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Oral Drug Dosing Following Bariatric Surgery: General Concepts and Specific Dosing Advice

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REVIEW ARTICLE

Relationship between serum vitamin D and hip fracture in the elderly: a systematic review and meta-analysis

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Abstract

Introduction This study investigated the relationship between serum 25-hydroxyvitamin D (25OHD) levels and the occurrence of hip fractures in the elderly using a systematic review and meta-analysis approach.

Materials and methods PubMed, Web of Science, and Scopus were used to identify studies that outlined an association between serum 25OHD and the occurrence of a hip fracture in a geriatric patient. The analysis calculated odds ratios (OR) for a hip fracture using a random-effects model.

Results In this study, 28 studies were included, 61,744 elderlies and 9767 cases (15.81%) of hip fractures. In the lowest vs. highest categories of vitamin D in the elderly, pooled OR of hip fractures was 1.80 (95% CI 1.56–2.07, $P \leq 0.001$), and modified OR was equal to 1.40 (95% CI 1.20–1.63 $P \leq 0.001$). A subgroup analysis showed that the OR of a hip fracture was 2.16 (1.49–3.11, $P \leq 0.001$) in case–control studies; 1.52 (1.29–1.79, $P = 0.001$) in cohort studies; and 1.41 (1.18–1.70, $P \leq 0.001$) in case–cohort studies.

Conclusion Low serum vitamin D levels in the elderly are associated with an increase in the odds of hip fracture.

Keywords Vitamin D · Vitamin D deficiency · Osteoporotic fractures · Hip · Aged · Elderly

Introduction

Vitamin D deficiency is one of the most common problems among elderlies in different countries around the world that leads to referral to the rehabilitation unit [1–5]. Vitamin D insufficiency has been defined as a circulating serum 25-hydroxyvitamin D (25OHD) level < 20 ng/mL [6]. Some reference ranges outline that 75–175 nmol/L of serum 25OHD is the normal range, as provided by the Institute of Medicine (IOM) [7, 8]. Low serum vitamin D levels are associated with various metabolic and systemic disorders [8, 9].

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Importantly, vitamin D has a crucial role in calcium homeostasis and, subsequently, bone metabolism [10, 11]. In those with chronic vitamin D deficiency, it has been observed that they have reduced phosphorus absorption, a decline in intestinal calcium, which leads to hypocalcemia and eventually secondary hyperparathyroidism [12, 13]. The continuation of secondary hyperparathyroidism is the development of phosphaturia, which accelerates the decline in renal function and precipitates bone demineralization [14]. In people aged 60 years or older, the consequence of low serum 25OHD is an increased potential risk of osteoporosis and osteoporotic hip fractures [15]. A hip fracture in the elderly imposes additional health and social costs. It impacts their ability to undertake activities of daily living independently, leads to psychosocial problems, and a general deterioration in their quality of life [16–19].

Aging is a special period of every person's life, in this period; people may be forced to use certain dietary patterns due to affecting various diseases (such as diabetes, hypertension, cardiovascular disease, cancer, etc.) [20, 21] or financial problems due to low income, which are less likely to receive micronutrients [22]. On the other hand, these people are at risk of bone fractures, especially hip fractures, due to diseases such as osteoporosis or physical problems caused by aging and as a result of the inability to maintain balance [23, 24].

Although some previous meta-analysis studies show that low serum 25 (OH) vitamin D level increases the risk of total hip fractures [25, 26], another meta-analysis study showed that vitamin D supplementation in the elderly did not have a preventive effect on hip fractures at any of the administered doses [27]. In addition, some other meta-analyses showed that co-supplementation with calcium and vitamin D was a more promising preventive strategy against hip fractures [28]. Due to the inconsistencies in the results of the studies, the need for newer meta-analysis studies seems to be necessary. On the other hand, despite recent observational studies on the field, more robust evidence could be drawn from this up-to-date meta-analysis to provide for the health professionals and researchers. Therefore, due to the ambiguity in this relationship, this study aimed to explore the association between serum vitamin D levels and hip fractures in the elderly using a systematic review and meta-analysis approach.

Materials and methods

Data sources and search strategy

This meta-analysis was performed following PRISMA guidelines (http://prisma-statement.org/prismastatement/Checklist.aspx). An extensive systematic review was undertaken on 8/8/2021 utilizing PubMed, Web of Science (ISI), and Scopus databases. The following main and MeSH keywords were used in the search: ((“serum 25-hydroxyvitamin D” OR “serum 25(OH)D” OR “serum vitamin D”) AND (hip fracture*) AND (“elderly” OR “age” OR “senile”)).

Study selection

The peer-reviewed publications were imported into EndNote X8 (8 November 2016, Thomson Reuters), where the software was used to identified and remove duplications. Two researchers independently evaluated the title and abstract of the studies based on the defined inclusion and exclusion criteria. To meet inclusion criteria, the studies had to have investigated the association between serum vitamin D levels and hip fractures. Exclusion criteria were applied when there was no full text of the publication available, and the study was in a non-English language. The study was excluded from being reviewed when it included those less than 60 years of age, involved supplementation with vitamin D, the study population had disabilities or mal-absorption disease, and bone diseases that could impact the final study outcome. The full text of all publications with studies identified as matching the criteria was independently reviewed. If there were any disagreements upon review, a consensus was achieved through discussion with a third team member. A flowchart of the search strategy is illustrated in Fig. 1.

Data extraction and quality assessment

Data were extracted independently by three individuals, and inconsistencies were resolved through discussion. For included studies, the following information was extracted: the first author's name, year of publication, country of study, sample size, age of study population, and duration of follow-up. Statistical information, including odds ratio (OR) or risk ratio (RR) or Hazard Ratio (HR) with 95% confidence interval (CI) of hip fracture in lowest vs. highest categories of vitamin D in the elderly.

A quality assessment scale, the Newcastle–Ottawa Scale (NOS), was utilized to assess the quality of non-randomized studies. Using the NOS, each study with a score range of 0–9 was assessed. Articles with a score range of 0–9 and articles with a score of 6 ≤ were considered to be low risk of bias or high-quality studies [29, 30].

Statistical analysis

For the meta-analysis, the odds ratio (OR) was used to assess the relationship of hip fracture with serum vitamin D levels. The effect size of the relationship between serum vitamin D levels and hip fracture was reported by OR with

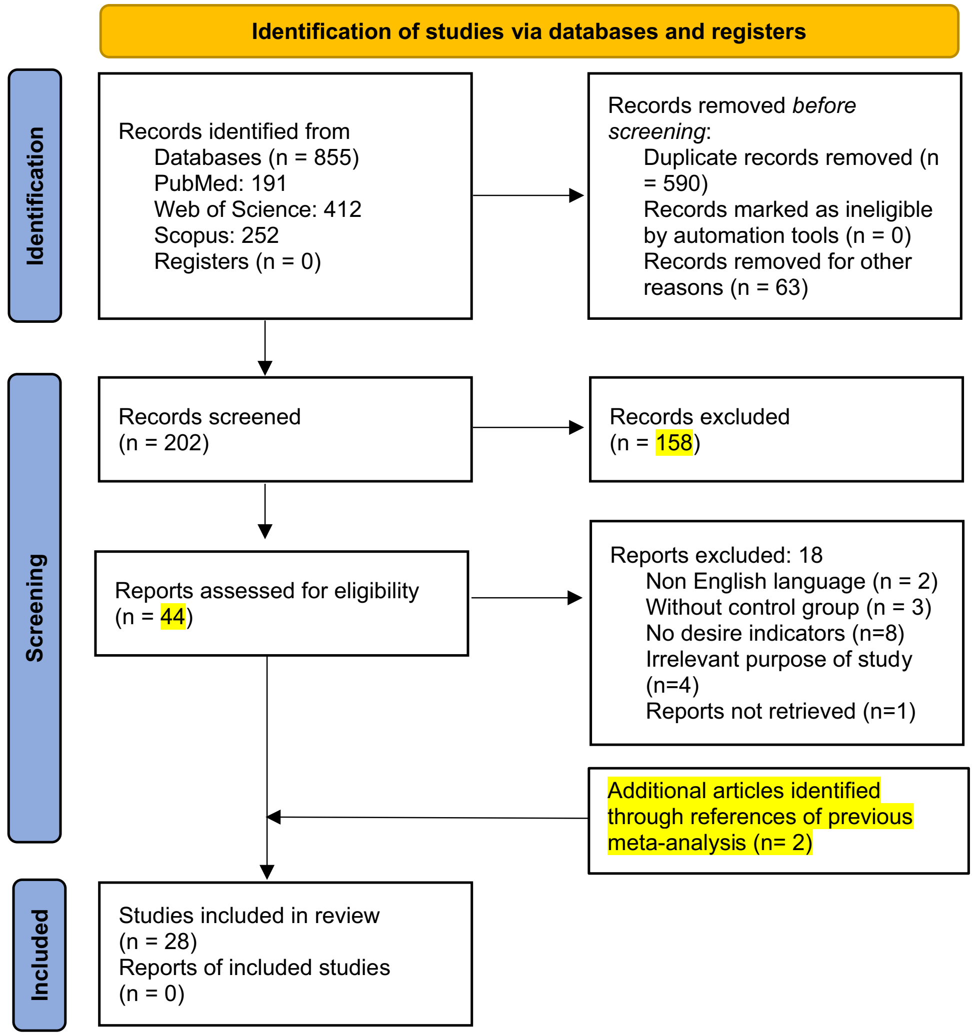

Fig. 1 Flowchart of selection studies for inclusion in the meta-analysis

a 95% confidence interval (CI). The method of random-effects models of the meta-analysis was used to calculate the overall summary estimates. Graphically, the illustration of the individual OR and summary estimates was done in the form of forest plots. Based on a priori decisions, subgroup analyses were conducted according to the geographical location (Europe, America, Asia, and Australia), study quality (low vs. high quality), the sample size for study ($^{>}$ 1000 vs. ≤ 1000), and type of study (case–control, case–cohort and cohort), gender (male, female and both), study period (1998–2010 and 2011–2021), and the follow-up period (> 5 years or ≤ 5 years). To reveal more clearly the sources of statistical heterogeneity between studies, as well as to evaluate the robustness of the findings, a series of sensitivity analyses were performed. First, we aimed to examine the effect of individual studies on the summary estimates, for which influence analyses were conducted where the pooled estimates were recalculated by omitting one study at a time. Second, a meta-regression analysis was conducted to identify the source of differences in the observed effect size between studies.

Heterogeneity among studies was tested by Cochran's Q test (reported with a χ^2 value and P value, with $P<0.1$ considered as the significance level) and the I^2 statistics. I^2 with values of 25%, 50%, and 75% demonstrated low, moderate, and high levels of heterogeneity, respectively. Publication bias was assessed using Begg's and Egger's tests. Metatarium command was used to estimate the effect size of relation in the missing studies. All statistical analyses were performed using Stata 14.0 software (Stata LLC, College Station, TX, USA). $P<0.05$ was considered as the level of significance.

Results

Search results, study characteristics of selected studies

The PRISMA statement flowchart of the search strategy is illustrated in Fig. 1. The initial electronic search retrieved 855 titles/abstracts. Omission of duplicate publications was 590 excluded and 63 removed for other reasons, leaving 202 titles/abstracts to be screened. After reviewing the remaining titles and abstracts, 158 articles unrelated to this study focus were excluded, leaving 44 to be retrieved for more in-depth screening. Additional titles/abstracts were excluded ($n = 18$); two because the publication was not available in English [31, 32], one as there was no full text available [33], four that were not related to the rationale of this study [34–37], three not undertaken in people with hip fractures (and did not include a control group) [38–40] and eight which had not calculated the desired indicators [15, 41–47]. Finally, 26 articles were selected for the final assessment of the association between serum vitamin D levels and the risk of hip fractures in the current systematic review and meta-analysis, and 2 other additional records were found through searching in previous meta-analyses [14, 48–74].

Characteristics of selected studies regarding the association between serum vitamin D levels and the risk of hip fractures

The 28 studies that were reviewed included 61,744 participants who met the inclusion criteria. There were 9767 (15.81%) cases that reported hip fractures [14, 48–74]. Among the studies included, four used a case–cohort design with a sample size of 5492 participants and 1631 (29.69%) cases of hip fracture [48–51], fifteen were cohort studies, with a sample size of 49,860 participants and 6617 (13.27%) cases of hip fracture [52–66], and nine studies used a case–control design with a sample size of 6392 participants and 1519 (23.76%) cases of hip fracture [14, 67–74] (Tables 1–3).

The articles selected for this systematic review and meta-analysis were published between 1998 and 2020. The studies were geographically diverse, with eleven conducted in the North America [48, 50–53, 56–58, 61, 70], six in Europe [49, 60, 62–65], seven in Asia [55, 59, 68, 69, 71, 73, 74], three in Australia [54, 66, 67], one in Brazil [14] and finally, one undertaken in Canada [72]. The mean follow-up of the participant's period was 69.64 months (Tables 1–3).

Relationship between serum vitamin D levels and hip fractures

Considering the adjusted odds ratios (OR) (Table 2) from each study in the meta-analysis, it is observed that compared to the group with high levels of serum vitamin D, the OR of hip fractures in the elderly with low levels is equal to 1.80 (95% CI 1.56–2.07, $P \le 0.001$) (Fig. 2).

There was significant heterogeneity identified within the results during the meta-analysis ($chi^2 = 86.64$, df = 27, $P \le 0.001$, $I^2 = 68.8\%$). A meta-regression was performed and included assessing the following variables: year, follow-up term, study type/design, gender, sample size, quality of study based on the Newcastle–Ottawa Scale (NOS), study period, and geographical location. The results from the meta-regression analysis determined there was no significant source of heterogeneity ($P > 0.10$). Also, sensitivity analysis was performed by excluding each study from the analysis one by one during each run. However, the estimated OR did not change significantly, further indicating the robustness of the meta-analysis results.

Evaluation of publication bias related to serum vitamin D levels and hip fractures

Evidence of publication bias was suspected upon examining the reported association between serum vitamin D levels and hip fracture. To investigate this, statistical tests were undertaken to evaluate potential publication bias in the reported studies; Egger's test (p value = 0.001) and Begg's test (p value = 0.009) produced statistically significant results. Therefore, published studies on the relationship between serum vitamin D levels and hip fracture are significantly associated with publication bias, which can affect the final results of the meta-analysis [75, 76].

Estimation of the relationship between serum vitamin D levels and hip fractures by considering the estimated effect size from missing studies

We tried to estimate the effect size for potentially missing studies within this meta-analysis, as depicted in Fig. 3, it was estimated that ten studies were missing. Hence, the analysis performed for this study incorporated and considered the estimated values for those potentially ten missing studies. Integrating the estimates OR from the ten missing studies into the analysis, the OR of the relationship between serum vitamin D levels and hip fracture occurrence was equal to 1.40 (95% CI 1.20–1.63 $P \le 0.001$).

Table 1 Characteristics of included studies for reviewing the relationship between serum vitamin D levels and the risk of hip fractures in the elderly

Publication lead author	Year	Study setting	Study design	Fracture ascertainment	25(OH) vitamin D(Reference value)	Sample size	N of Hip fractures	*RR	95% CI	Study period	Follow-up (months)	NOS
Diamond [67]	1998	Australia	Case–control	Verified medical and radiological records	˃50 nmol	123	41	3.90	(1.71, 8.91)	1997	12	8
Cummings [52]	1998	USA	Cohort	Verified radiological records	˃ 19 ng/mL	878	133	2.10	(1.22, 3.63)	1986–8	24	7
Sakuma [69]	2006	Japan	Case–control	Verified radiological records	˃ 20 ng/ml	85	85	7.01	(2.56, 19.23)	2004	12	7
Bakhtiyarova [68]	2006	Russia	Case–control	Verified radiological records	˃ 20 ng/ml	164	64	2.06	(1.00, 4.24)	2002–3	12	6
Cauley [70]	2008	USA	Nested case–control	Verified radiological records	˃ 20 ng/ml	800	400	1.33	(1.05, 1.68)	2004	85	9
Looker [53]	2008	USA	Cohort	Verified medical and radiological records	˃ 30 ng/mL Per SD decrease	1917	156	2.40	(1.55, 3.71)	1988–94	79	7
Bolland [54]	2009	New Zealand	Cohort	Verified medical and radiological records	˃ 50 nmol/L	1471	22	1.00	(0.40, 2.50)	1998–2003	60	7
Cauley [48]	2010	USA	Case–cohort	Verified medical records	˃ 20 ng/mL	1929	81	2.36	(1.06, 5.24)	2000–2	63	8
Nakano [71]	2011	Japan	Case–control	Verified medical records	˃ 10 ng/mL	147	99	4.07	(1.46, 11.35)	2010	6	6
Chan [55]	2011	China	Cohort	Verified medical records	˃ 25 ng/mL	712	24	1.58	(0.34, 7.38)	2001–3	48	8
Robinson [56]	2011	USA	Cohort	Verified medical records	˃ 15 ng/mL	2249	242	1.61	(1.11, 2.33)	1989–2009	156	8
Rouzi [59]	2012	Saudi Arabia	Cohort	Verified medical records	˃ 18 nmol/L	707	62	1.63	(1.05, 2.53)	2004–10	62	7
de Boer [58]	2012	USA	Cohort	Verified radiological records	˃ 20 ng/ml	1621	17	1.34	(0.97, 1.86)	1992–2006	132	7
Barbour [57]	2012	USA	Cohort	Verified radiological records	˃ 18 ng/mL	2614	84	1.73	(0.79, 3.81)	1997–9	24	9
Holvik [49]	2013	Norway	Case–cohort	Verified medical and radiological records	˃ 17 ng/mL	2526	1162	1.34	(1.05, 1.70)	1994–2001	127	8
De Koning [72]	2013	Canada	Case–control	Verified medical and radiological records	˃ 70 nmol/L	2656	254	1.12	(0.93, 1.35)	2007–11	55	6
Kauppi [60]	2013	Finland	Cohort	Identified National Hospital Discharge Register	Per SD decrease	3305	95	1.67	(1.16, 2.40)	2000–1	12	6
Looker [61]	2013	USA	Cohort	Verified medical and radiological records	˃ 30 ng/mL	4749	287	2.63	(1.58, 4.37)	2000–4	48	7
Bunchebner [62]	2014	Sweden	Cohort	Verified medical and radiological records	˃ 20 ng/mL	1044	130	2.70	(1.37, 5.33)	1995–9	157	8
Steingrimsdottir [64]	2014	Iceland	Cohort	Verified medical and radiological records	˃ 20 ng/mL	5471	261	2.24	(1.62, 3.10)	2002–6	64	8
Snellman [63]	2014	Sweden	Cohort	Verified medical and radiological records	˃ 10 μg/d	61 433	3871	1.27	(1.02, 1.57)	1990–2009	228	9

Table 1 (continued)

Publication lead author	Year	Study setting	Study design	Fracture ascertainment	25(OH) vitamin D(Reference value)	Sample size	N of Hip fractures	*RR	95% CI	Study period	Follow-up (months)	NOS
Fu [73]	2015	China	Case–control	Verified medical and radiological records	˃ 50 nmol/L	698	349	3.02	(2.12, 4.30)	2012–14	23	7
Swanson [50]	2015	USA	Case–cohort	Verified radiological records	˃ 51.60 pg/mL	1000	81	1.99	(1.18, 3.36)	2000–2	23	7
Guerra [14]	2016	Brazil	Case–control	Verified radiological records	˃ 30 ng/mL	341	110	2.76	(1.66, 4.58)	2013–15	28	6
Finnes [65]	2016	Norway	Cohort	Verified radiological records	˃ 50 nmol/l	21,774	1090	1.09	(0.83, 1.42)	1994–2001	84	8
Ginsberg [51]	2018	USA	Case–cohort	Verified radiological records	˃ 20 ng/mL	890	289	1.37	(1.14, 1.64)	1989–2006	100	8
Zhu [66]	2019	Australia	Cohort	Verified radiological records	˃ 50 nmol/L	1348	143	1.67	(1.10, 2,54)	1998–2013	173	8
[74]Zhuang	2020	China	Retrospective	Verified medical and radiological records	˃ 30 ng/mL	525	135	4.46	(1.55, 12.85)	2015–18	41	6

*Adjusted RR (The adjusted variables in each study can be seen in Table 2)

Subgroup analysis

A subgroup analysis was performed to determine the association between serum vitamin D levels and hip fractures based on study design, gender, sample size, follow-up period, study period, NOS score, and geographical location. The OR of hip fractures in those with a low serum vitamin D level was (OR = 2.16, 95% CI 1.49–3.11, $P \leq 0.001$) in case–control studies; it was (OR = 1.52, 95% CI 1.29–1.79, $P \leq 0.001$) in cohort studies; and (OR = 1.41, 95% CI = 1.18–1.70, $P \leq 0.001$) in case–cohort. The results of subgroup analysis for geographical location, gender, study period, article quality according to Newcastle–Ottawa Scale (NOS) score, sample size, and length of follow-up period are observable in Table 3.

Discussion

This study used systematic and meta-analysis review methodology to investigate a potential association between 25(OH)D levels and the risk of hip fracture in the elderly. This in-depth analysis concluded that serum vitamin D levels were associated with the risk of hip fractures. Therefore, the risk of hip fracture is higher in the elderly when they have insufficient or low levels of serum 25(OH)D levels (OR = 1.80, 95% CI 1.56–2.07, $P \leq 0.001$). Also, Modified OR (considering the effect size for missing studies) of the relationship between serum vitamin D levels and hip fracture occurrence was equal to 1.40 (95% CI 1.20–1.63 $P \leq 0.001$). In line with the results of the present study, Feng et al. showed that low serum 25(OH) vitamin D level was significantly associated with the increased risk of hip fractures (RR 1.48, 95% CI 1.29–1.68). For each SD decrease in serum 25(OH) vitamin D level (RR 1.40, 95% CI 1.20–1.61; $I^2 = 0\%$, p for heterogeneity = 0.51), there was seen an increase by 40% in the hip fracture risk [25]. In Feng et al. study, which was conducted in 2017, 19 records were included. But in the present meta-analysis, 28 articles were analyzed and similar results were obtained in both our study and Feng et al. study [25]. In a study conducted by Lv et al., in a systematic review and meta-analysis, it was stated that the relative risk (RR) of the lowest vs. the highest categories indicated that lower levels of serum 25OHD were more likely to be a risk factor for hip fracture with RR equal to 1.58 (95% CI 1.41–1.77) [77]. The results of this study are somewhat similar to the results of our study because in our study the estimated odds ratio of hip fractures is equal to 1.80 (95% CI 1.56–2.07). However, when the effect size in missing studies is estimated and entered into the analysis, it is observed that the numerical value of the calculated effect size decreased. In our study, after considering the effect size of the missing studies, the calculated odds ratio is equal to

Table 2 Adjusted variables in assessment relationship between serum vitamin D levels and the risk of hip fractures in the elderly

Publication lead author	Year	Adjusted variables
Diamond [67]	1998	Age, body weight, comorbid illnesses, alcohol intake, cigarettes smoked, and corticosteroid use
Sakuma [69]	2006	–
Bakhtiyarova [68]	2006	–
Cauley [70]	2008	Age, body mass index, parental history of hip fracture, history of fracture, smoking, alcohol use, and total calcium intake, oral corticosteroid use, and geographic region
Looker [53]	2008	Age, sex, femoral neck BMD, BMI, previous fracture, dietary calcium, kilocalories, and weight loss from maximum
Bolland [54]	2009	Treatment allocation (calcium or placebo) and baseline age, body weight, and smoking status
Cauley [48]	2010	Age, race, clinic, the season of blood draw, physical activity, weight, and height
Nakano [71]	2011	Sex, circulating concentrations of albumin, hemoglobin, 25OH-D, PK, and MK7
Chan [55]	2011	Age, BMI, education, PASE, DQI, smoking status, and alcohol use
Robinson [56]	2011	Age, race, sex, clinic site, season, education, smoking status (never smoker, former smoker, or current smoker), alcohol use (any vs. none), diabetes status (normal, impaired fasting glucose, or diabetes), body mass index, self-reported health status, physical activity level, oral steroid use, estrogen use, thiamine and loop diuretic use, serum cystatin C level, and calcium supplement use
Rouzi [59]	2012	–
de Boer [58]	2012	Age, sex, clinical site, smoking, body mass index, and physical activity
Barbour [57]	2012	Age, gender, race, education level, the season of blood draw, BMI, current drinking, fracture after age 45, and clinical comorbidity index
Cummings [52]	1998	Age and weight
Holvik [49]	2013	Age, gender, study center, BMI, and month of blood sample
De Koning [72]	2013	Sex and age
Kauppi [60]	2013	Gender, age, height, weight, BMI, QU, alcohol consumption, smoking, and PA
Looker [61]	2013	Age, sex, race/ethnicity, and survey
Bunchebner [62]	2014	Smoking, bisphosphonate use, and physical activity level
Steingrimsdottir [64]	2014	Age, sex, body mass index, height, smoking, alcohol intake and season, physical activity
Snellman [63]	2014	Age, weight, height, and season
Fu [73]	2015	Age, inadequate sun exposure, history of falls during the last year, neurologic impairment, cognitive impairment, and serum levels of Hs-CRP, ALP, and iPTH
Swanson [50]	2015	–
Guerra [14]	2016	Sex, age, and ethnicity
Finnes [65]	2016	Age, sex, study site, BMI, smoking, triglycerides, and α-tocopherol
Ginsberg [51]	2018	Age, sex, race, the season of measurements, site of measurement and BMI, eGFR, serum calcium, phosphate, and FGF-23
Zhu [66]	2019	Season of blood sampling to baseline age and BMI, treatment group during the intervention phase, and fracture history
Zhuang [74]	2020	Age, serum 25OHD levels, one mineral density, and BMI

1.40 (95% CI 1.20–1.63). Therefore, we think that in the systematic review and meta-analysis study that conducted by Lv et al., due to publication bias, most studies have been considered that the results of which confirm the increased risk of hip fractures due to deficiency in serum levels of vitamin D, and finally the result obtained in this meta-analysis is overestimated [77].

In another systematic review and meta-analysis study conducted by Lai et al., the RR of hip fractures was equal to 1.13[95% CI 0.98–1.29] based on seven eligible randomized controlled trials (RCT) studies [27]. Although this study confirms the increased relative risk of hip fractures in individuals receiving lower doses of vitamin D, it is not statistically significant. It seems that the smaller sample size of the studies considered in this meta-analysis has negative effects on its results, because often in clinical trial studies the number of subjects and their follow-up time is limited, although the results of these studies have more credibility. In addition, in another systematic review and meta-analysis study conducted with Wang et al., the study was performed using reported serum 25(OH)D levels from 3237 patients who were > 60 years of age and had experienced a hip fracture. The study showed that low serum 25(OH) D levels increase the risk of hip fracture when compared to those who have high serum 25(OH)D levels 1.12 (95% CI 1.02–1.25) after adjustments [78]. As can be seen, different

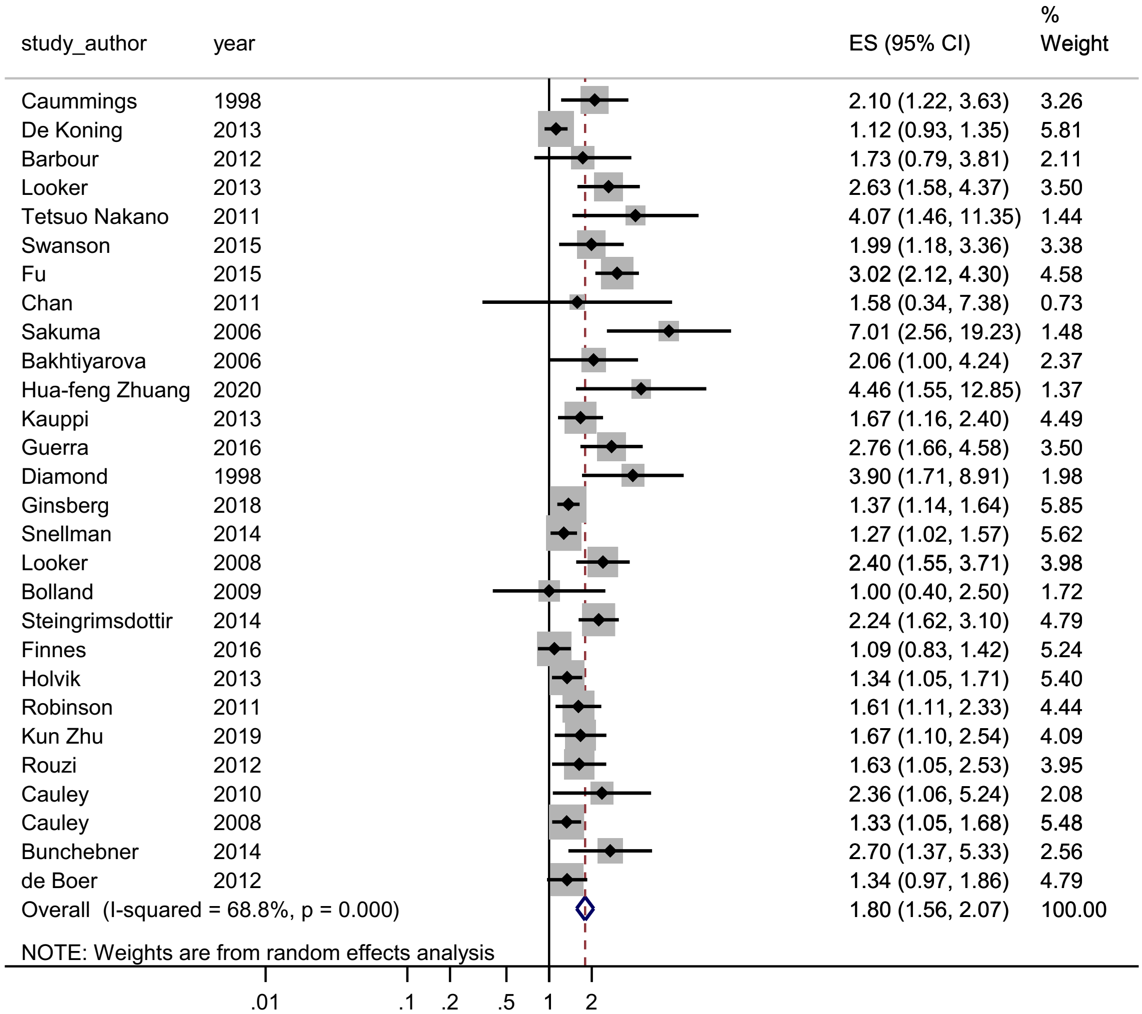

Fig. 2 Overall analysis of serum vitamin D levels and the risk of hip fractures

Fig. 3 Estimation of the amount of effect size in the missing studies

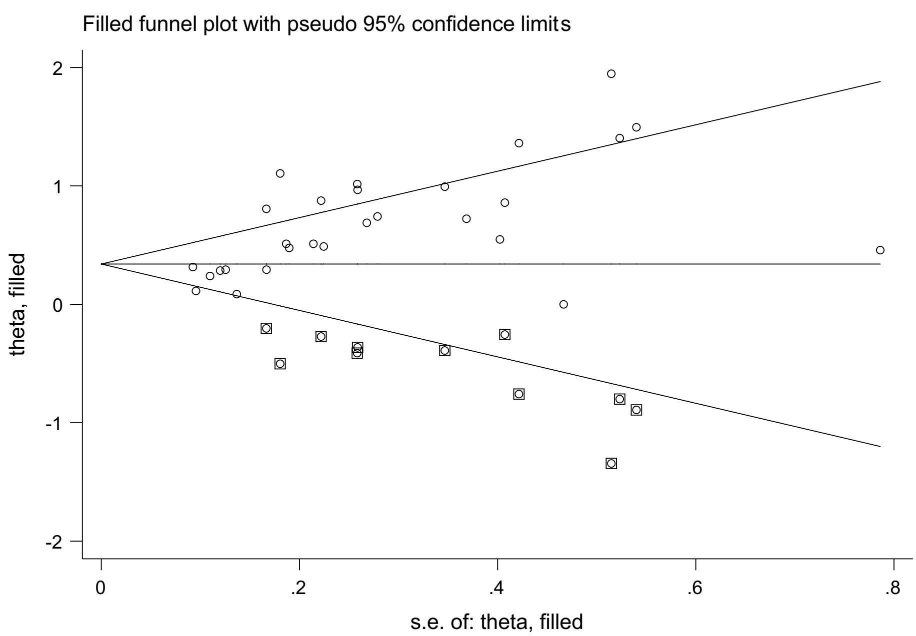

Table 3 Subgroup analysis of the association between serum vitamin D levels and the risk of hip fractures in the elderly

Characteristics		Study no	OR (95% CI)	*P* value
Study type	Case–cohort	4	1.41(1.18–1.70)	≤0.001
	Cohort	15	1.52(1.29–1.79)	≤0.001
	Case–control	9	2.16(1.49–3.11)	≤0.001
Study location	North America	11	1.59(1.35–1.88)	≤0.001
	Europe	6	1.44(1.14–1.82)	≤0.001
	Asia	7	2.76(1.89–4.02)	≤0.001
	Australia and New Zealand	3	1.86(0.97–3.56)	0.059
	Brazil	1	2.76(1.68–4.53)	≤0.001
Gender	Male	4	2.34(1.60–3.41)	≤0.001
	Female	9	1.87(1.45–2.40)	≤0.001
	Both	15	1.31(1.01–1.62)	≤0.001
Study period	1980–2009	7	1.34(1.13–1.58)	≤0.001
	2010–2021	21	2.16(1.45–3.22)	≤0.001
Follow-up period	less than five years	14	2.17(1.63–2.89)	≤0.001
	More than five years	14	1.41(1.23–1.62)	≤0.001
Newcastle–Ottawa scale	Good	14	1.86(1.44–2.40)	≤0.001
	Excellent	14	1.34(1.14–1.57)	≤0.001
Sample size	>1000	13	1.98(1.54–2.54)	≤0.001
	≤1000	15	1.41(1.20–1.65)	≤0.001

studies show different effect sizes of low serum levels of vitamin D on hip fractures, which seems to be one of the most important reasons for this difference in addition to the age groups studied in each meta-analysis, is lack of considering the effect of publication bias on the results.

Previous meta-analyses conducted in this regard have assessed the effect of vitamin D supplementation in conjunction with hip fractures. However, there has been no consensus reached, and different results have been reported. For instance, Bischoff-Ferrari et al. [79] suggested that the effect was positive on hip and any non-vertebral fractures. In contrast, Lai et al. reported that varying doses of vitamin D supplementation were effective in preventing a hip fracture [27]. Another meta-analysis indicated that vitamin D supplementation in the elderly had no effect on hip bone mineral density (BMD) and that its effect on femur BMD was low [80]. These discrepancies in study results may be caused by differences in the methods of studies undertaken, varying characteristics in bone compartments (cortical or trabecular-rich sites), and other potentially confounding factors. The hip bone is considered a cortical site and is generally less responsive to vitamin supplementation than other trabecular-rich sites (e.g., pelvis, femoral neck, and calcaneus) [80–83]. These already established associations support the need for more studies to determine the interaction or synergistic effects of micronutrients on the proper mineralization of bone for optimal skeletal health.

Consequently, it seems that normal serum 25(OH)D levels can benefit bone health when considering its interaction with other biochemical factors, which provide a protective effect against bone fractures. It has been established that minerals including calcium, phosphorus, fluoride, magnesium, copper, iron, selenium, zinc, manganese, sodium, potassium, and vitamins including D, A, K, C, B6, B12, in addition to folate, play a crucial role in bone health [84–88].

Compared to previously published studies, this study calculated that the OR of hip fractures was different based on geographical locations. The rationale for this is that lifestyle, diet, and race can affect vitamin D levels and, therefore, the risk of hip fractures. Muñoz-Garach et al. reported that 80–90% of vitamin D is supplied from cutaneous synthesis from exposure to sunlight, while the remaining 10–20% is obtained from a limited number of foods, such as fortified foods, oily fish, and mushrooms [85]. Therefore, the geographical region and consequently vitamin D serum levels are affected by sunlight, culture, and diet. These already established associations support the need for more studies to determine the interaction or synergistic effects of micronutrients on the proper mineralization of bone for optimal skeletal health. Additionally, encouraging the development of education programs that could inform the elderly regarding the need to monitor and increase vitamin D levels could improve health outcomes.

This systematic and meta-analysis study involved a comprehensive and complete search of the articles related to the topic. Statistical tools were used to estimate the effect size of missing studies and assess the influence of subgroups on the strengths of the reviewed article. In addition, one of the most important strengths of this study is the calculation of the modified OR by estimating the effect size of missing studies (due to diffusion bias), so it seems that considering the impact of missing studies, the estimated OR is more reliable. The inclusion of only English-language articles is a potential limitation of this study. In addition, lack of access to some databases such as EMBASE and Cochrane was another limitation of this study. Because in the analysis of subgroups, the results of the study are presented specifically for specific geographical areas, we must be careful about generalizing the results, especially in areas where the number of studies included in the meta-analysis (Brazil, Australia and, New Zealand) is small. Also, although this systematic review and meta-analysis study specifically assessed the association between serum vitamin D levels and hip fractures in the elderly, the results of it can be attributed to other age groups, but it is better to do similar studies in the desired age groups. The development of low serum 25(OH)D levels, especially in the elderly, significantly increases the risk of a hip fracture being incurred. Vitamin D deficiency is a significant health issue given that it increases the risk of osteoporosis, hip fracture and causes other health complications that have a significant impact on the quality of life. The conclusions from this study support encouraging the monitoring of serum 25(OH)D levels at appropriate intervals during age progression to reduce the risk of hip fractures in the elderly.

Declarations

Conflict of interest We declare that we have no conflict of interest.

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