group 12.8 (5.2) in ESRD group		
Turrini et al. 2017	RCT	Participants were adults older than 60 years old who were diagnosed with stable chronic heart failure and vitamin D deficiency (25(OH)D < 20 ng/mL). Participants must not have the following conditions: acute coronary syndrome, stroke, or major vascular surgery within 3 months; active neoplasms, liver cirrhosis, nephrolithiasis and sarcoidosis; glomerular filtration rate < 30 mL/min/1.73/m2; hypercalcemia; use of the following medications: anticonvulsants, steroids, thiazides, aluminum, magnesium, colestipol, cholestyramine, calcium supplements.	One group randomized to receive a single oral dose of 300,000 IU of D_3 followed by 50,000 IU of oral D_3 per month Another group randomized to receive placebo	17	65	77 (7)	9.4 (5.2)	Enzyme-linked immunosorbent assay for intact FGF23	3 months
Carvalho et al. 2017	RCT	Participants were dialysis patients aged 18–80 years old from single dialysis unit of the Oswaldo Ramos Foundation (Sao Paulo, Brazil) who were diagnosed with vitamin D deficiency (25(OH)D < 20 ng/mL). Participants must not have the following conditions: use of any vitamin D compound, glucocorticoids or immunosuppressant drugs; history of liver failure, intestinal malabsorption, malignancy, autoimmune disease, active infection, HIV, peritonitis in the last month, and elevated serum ionized calcium (> 1.40 mmol/L).	One group randomized to receive oral 50,000 IU of D_3 twice a week for 3 months Another group randomized to receive placebo	16	55	53 (13)	16 (4)	Enzyme-linked immunosorbent assay for intact FGF23	12 weeks

Table 1 (continued)

Study	Study design	Recruitment of subjects	Intervention	Number of subjects in D_3 treatment arm	Female (%)	Age (SD) in years	Baseline 25(OH)D level (SD) in ng/mL	Assay of FGF23 measurement	Follow-up duration
		Participants were recruited from Nuovo Ospedale Civile Sant' Agostino Estense, AUSL Modena, Italy.							
Kamelian et al. 2017	RCT	Participants were individuals aged > 15 years old with vitamin D deficiency (25(OH)D > 20 ng/mL). Participants must not have the following conditions: renal insufficiency (GFR < 60 mL/min/1.73m^2), metabolic bone disease, osteoporosis, pregnancy, lactation, use of certain medications such as calcium supplements and vitamin D absorption interfering drugs. Participants were recruited from Shiraz University of Medical Sciences between January 2016 and August 2016.	One group randomized to receive oral weekly 50,000 IU of D_3 for 12 weeks Another group randomized to receive placebo	60	69	39 (13)	8.3 (4.5)	Enzyme-linked immunosorbent assay for intact FGF23	12 weeks
De Niet et al. 2018	RCT	Participants were Caucasian healthy adults aged 18–55 years old with vitamin D deficiency (25(OH)D 10–20 ng/mL) and a body mass index of 18–25 kg/m^2. Participants must not have the following conditions: unstable clinically significant medical or psychiatric conditions, past or current granulomatosis, sarcoidosis, urinary lithiasis, renal insufficiency, osteomalacia, abnormal digestive functions and abnormal thyroid function, vitamin D supplement within 2 months, and use of UV light solarium. Participants with a serum creatinine > 150 μmol/L and an albumin-corrected serum calcium > 2.65 mmol/L were excluded at screening. Participants were recruited from one clinical site in Belgium.	One group randomized to receive oral daily 2000 IU of D_3 for 75 days Another group randomized to receive oral 50,000 IU of D_3 every 25 days for 3 doses	30 in daily regimen group 30 in monthly regimen group	56.7 in daily regimen group 70 in monthly regimen group	29.4 (7.7) in daily regimen group 29.8 (9.5) in monthly regimen group	14.1 (3.4) in daily regimen group 14.3 (3.7) in monthly regimen group	Diasorin XL analyzer for intact FGF23	\ 105 days
Trummer et al. 2018	RCT	Participants were adults aged > 18 years old who were diagnosed with hypertension and 25(OH)D < 30 ng/mL. Participants must not have the following conditions: regular intake of	One group randomized to receive oral daily 2800 IU of D_3 for 8 weeks	30 in 25(OH)D < 20 ng/mL subgroup	46	61 (11)	22.1 (5.4)	Enzyme-linked immunosorbent assay for C-terminal FGF23	8 weeks

Table 1 (continued)

Study	Study design	Recruitment of subjects	Intervention	Number of subjects in D_3 treatment arm	Female (%)	Age (SD) in years	Baseline 25(OH)D level (SD) in ng/mL	Assay of FGF23 measurement	Follow-up duration
		$D_3 > 880$ IU/day within 4 weeks, SBP > 160 mmHg or < 120 mmHg, DBP > 100 mmHg, change of antihypertensive therapy within 4 weeks or planned changes of antihypertensive therapy, hypercalcemia, pregnancy or lactation, drug intake as part of another clinical study, acute coronary syndrome or cerebrovascular events within 2 weeks, eGFR < 15 mL/min/L.73 m^2, and any clinically significant acute disease requiring drug treatment, chemotherapy or radiation therapy, or any disease with an estimated life expectancy of less than 1 year. Participants were recruited from University of Graz, Austria between June 2011 and August 2014.	Another group randomized to receive placebo						
Mesinovic et al. 2018	RCT	Participants were adults aged 18–60 years old who were overweight or obese and vitamin D deficient (25(OH)D < 20 ng/mL), but otherwise healthy. Participants must not have the following conditions: smoking or high alcohol use, hypercalcemia, allergies, diabetes mellitus, and the use of medications or vitamin supplements. Participants were recruited from a local community in Melbourne, Australia via print and online advertising over 2-year period.	One group randomized to receive a single oral dose of 100,000 IU of D_3 followed by oral daily 4000 IU of D_3 Another group randomized to receive placebo	28	Not reported	30.5 (7.4)	12.4 (5.0)	Enzyme-linked immunosorbent assay for C-terminal FGF23	16 weeks

RCT, randomized controlled trial; 25(OH)D, 25-hydroxtvitamin D; D_3, vitamin D_3; FGF23, fibroblast growth factor 23; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *CKD*, chronic kidney disease; *ESRD*, end-stage renal disease

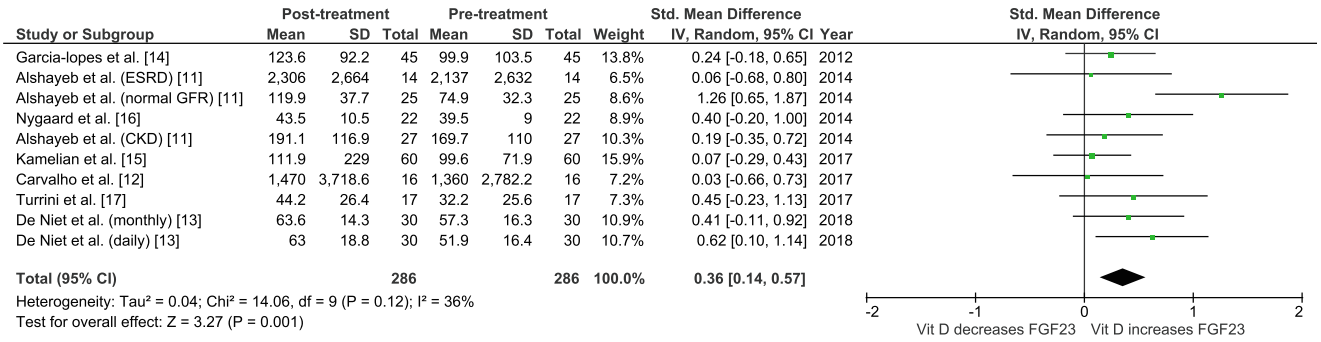

Fig. 2 Forest plot of the meta-analysis of change in serum intact FGF23 concentration after oral vitamin D_3 supplementation in vitamin D-deficient patients

removed, leaving 3259 articles for title and abstract review. Based on title and abstract review, a total of 3217 articles were excluded as they clearly did not fulfill the inclusion criteria on the basis of type of article and study design. A total of 42 articles underwent full-length article review in which 33 articles were excluded as they did not report the outcome of interest. Finally, a total of nine studies consisting of seven randomized-controlled studies and two prospective interventional single arm studies met the inclusion criteria and were included into the meta-analysis [11–19]. Seven of the nine included studies measured serum intact FGF23 [11–17], while the other two studies measured serum C-terminal FGF23 [18, 19]. Therefore, two meta-analyses were performed separately; one for the studies that measured serum intact FGF23, and the other for the studies that measured serum C-terminal FGF23. Please note that the study by Alshayeb et al. [11] reported concentration of FGF23 among individual subgroup (which was based on renal function status) but did not report concentration of FGF23 for the entire cohort. Therefore, data from each subgroup were used for the calculation of pooled SMD. Please also note that the study by De Niet et al. [13] randomized their participants into two groups and both groups received oral vitamin D_3 supplementation (the difference was in dosage and frequency). Therefore, both subgroups were eligible and included in this meta-analysis. The study review and selection process are described in Fig. 1. The basic characteristics of the included studies are summarized in Table 1.

Change in serum intact FGF23 concentration after vitamin D_3 supplement in vitamin D-deficient patients

The meta-analysis found that serum intact FGF23 concentration increased significantly after oral vitamin D_3 supplementation in vitamin D-deficient participants with the pooled SMD of 0.36 (95%CI, 0.14, 0.57; $p = 0.001$). The statistical heterogeneity of this meta-analysis was low with I^2 of 36% (Fig. 2).

Change in serum C-terminal FGF23 concentration after oral vitamin D_3 supplementation in vitamin D-deficient patients

The meta-analysis found that serum C-terminal FGF23 concentration increased after vitamin D_3 supplementation in vitamin D-deficient participants with the pooled SMD of 0.28 although without reaching statistical significance (95%CI, −0.08, 0.65; $p = 0.13$). The statistical heterogeneity of this meta-analysis was insignificant with I^2 of 0% (Fig. 3).

Evaluation for publication bias

Funnel plot was used to assess for publication bias in the meta-analysis of change in serum intact FGF23. The plot was reasonably symmetric and did not show a suggestive evidence for the presence of publication bias (Fig. 4).

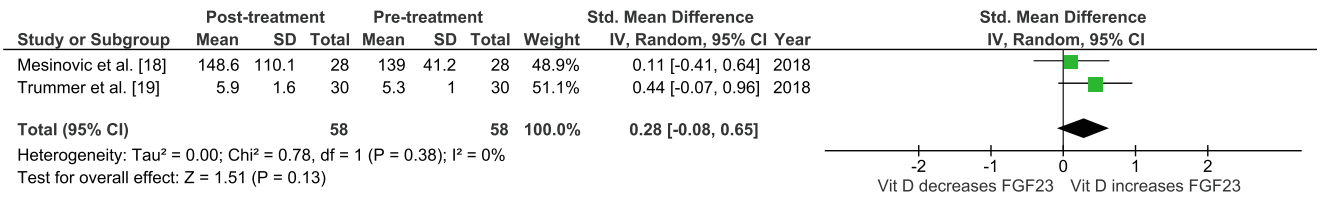

Fig. 3 Forest plot of the meta-analysis of change in serum C-terminal FGF23 concentration after oral vitamin D_3 supplementation in vitamin D-deficient patients

Discussion

The present study is the first systematic review and meta-analysis that summarizes the results of all available prospective interventional single-arm and randomized controlled studies that gave oral vitamin D_3 supplement to participants with vitamin D deficiency and measured serum intact or C-terminal FGF23 at baseline and after vitamin D_3 supplementation. The meta-analysis of both intact and C-terminal FGF23 revealed an increase in concentration of FGF23 after vitamin D_3 supplementation in vitamin D-deficient patients. However, statistical significance was not achieved in C-terminal FGF23 analysis, probably due to limited number of participants as only two studies were included in this meta-analysis. PTH is a known sensitive biomarker of vitamin D and calcium status and normalization of serum PTH reflects response to vitamin D supplementation among vitamin D-deficient patients [1, 3]. The results of this study may suggest that FGF23 could be another possible surrogate marker for vitamin D status and response to vitamin D supplementation.

A few possible explanations exist for the observed increase in serum FGF23 in response to vitamin D_3 supplementation in vitamin D-deficient patients. The first proposed mechanism is based on the evidence from vivo studies that $1,25(OH)_2D$ can independently stimulate mRNA expression of FGF23 in osteocyte by interacting with vitamin D responsive element in the promotor region of the gene encoding for FGF23 [8, 21, 22]. Serum concentration of $1,25(OH)_2D$ is usually normal even in the presence of vitamin D deficiency as a result of secondary hyperparathyroidism that enhances renal conversion of 25(OH)D into $1,25(OH)_2D$ [1–3]; however, tissue and cellular level of $1,25(OH)_2D$ in osteocyte could still be low [23]. Therefore, repletion of vitamin D might lead to an increase in intracellular $1,25(OH)_2D$ concentration in the osteocyte which would then increase synthesis and secretion of FGF23. The second possible explanation is that vitamin D-deficient state is associated with impaired intestinal phosphate absorption and secondary hyperparathyroidism, which would lead to a decrease in renal tubular reabsorption of phosphate [1, 3]. Both will cause a relative phosphate-deficient state and, thus, suppression of osteocyte production of FGF23 [4, 6]. Correction of vitamin D deficiency will improve intestinal phosphate absorption and reverse secondary hyperparathyroidism, resulting in normalization of phosphate status and, subsequently, serum FGF23 concentration. This explanation is also supported by the fact that eight of the nine included studies reported a decrease in serum PTH concentration after vitamin D_3 supplementation [11–18]. Theoretically, secondary hyperparathyroidism seen in vitamin D-deficient individuals should accelerate urinary phosphate loss, giving rise to hypophosphatemia. However, serum phosphate concentration of vitamin D-deficient individuals is usually within the normal

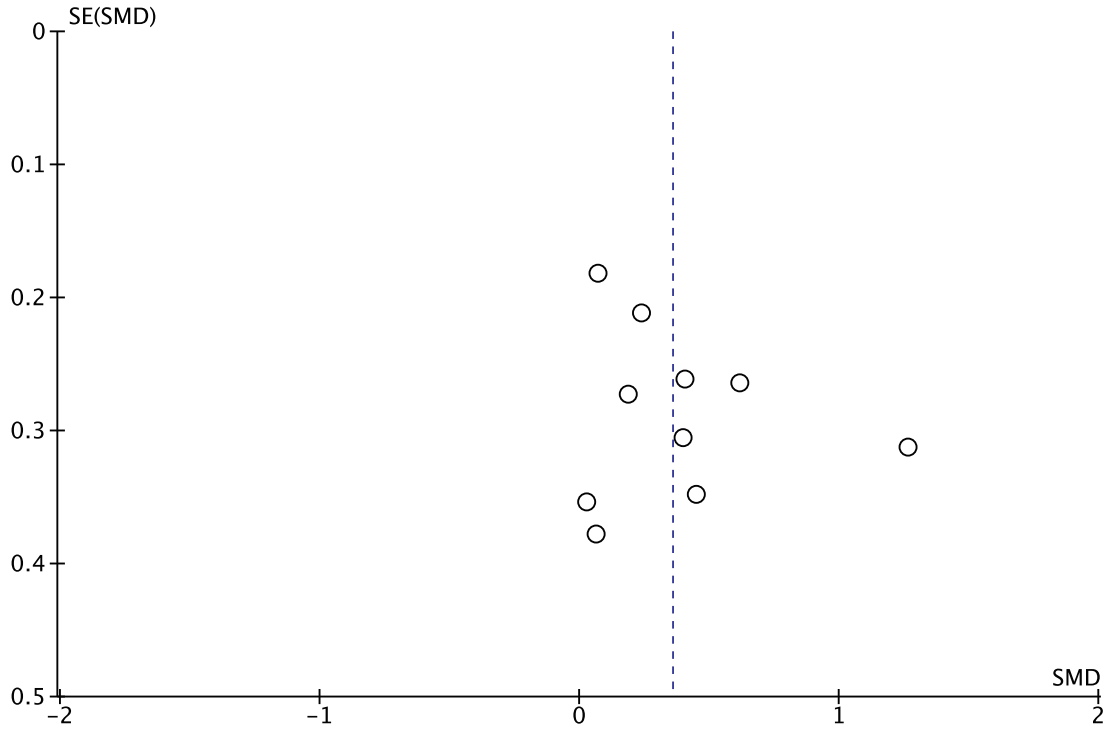

Fig. 4 Funnel plot of the meta-analysis of change in serum intact FGF23 concentration after oral vitamin D_3 supplementation in vitamin D-deficient patients

range. One potential explanation is related to this suppression of FGF23 production, resulting in compensatory decreased urinary phosphate excretion [24].

In addition, it is worth noting that in vivo studies have demonstrated that PTH can directly stimulate osteocytic production of FGF23 by activating nuclear receptor-associated protein-1 to induce FGF23 transcription [7]. Therefore, the lower level of PTH as a result of treatment of vitamin D deficiency could theoretically decrease the concentration of FGF23. However, the current meta-analysis found an increase in serum FGF23 after vitamin D supplementation, suggesting that change in phosphate status or change in cellular/tissue concentration of $1,25(OH)_2D$ in osteocyte plays a more vital role to regulate level of FGF23 concentration than the direct effect of PTH.

Since the physiologic effect of vitamin D_2 (ergocalciferol) on calcium and phosphate metabolism is very similar to vitamin D_3 [25], it is possible that prescribing vitamin D_2 to vitamin D-deficient patients would also increase osteocytic production of FGF23. In fact, increased serum FGF23 concentration after treatment with vitamin D_2 has been observed by some interventional studies although the number of included participants was relatively small [26, 27].

This systematic review and meta-analysis has some limitations and the results must be interpreted with caution. First, there was some between-study heterogeneity in the intact FGF23 analysis which was probably due to the difference in dosage, frequency, and duration of vitamin D supplementation across the included studies. Second, the analysis did not have comparators and, therefore, we cannot be certain that the change in serum FGF23 concentration was a result of vitamin D_3 supplementation. It is still possible that serum FGF23 concentration will spontaneously increase over time without any intervention. This particular concern exists for studies that included participants with chronic kidney disease and end-stage renal disease [11, 14] as serum FGF23 in those participants might increase because of their declining renal function and worsening phosphate retention over time [28].

In summary, this study found that vitamin D_3 supplementation leads to a significant increase in serum intact FGF23 among patients with vitamin D deficiency. An increase in serum C-terminal FGF23 was also observed although the number of included studies was too small to demonstrate statistical significance.

Compliance with ethical standards

Conflict of interest Nipith Charoenngam, Pongprueth Rujirachun, and Patompong Ungprasert declare that they have no conflict of interest. Michael F. Holick is a consultant for Quest Diagnostics Inc. and Ontometrics Inc., and on the speaker's Bureau for Abbott Inc.

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