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The antifracture efficacy of vitamin D in adults — are we assessing it reliably? A systematic review

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Abstract

Introduction: The antifracture efficacy of vitamin D is still controversial. The aim of this systematic review was to examine if the vitamin D trials were designed adequately to reliably assess its antifracture activity.

Material and methods: The electronic databases PubMed, Medline, Embase, Web of Science, and Cochrane Library were searched to identify clinical trials evaluating the antifracture efficacy of vitamin D in adults. We compared the protocols of the trials against the opinions of the American Society for Bone and Mineral Research (ASBMR), International Society for Clinical Densitometry (ISCD), National Osteoporosis Foundation (NOF), European Medicines Agency (EMA) experts, and the consensus statement from the 2nd International Conference on Controversies in Vitamin D, and against the protocols of the trials of the medications with proven antifracture efficacy (bisphosphonates, teriparatide, abaloparatide, raloxifene, denosumab, romosozumab). We assessed the prospective character, study design, group description, number of patients, study duration, and vitamin D (serum examination and dosage) supplementation. A description of the desired characteristics of the study protocol was presented.

Results: Thirteen eligible trials were identified. All but 2 were conducted in the elderly population only. Nine trials were included in the final analysis. Serum 25 hydroxy vitamin D (25OHD) was not measured in a representative number of subjects before (except in 2 studies), during, or after treatment in any study.

Conclusions: The analysed studies did not conclusively assess the vitamin D antifracture efficacy in patients with prestudy low serum vitamin levels, due to the lack of assessment of whether sufficient doses of vitamin D were used. They informed about the relevant doses and preparations of vitamin D in particular groups (specific fracture risk, age, place of residence) only. (*Endokrynol Pol* 2023; 74 (5): 499–510)

Key words: bone; fracture; osteoporosis; systematic review; vitamin D

Introduction

Vitamin D is commonly used in patients with osteoporosis. The question of whether vitamin D is effective in preventing osteoporotic bone fractures remains unanswered. Some of the clinical trials confirm its antifracture efficacy [1, 2], while others do not support this [3, 4]. Similar inconsistency is shown in meta-analyses and systematic reviews with positive [5, 6] or negative [7, 8] opinions. The latest statement from the 2nd International Conference on Controversies in Vitamin D [9] concludes that vitamin D supplementation with adequate calcium intake can decrease the incidence of fractures in elderly, vitamin D deficient subjects, but it is unclear if it also applies to mobile subjects. Therefore, there is no unanimous guidance for those who treat osteoporosis.

This prompts the question of why the antifracture efficacy of vitamin D has not been clearly shown, despite several clinical trials and meta-analyses or systematic reviews. The aim of the current systematic review of the literature is to answer the question of whether

the vitamin D studies were carried out under conditions that offered a chance to demonstrate its antifracture activity in adults. We compared their protocols with the American [10] and European experts' opinions [11], the data from the 2nd International Conference on Controversies in Vitamin D [9], and with the trial protocols of several antifracture medications with subsequently proven antifracture efficacy, further referred to as the "reference trials".

Material and methods

Search strategy and selection criteria

The electronic databases PubMed, Medline, Embase, Web of Science, and Cochrane Database of Systemic Reviews were searched for meta-analyses and systematic reviews of the prospective trials that assessed the efficacy of vitamin D in reducing the risk of low-energy bone fracture in adults as the primary or secondary outcome. The search encompassed the period from the inception of the databases to the end of 2022. The following keywords were used: "vitamin D", "vitamin D₃", "vitamin D₂", "cholecalciferol", "ergocalciferol", and "fracture", each in conjunction with the terms "meta-analysis" and "systematic review". No language restrictions were applied. To avoid missing the latest trials, for



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the last period (2019 to the end of 2022) screening with the use of the following keywords “vitamin D”, “vitamin D₃”, “vitamin D₂”, “cholecalciferol”, “ergocalciferol”, and “fracture” for the eligible vitamin D trials was performed. Duplicate articles and conference abstracts were excluded. The title, abstract, and full text screening was performed independently by 2 reviewers. Any disagreements between the reviewers were resolved through discussion until a consensus was reached. The systematic review was registered in PROSPERO (CRD42020211195). The manuscript was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline [12].

Inclusion and exclusion criteria

The main inclusion criteria were the prospective trial design and subjects’ adult age. The following exclusion criteria we applied: concurrent assessment of other medications with proven antifracture efficacy (e.g. bisphosphonates) or non-pharmacological interventions, age below 18 years, use of steroids, and the presence of secondary osteoporosis or chronic kidney disease.

Data extraction

The following data were extracted: publication year, sample size, characteristics of population (age, sex, place of living, fracture risk), duration of intervention, study design (double-blind placebo-controlled, noninferiority active-comparator studies, or other), antifracture aim, and study outcome.

Data analysis

There is not a single widely accepted reference protocol for the conduction of antifracture studies; therefore, our criteria of eligibility were based on the consensus of the American specialist groups, i.e. the American Society for Bone and Mineral Research (ASBMR), International Society for Clinical Densitometry (ISCD), National Osteoporosis Foundation (NOF) [10], the guideline of European Medicines Agency (EMA) [11], the 2nd International Conference on Controversies in Vitamin D [9], and the characteristics of the studies (phase III) of medications with proven antifracture efficacy (bisphosphonates, raloxifene, teriparatide, abaloparatide, denosumab, and romosozumab) [13–24]. The accordance of the protocols of vitamin D trials with the created reference protocol was examined. The following characteristics of the study protocols were assessed:

- clearly defined characteristics of the patient groups;
- the number of patients enrolled in the study;
- clear aim and outcome of the study;
- study duration;
- study design;
- dose and preparation of vitamin D.

The optimal characteristics of the study protocols

The data from the antifracture medications’ trials, which served to identify the optimal protocol, are presented in Table 1.

We considered the following characteristics as desirable:

1. Clear inclusion and exclusion criteria of the antifracture medication trials:

Inclusion criteria: specified age, gender, and defined fracture risk on the basis of previous bone fractures and dual-energy X-ray absorptiometry (DXA) results. The assessment of the fracture risk will be performed on the basis of these criteria.

Exclusion criteria: previous or current use of medications with known antifracture efficacy or affecting bone metabolism, hypercalcaemia, presence of neoplasms, and contraindications to calcium and vitamin D treatment.

2. Calculation of the number of patients sufficient to demonstrate specific reduction in the number of fractures [25]. When calculation was not performed, the value of 1226 patients as in the risedronate study [24], which has the lowest number of patients among the reference trials, served as the lower limit value.

3. Clear statement on the reduction in frequency of spinal and/or non-spinal fractures (hip and major nonvertebral fractures) as the primary or secondary aim.

4. Optimal minimal study duration of 1.5 years based on the experts’ conclusion for the efficacy trials [10].

5. A double-blind, placebo-controlled design, as in all studies with antifracture medications, and as proposed by the experts’ boards [9–11], or noninferiority active-comparator trials.

6. The measurement of serum 25-hydroxy vitamin D (25OHD) concentration before, during, and/or after observation, performed at least in subgroups of patients.

The optimal dose of vitamin D in the treatment of osteoporosis is calculated on the basis of its serum concentration considered as sufficient [26]. We calculated the required number of patients who would need to have vitamin D levels measured to be representative of the whole study sample with the use of the calculator available online (www.checkmarket.com/sample-size-calculator). Next, we compared these numbers to the actual number of 25OHD measurements in each study.

The analysis of the quality of vitamin D antifracture efficacy trials was performed in two stages. In the first stage we selected the studies that met criteria numbers 2–6. In the second stage, the studies that fulfilled these criteria were further descriptively analysed with the focus on the patients’ characteristics with regards to their fracture risk (criterion 1) and the assessment of the optimal vitamin D dose was given.

Results

The number of screened studies (meta-analyses, systematic reviews, and clinical trials) is presented in a flow diagram (Fig. 1, PRISMA flowchart). There were 34 meta-analyses/systematic reviews [5–8, 27–56], which included 19 eligible trials. With one trial [3] found in an additional search, there were a total of 20 clinical trials [1–4, 57–72] eligible for analysis based on the inclusion and exclusion criteria (criterion 2–6). Detailed information on the fulfilment of the individual criteria is presented in Figure 2 (first stage analysis).

In 9 out of 20 studies [1, 4, 61, 64, 66, 67, 70–72] the authors calculated the optimal number of participants on the basis of the power calculation (usually 80%) and the level of significance (5%), to demonstrate the specific reduction in the number of fractures. Because the final number of enrolled patients in one study [67] was lower than it was set out to be, we accepted 8 [1, 4, 61, 64, 66, 70–72] out of these 9 trials. There were 5 further trials [2, 3, 63, 65, 69] in which the sample calculation was not performed; however, the number of participants exceeded 1226 (our minimal accepted number). In total, there were 13 trials eligible for further analysis [1–4, 61, 63–66, 69–72]. The characteristics of the patients of these 13 clinical trials are presented in Table 2 and Table 3. In the other 7 trials not included in the analysis [57–60, 62, 67, 68], the number of subjects was between 232 and 1144, with a median of 610 subjects.

In all 13 studies further analysed, their aims and outcomes were clearly described. They all clearly answered

Table 1. Characteristics of the trials of medications with proven antifracture efficacy in postmenopausal osteoporosis (presented by ascending year of publication)

Study medication/Acronym, Year of publication	Patients enrolled [N]	Sex [W/M]	Age [Years]	Study duration [Years]	Double-blind placebo [Yes/No]	Previous fracture as an inclusion criterion [Yes/No]	Supplementation with:	
							Vitamin D [IU/day]	Calcium [mg/day]
Alendronate/FIT1, 1996 [13]	2027	W	55–81; at least 2 yrs since menopause	3	Yes	Yes: vertebral	500	1000
Alendronate/FIT, 1998 [18]	4432	W	55–80; at least 2 yrs since menopause	4	Yes	No: not allowed	500	1000
Raloxifene/MORE, 1999 [20]	7705	W	31–80; at least 2 yrs since menopause	3	Yes	No**	400–600	500
Risedronate/VERT-NA, 1999 [21]	2458	W	5 yrs since menopause — 85	3	Yes	Yes: vertebral	≤ 500 if 25(OH)D < 16 ng/mL	1000
Risedronate/VERT-MN, 2000 [24]	1226	W	5 yrs since menopause — 85	3	Yes	Yes: vertebral	≤ 500 if 25(OH)D < 16 ng/mL	1000
Risedronate/HIP, 2001 [16]	9331	W	70–79 and > 80	3	Yes	Not	≤ 500 if 25(OH)D < 16 ng/mL	1000
Teriparatide (1–34), 2001 [23]	1637	W	5 yrs since menopause	Median: 21 mths	Yes	Yes: vertebral	400–1200	1000
Ibandronate/BONE, 2004 [15]	2946	W	55–80; at least 5 yrs since menopause	3	Yes	Yes: vertebral	400	500
Zoledronic acid/HORIZON, 2007 [14]	7736	W	65–89	3	Yes	No**	400–1200	1000–1500
Denosumab/FREEDOM, 2009 [19]	7808	W	60–90	3	Yes	No†	≥ 800 if 25(OH)D 12–20 ng/mL or ≥ 400 if 25(OH)D > 20 ng/mL	≥ 1000
Abaloparatide/ACTIVE, 2016 [22]	1645	W	49–86	1.5	Yes	No#	Mean: ABL: 723; PLB: 613‡	Mean: ABL: 955; PLB: 986‡
Romosozumab/FRAME, 2016 [17]	7180	W	55–90	1 year*	Yes	Not	600–800 D ₃ or D ₂ ; 50,000 to 60,000 IU at the start of the study if 25(OH)D12–20 ng/mL	500–1000

*Then translocation to denosumab for 1 year; **Vertebral fracture or low DXA result; †Nonskeletal risk factors for hip fracture or low DXA result; ‡Two moderate vertebral fractures were allowed; #Other low-traumatic fractures allowed or low DXA result; †Patients with history of hip fracture, one severe or more than two moderate vertebral fractures were excluded; ‡ABL — abaloparatide group; PLB — placebo group

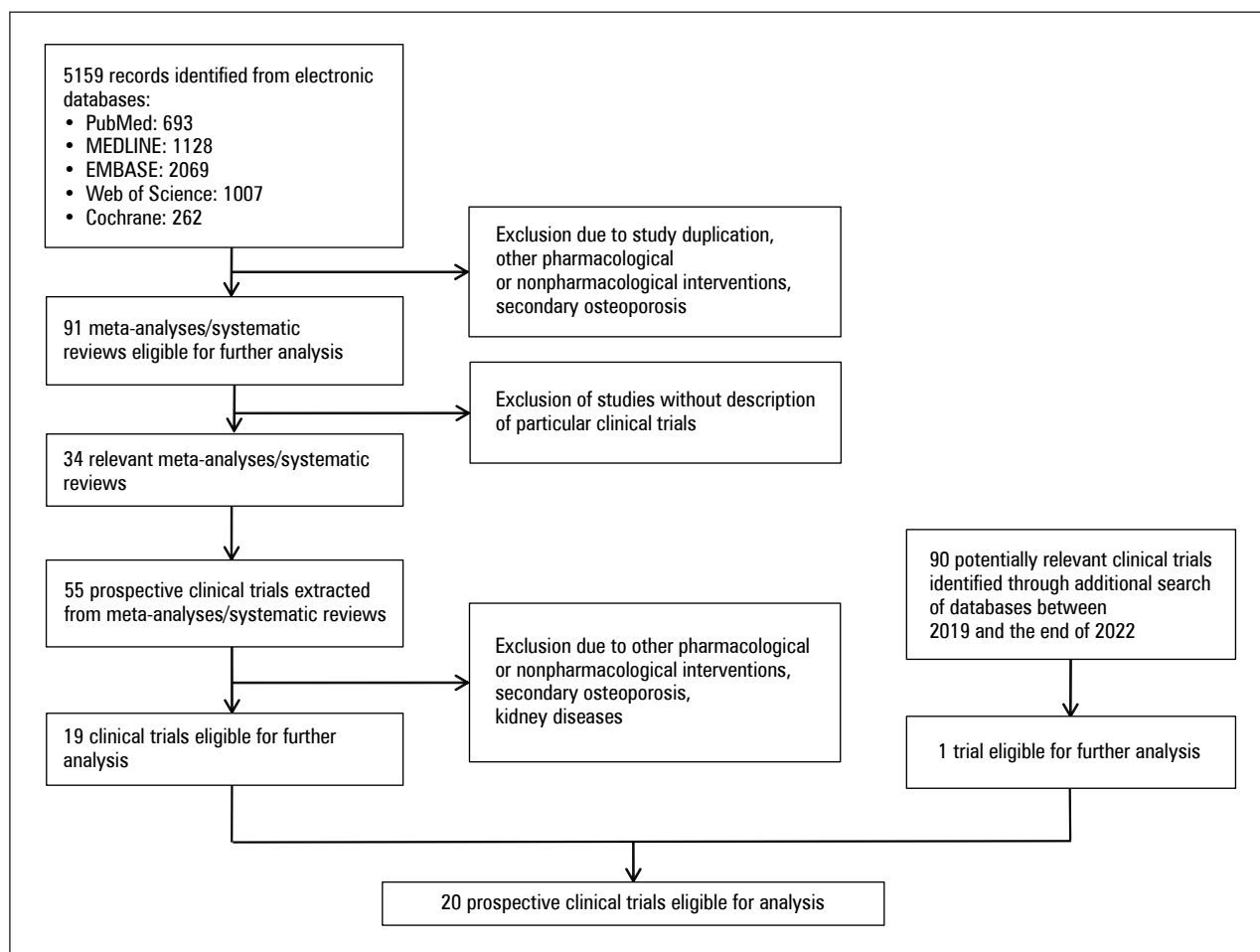


Figure 1. PRISMA flowchart

the study questions regarding the fracture risk reduction specified in the study aims.

In all but 2 of the accepted studies [3, 61] the patient populations were described as elderly. In all studies early postmenopausal women were excluded. DXA examination was performed only in one out of 13 analysed studies [1]. It was done in the minority of patients (56/3270; 1.7%), and there was no information on the results of DXA before the commencement of the study, except the information that there was no difference between the vitamin D treated and placebo groups. X-ray of the spine was not performed in any study; thus, only clinically diagnosed spine fractures could be recognized.

The number of vitamin D measurements is presented in Table 2, together with the calculated representative number of 25OHD measurements. The total number of serum vitamin D measurements was small. Only in 2 studies [3, 61], vitamin D serum concentration was measured in all subjects prior to the commencement of treatment. In one of them [61], it was repeated during, and after the study only in 6.5% of patients (non-representative number), while in another study [3]

no repeat measurements were performed. The number of vitamin D serum measurements was not representative in all other trials. The mean baseline serum vitamin D concentration was insufficient (< 20 ng/mL; [26]) in 3 out of 7 trials with known prestudy serum 25OHD concentration in the final analysis [1, 4, 65], and it was not deficient (< 10 ng/mL; [26]) in any study. There was only one study [71] that provided information on the number of patients with vitamin D deficiency; however, this number was very low (less than 3% of the study population). In another study [3], the values of 25OHD concentration were not defined as deficient or insufficient, but they were divided into quartiles. The number of patients in the subgroup with the lowest 25OHD concentration (< 12 ng/mL) was very low (401 patients) and accounted for 1.5% of the study cohort. In all repeated measurements (all non-representative) in vitamin D treated groups the mean serum vitamin D concentration was sufficient (> 20 ng/mL; [26]). The full characteristics of these 9 studies are presented in Table 2 and Table 3 (marked with an asterisk).

On the basis of the data presented in Figure 2, in the first stage of analysis, 9 trials [1-4, 61, 65, 66, 71, 72]

Table 2. Description of the study groups of vitamin D eligible for analysis (presented by ascending year of publication)

Study/Year	Patients enrolled (N)	Sex [M/W]	Age [years]	Study duration [years]	Double-blind placebo [Yes/No]	Supplementation			s-25OHD examination		Antifracture efficacy	
						Vitamin D IU/day [mean/day]	Calcium [mg/day]	Before study (N)	During/ after study (N)	Cal. N	Aim: I — primary, II — secondary	Outcome
Chapuy [1] 1994*	3270	W	≥ 69	3	Yes	800 p.o.	1200	142	Every 1 yr (142)	344	I: hip, nonvertebral	Positive
Lips [65] 1996*	2578	M/W	≥ 70	3–3.5	Yes	400 p.o.	Diet: 800–1000	270	After 1 yr (270) and 3 yrs (96)	335	I: hip and other peripheral	Negative
Trivedi [2] 2003*	2686	M/W	65–85	5	Yes	100,000 p.o./4 mths (822)	Diet: mean 742/day	0	After 4 yrs (270)	337	I: any	Positive
Larsen [63] 2004	9605	M/W	> 65	3	No	400 p.o.	1000	104	After 1 mth and 2 yrs (104)	370	I: osteoporotic fractures†	Positive: when low s-25OHD
Grant [4] 2005*	5292	M/W	≥ 70	2–6	Yes	800 p.o.	1000	60	After 1 yr (60)	359	I: any secondary fracture	Negative
Porthouse [69] 2005	3314	W	≥ 70	18–42 mths, median: 25 mths	No	800 p.o.	1000	0	Not done	345	I: any, II: hip	Negative
Law [64] 2006	3717	M/W	≥ 60	mean: 10 mths	No	100,000 D2/3 mths p.o.(1100)	No data	18	After 1 and 3 mths (18)	349	I: Nonvertebral	Negative
Lyons [66] 2007*	3440	M/W	62–107	3	Yes	100,000 D2/4 mths p.o. (822)	No data	0	After 3 yrs (102)	346	I: first any fracture, II: hip, wrist, forearm, spine	Negative
Smith [72] 2007*	9440	M/W	≥ 75	3	Yes	300,000 D2/yr i.m. (822)	No data	43	After 1, 4, 8, 12, 13 and 16 mths(43)	370	I: nonvertebral, II: hip, wrist	I: Negative: II hip — Increased risk, Wrist — negative
Salovaara [70] 2010	3432	W	65–71	3	No	800 p.o.#	1000#	574	After 3 yrs (574)	346	I: fracture prevention	Negative
Sanders [71] 2010*	2256	W	≥ 70	3–5	Yes	50,000 p.o./yr (1370)	Diet (median): 976/day	131	12 mths after dose, just prior to the next dose (131)	329	I: all	Increased risk
Khaw [61] 2017*	5108	M/W	50–84	Mean: 3.4 (2.5–4.2)	Yes	I dose: 20,000 p.o., next: 10,000 /mth, (3290)	No data	5108	After 6, 12, 24 and 36 mths (334)	358	II: nonvertebral	Negative
LeBoff [3] 2022*	25871	M/W	M: ≥ 50, W: ≥ 55	Median: 5.3	Yes	2000√	Not	All	0	NA	I: first — total, nonvertebral, hip	Negative

M — men; W — women; Cal. N — calculated representative number of patients with available 25(OH)D examinations (calculator available online: www.checkmarket.com/sample-size-calculator); Pt. N — number of patients; p.o. — per os; *studies accepted for the final analysis; #They were free to use supplements, but they were asked not to change their use of supplemented or dietary vitamin D or calcium; √ — participants agreed to limit any non-trial supplements of vitamin D to 800 IU per day; † — participants agreed to limit supplements of calcium to 1200 mg per day, NA — not applicable; † — osteoporotic fractures: low-energy fractures of the proximal humerus, distal forearm, vertebral column, pelvis, cervical femur, and intertrochanteric femur

Table 3. Description of the study groups of 13 clinical trials of vitamin D eligible for analysis (continuation, presented by ascending year of publication)

Study	Inclusion criteria		Exclusion criteria				Fracture risk (clinical)	Serum 25OHD (mean)	
	Clinical		Previous treatment		Clinical			Before treatment [ng/mL]	After/during treatment [ng/mL]
	Place of living	Previous fracture	Anti-fracture medicines	Vit. D	Ca suppl.	Previous fractures			
Chapuy [1] 1994*	Institutionalized but ambulatory	No	Yes	Yes	Yes	No	Serious medical condition	Vit D: 16.0, PLB: 13.0	After treatment, Vit D: 42.0
Lips [65] 1996*	Institutionalized	No	No	No	No	Yes	Hypercalcaemia, nephrolithiasis, sarcoidosis	Vit D: 10.8, PLB: 10.8	After treatment, Vit D 21.6 PLB: 17.8
Trivedi [2] 2003*	Community dwelling	No	No	Yes	Yes	Yes	Contraindication to vitamin D	Not done	After 4 yrs, Vit D: 29.7, PLB: 21.4
Larsen [63] 2004	Community dwelling	No	No	No	No	No	Severely impaired	Vit D: 14.8, PLB: 13.2†	After 2 yrs: Vit D: 18.8, PLB: no increase
Grant [4] 2005*	Community dwelling	Yes	Yes	> 200 IU/day	> 500 mg/day	No	Nephrolithiasis, general bad condition, carcinoma, hypercalcaemia	15.2	After 1 yr, Vit D: increase of 9.6, PLB: increase of 3.1
Porthouse [69] 2005	Community dwelling	Yes	No	No	> 500 mg/day	No	Kidney failure, nephrolithiasis, hypercalcaemia	Not done	Not done
Law [64] 2006	Institutionalized	No	No	Yes	Yes	No	Sarcoidosis, malignancy	Vit D: 23.6	After 3 mths, Vit D: 30.8
Lyons [66] 2007*	Institutionalized	No	No	≥ 400 IU/day	No	No	Contraindication to vitamin D	Not done	After treatment, Vit D: 32.0, PLB: 21.6
Smith [72] 2007*	91% of community dwelling	No	Yes	No	No	No	Cancer, kidney failure, nephrolithiasis, hypercalcaemia, sarcoidosis	22.6	After 16 mths, Vit D and PLB: not significant increase
Salovaara [70] 2010	Community dwelling	No	No	No	No	No	No	Vit D: 20.0, PLB: 19.6	After treatment, Vit D: 29.8, Control: 22.4
Sanders [71] 2010*	Community dwelling	Yes√	Yes	≥ 400 IU/day	No	No	Hypercalcaemia, chronic kidney disease	Vit D: 21.2, PLB: 18.0†	Median during control exams: 29.6
Khaw [61] 2017*	Healthy volunteers	No	No	≥ 600–800 IU/day	No	No	Hypercalcaemia, nephrolithiasis, sarcoidosis, PTH disease, gastric bypass surgery, psychiatric disorders	Vit D: 25.6, PLB: 25.2	After 3 yrs, The mean values in Vit D 21.6–27.6 higher than in PLB
LeBoff [3] 2022*	Healthy adults	No	No	No	No	No	Hypercalcaemia, cancer, cardiovascular disease	30.7	NA

*Studies accepted for the final analysis; low fracture risk: exclusion criteria – bone fracture in the past; high fracture risk: inclusion criteria: bone fracture in the past, presence of bone fracture risk factors; Vit D — group treated with vitamin D; PLB — placebo group; √ — were at higher risk of hip fracture (past fracture, maternal hip fracture, self-reported faller); † 80% had a baseline serum 25(OH)D below 20 ng/mL; ‡ Less than 3% of the substudy participants (vitamin D and placebo group) were deficient and had 25-hydroxycholecalciferol levels lower than 10 ng/mL; NA — not applicable

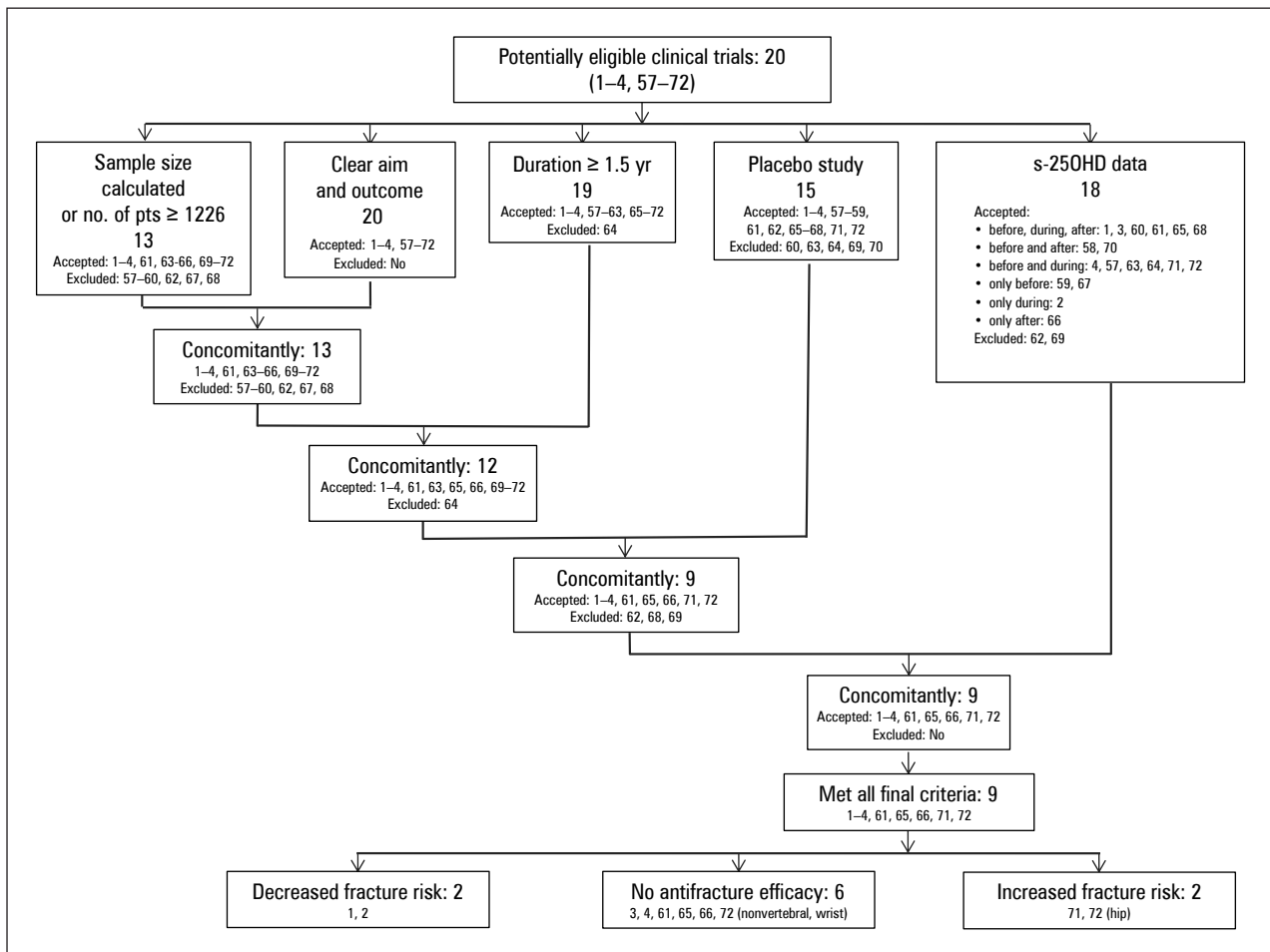


Figure 2. First stage analysis of vitamin D trials

met all the criteria considered necessary for the final analysis of the quality of the study protocols. In 2 studies, before the start of treatment, fracture risk was recognized as high [4, 71], in 2 as low [2, 65], and in 5 it was not specified [1, 3, 61, 66, 72]. At the end of the trials, decreased fracture risk was shown in 2 studies [1, 2], no fracture efficacy in 6 studies [3, 4, 61, 65, 66, 72 (nonvertebral and wrist fractures)], and increased fracture risk in 2 studies [71, 72 (hip fractures)].

Discussion

In the first stage of our analysis, we found 9 clinical trials eligible for the second stage of analysis, in which we aimed to evaluate if the optimal dose of vitamin D was used. The outcomes of these 9 trials on the antifracture efficacy of vitamin D are ambiguous and provide different conclusions (positive effect, no effect, or even negative effect). Our hypothesis was that if no clear conclusion on the antifracture efficacy of vitamin D can be reached despite several clinical trials, it should be examined whether it is the design of the studies that could explain the lack of conclusion. We assessed

the accordance of the vitamin D study protocols with the guidelines created by experts [9–11], and with the protocols of the trials of medications with proven antifracture efficacy as reference.

The need for specified characteristics of clinical trials, such as prospective character, clear definition of the study aims and outcomes, the need for minimal optimal number of patients, duration of the study, and optimal study design, is widely recognized. However, the other factors, such as clear description of patients' characteristics, especially of their fracture risk, need for calcium supplementation, and specification if the optimal vitamin D dose was used, require comment.

Although the expert boards accept non-inferiority comparator-controlled trials [12], a double-blind placebo-controlled design was applied in all reference studies and was considered as optimal by experts [10, 11]. The consensus statement on vitamin D indicates that the controls may be subjects receiving either placebo or poorly effective low dose of vitamin D [9]. In all 9 studies analysed, a placebo was used as a comparator.

The general clinical description of the study groups (age, sex, place of living) was clear. All patients were el-

derly in 7 out of 9 trials, with clear information on their general condition and place of living. In all studies early postmenopausal women were excluded, because due to a rapid bone loss phase resulting from a decline in oestrogen levels, this group is generally unresponsive or minimally responsive to nutritional interventions.

Unlike in the reference studies, which examined only women, in some vitamin D trials both genders were included. In the experts' opinion, if the action of treatment is independent of sex steroids, both men and women can be examined together [10]. The authors of the discussed studies attached great importance to the patients' general condition and their place of living. Older people who lived independently in local communities were distinguished in some studies from those who were taken care of in nursing homes for the purpose of assessing the antifracture activity of vitamin D separately in these groups.

An important characteristic of the reference antifracture medication studies is the stratification of the bone fracture risk. It is recommended by the experts that patients with a similar risk of fractures be included in trials [11], while other experts recommend that only high-risk patients are entered [10]. The preferable method of fracture risk assessment is based on previous low-energy vertebral and/or nonvertebral fractures with additional DXA and spine X-ray examinations, which were utilized in all reference trials. In all reference trials, the risk of bone fractures was recognized as high, based mainly on the history of previous bone fractures. In all vitamin D studies, the risk of bone fractures was assessed only clinically. The DXA examinations performed in one study [1] were not helpful in the assessment of the fracture risk because the pre-treatment values were not shown. When considering the fracture risk, we can regard all 9 studies included in the final analysis, and especially the 4 with the strictly defined fracture risk, as informative but only provided that their conclusions are restricted to the specific cohorts, i.e. patients with high or low fracture risk. In cases of different baseline fracture risk, the conclusion on the antifracture efficacy should be consistent in all groups, as the experts state [11].

We would like to draw attention to the calcium supplementation used in the studies. Some studies contain no information on the use of calcium supplementation, and in others, the information is imprecise or incomplete. Conversely, elementary calcium supplementation was applied in all reference trials, 500 mg daily or more often 1000 mg daily, which is widely recommended. In the pharmacological recommendations of the National Osteoporosis Societies, supplementation with calcium is recommended with specified dosing of elementary

calcium. This allows us to assume that in their opinion calcium supplementation is necessary to achieve antifracture efficacy of a pharmacological agent, and it suggests that the antifracture efficacy of vitamin D is also dependent on calcium intake. However, ultimately, we did not use calcium supplementation in our analysis as a marker of the trail value because in some experts' opinions [10, 11] calcium supplementation was not necessary for vitamin D antifracture efficacy, and in one study [73] the authors showed that zoledronic acid prevents fractures without calcium co-supplementation, with risk reduction similar to that achieved in the trial with calcium supplementation. Considering the uncertainty regarding the role of calcium in bone fracture prevention, we are unable to exclude the possibility that the lack of antifracture efficacy of vitamin D could, at least in part, depend on the insufficient dose of calcium in some studies.

An important part of the analysis of the reliability of the vitamin D efficacy studies is the assessment of whether the optimal dose of vitamin D was used. Because deficiency in vitamin D increases fracture risk, vitamin D-deficient populations are most likely to benefit from vitamin D supplementation [26]. Knowledge of the baseline and post-treatment vitamin D concentrations is required in efficacy studies. Sufficient vitamin D serum concentration with regards to the bone metabolism is still under discussion, but a concentration below 20 ng/mL is considered as insufficient, and below 10 ng/mL as deficient [26]. Some authors believe that many of the vitamin D studies, including the studies examining the risk of bone fractures as their endpoints, could be considered research waste because the cohorts studied were not vitamin D deficient [74]. The authors of the consensus statement on vitamin D also stress that the efficacy of vitamin D supplementation should be tested in vitamin D deficient subjects [9]. The data on the vitamin D serum level in the analysed trials is very limited. There was no trial with full data on the pre-study and post-study serum 25OHD concentrations. We do not know how many patients needed vitamin D supplementation and how many patients benefited from this treatment.

The reference studies are not helpful with regards to the optimal dose of vitamin D because the serum vitamin D level was not examined in most of them and not at all during or after the duration of studies. The optimal doses of antifracture medications were established in phases I-III of the trials. The optimal vitamin D doses used in the trials were not established because they did not have the preliminary phases.

If it is not possible to measure serum vitamin D levels in all patients, they should be measured at least in

the group representative of the whole cohort, the size of which can be calculated [25]. In 5 out of 7 trials with known prestudy serum 25OHD concentration, the number of vitamin D measurements was not representative. The number of all subsequent measurements (including the trial with representative prestudy measurements) was not representative either. The lack of the representativeness of vitamin D measurements for the study groups makes it difficult to conclude if the dosing of vitamin D was optimal in the whole treated cohort. From this point of view, no study was able to answer the general question concerning the antifracture efficacy of vitamin D, but only the efficacy of its dose. The importance of repeating measurements of vitamin D before and after the study intervention is emphasized by the experts in the consensus statement on vitamin D [9].

The study by LeBoff et al. [3] requires separate comment. The authors reported a lack of anti-fracture efficacy of vitamin D (all patients received 2000 IU of vitamin D, regardless of baseline 25OHD concentration or fracture risk) in an overall healthy middle-aged and elderly patient population. Due to the very large sample size, the length of observation, measurements of vitamin D concentration before treatment in all participants, and the use of placebo as a control, the obtained results are very reliable. The authors convincingly show that patients with the prestudy optimal level of 25OHD (> 30.0 ng/mL) do not benefit from additional treatment with vitamin D. However, this may not be the case in patients in the lowest quartile of 25OHD concentration (≤ 24 ng/mL), especially in the carefully selected small subgroup of patients with 25OHD below 12 ng/mL (1.5% of the study population). The concentration of 25OHD achieved after the treatment was not measured, nor whether it was a concentration that ensured anti-fracture effectiveness.

The strength of our study lies in the new approach to the question of the antifracture efficacy of vitamin D and addressing it through the analysis of the vitamin D studies' protocols and comparison with the protocols of the studies, which resulted in the demonstration of the antifracture efficacy of several other medications, including bisphosphonates, and led to their subsequent registration.

The study has limitations. While the proposed protocol is based on reliable sources, such as the American and European studies and the 2nd International Conference experts' opinions, as well as the study protocols of the accepted antifracture medications, it cannot be seen as the only acceptable protocol for validation of the efficacy of an agent. Some of our decisions, when formulating the proposed protocol

were made arbitrarily. The minimal sample size (1226 patients) in the case of studies without the sample size calculation was established arbitrarily, based on the trial protocols of the other antifracture medications. The decision on the minimal study duration was arbitrary also. According to the consensus statement from the 2nd International Conference on Controversies in Vitamin D, the study duration should be long enough to record an adequate number of events [9]. Our decision concerning the minimal study duration of 1.5 years, and not 3 years as in most reference studies, was based on the expert panel recommendation on the efficacy trials [10]. However, the assessment of the vitamin D studies' duration on the basis of the trials of the antifracture medications is difficult due to uncertainty whether correcting a nutrient deficiency would have an effect size as large as that achieved by these medications.

Conclusions

Based on the analysis of the studies included in our review, we conclude that the general question of the antifracture efficacy of vitamin D in the overall adult population cannot be explicitly answered. The studies examined predominantly elderly populations. Rather than unambiguously confirming or rejecting the antifracture efficacy of vitamin D, the analysed studies can refer to the effects of its specific doses and forms given in particular (age, place of living) groups of patients only. An important concern with regards to the credibility of the vitamin D trials was drawn to the lack of the complete assessment of the fracture risk in some of the studies and, even more importantly, to the lack of certainty that the optimal vitamin D doses were used, which is especially relevant in patients with deficient or insufficient prestudy serum levels of vitamin D concentration.

In the authors' opinion, considering the data presented, the optimal protocol of the study designed to assess the antifracture efficacy of vitamin D should be based on several pillars. The first one refers to the widely accepted characteristics, such as an optimal number of patients, optimal duration of the study, clearly defined patients' characteristics and study aims and outcomes, and an optimal comparator to the active treatment. A clearly defined, ideally homogeneous, fracture risk level of the study population should form the second pillar. The third pillar should be a precisely defined dose and form of the medication used in the study. To draw conclusions on the antifracture efficacy of vitamin D, the post-treatment serum level of 25OHD (measured in all patients) should reach the optimal serum concentration. To address any doubts concern-

ing the role of calcium in fracture prevention, calcium supplementation at a locally recommended dose should be given. We agree with the authors who believe that study of the antifracture vitamin D efficacy should be dedicated to the subjects with decreased serum level of 25OHD only.

Author contributions:

J.P. designed the study and prepared the first draft of the paper. J.P. and U.O.-J. performed the literature search and data analysis, revised the paper and approved the final version.

Conflict of interest

None declared.

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