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Vitamin D supplementation and disease activity in patients with immune-mediated rheumatic diseases
A systematic review and meta-analysis

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Abstract

Background: Vitamin D serum levels and the presence and activity of rheumatic conditions have been associated. However, many studies are merely observational, and the existent randomized clinical trials were never systematically analyzed. Therefore, this study aims to provide a systematic review and meta-analysis of such a topic.

Methods: MEDLINE, EMBASE, LILACS, COCHRANE, and CINAHL were explored to identify randomized trials that investigated clinical repercussions of vitamin D (or analogs) supplementation for at least 3 months in rheumatic diseases. Standardized clinical and/or laboratorial outcomes related to disease activity were analyzed according to each disease before and after supplementation.

Results: Database searches rendered 668 results; 9 were included—5 on rheumatoid arthritis, 3 on systemic lupus erythematosus, and 1 on systemic sclerosis. Seven of the studies were meta-analyzed. After vitamin D supplementation, rheumatoid arthritis recurrence decreased; however, not significantly (risk difference $= -0.10$, 95% CI $= -0.21$, 0.00, $P = .05$). No statistical significance was observed regarding visual analog scale (mean difference $= 2.79$, 95% CI $= -1.87$, 7.44, $P = .24$) and disease activity score28 (mean difference $= -0.31$, 95% CI $= -0.86$, 0.25, $P = .28$). Regarding systemic lupus erythematosus, anti-dsDNA positivity was significantly reduced (risk difference $= -0.10$, 95% CI $= -0.18$, -0.03; $P = .005$).

Conclusion: Vitamin D supplementation reduced anti-dsDNA positivity on systemic lupus erythematosus and could possibly reduce rheumatoid arthritis recurrence, although novel randomized clinical trials are needed to confirm and extend the benefits of this hormone in immune-mediated rheumatic diseases.

Abbreviations: 95% CI = 95% confidence interval, ACR = American College of Rheumatology, DAS-28 = Disease Activity Score for Rheumatoid Arthritis, ECLAM = European Consensus Lupus Activity Measurement, EULAR = European League Against Rheumatism, K-FSS = Fatigue Severity Scale/children version, NNT = number needed to treat, RA = rheumatoid arthritis, SD = standard deviation, SLE = systemic lupus erythematosus, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index, SSc = systemic sclerosis, VAS = visual analog scale.

Keywords: disease activity, meta-analysis, rheumatic diseases, rheumatoid arthritis, systemic lupus erythematosus, vitamin D

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1. Introduction

The association between vitamin D deficiency and rheumatic diseases has been described since a lower risk of developing autoimmune diseases was identified near the equator,[1,2] where people synthesize cholecalciferol on their skin for a longer period within the year.[3] Based on this finding, many researchers have investigated correlations between vitamin D serum levels and the presence/activity of rheumatic conditions.[1,4–6] With its increasing visibility, clinical repercussions of vitamin D supplementation have been studied in rheumatic diseases such as systemic lupus erythematosus (SLE)[1,4] and rheumatoid arthritis (RA)[7] and in non-rheumatic conditions such as tuberculosis[8] and psoriasis.[2] The results, then, prompted research on known and novel biomolecular and cellular functions of vitamin D.[2,3]

In addition to its classic action on the bone, kidneys and gastrointestinal tract, maintaining calcium and phosphorus homeostasis, the expression of the nuclear Vitamin D receptor was described in cells of the pituitary and parathyroid glands, kidneys, skin, gastrointestinal tract,[9] and the immune system.[10] Such discoveries have led to new research on fields that are not only related to bone metabolism[11] but also to the finding of new

functions for vitamin D.[2] Pleiotropic actions of vitamin D on the immune system were described[11–14] and are of particular interest to this study because immune cells and cytokines participate directly in the pathobiology and activity of immune-mediated rheumatic diseases.

Recent in vitro studies have shown that vitamin D plays an important role in immune modulation by stimulating innate immunity, enhancing its activity, and decreasing adaptive immune activity.[15] This immunomodulatory action[16] is explained by a decreased production of cytokines such as interleukin-2 and interferon-γ, which is essential to the pro-inflammatory Th1 response,[17] as well as an increased interleukin-4 production, which is essential to Th2 response.[18] Vitamin D also stimulates regulatory T cells[19,20] while inhibiting Th17 and Th9 lymphocytes,[19] both involved in autoimmune disorders development as SLE,[21] RA,[22] and multiple sclerosis.[23] Following such findings, a therapeutic role for vitamin D in inflammatory and autoimmune conditions was theorized.

To assess this hypothesis, in vivo studies have used experimental models of autoimmune encephalomyelitis[24] and SLE.[25,26] Despite confirming the induction of regulatory T lymphocyte and double-positive CD4+/CD8+ T lymphocytes,[25] besides the inhibition of Th9 and Th17 lymphocytes by vitamin D, these studies still do not verify the clinical benefits of vitamin D supplementation as a treatment of autoimmune diseases.[3]

To this date, vitamin D supplementation is considered safe,[27] with a low risk of hypercalcemia[3] and urolithiasis[28] and with cardiovascular protection.[29] In rheumatology, vitamin D supplementation is well known to prevent glucocorticoid-induced osteoporosis[30,31] and to reduce fractures in elderly people with osteoporosis[32]; however, vitamin D supplementation is not well established in immune-mediated rheumatic diseases such as SLE, RA, systemic sclerosis (SSc), vasculitis and Sjögren Syndrome.[33]

These rheumatic conditions are prevalent[34] with decrease in quality of life and severe sequelae,[35,36] and they do not have accessible specific therapeutic targeting molecular structures.[37]

Despite scientific evidence of the possible therapeutic outcomes of vitamin D supplementation, many studies have been merely observational and have not led to precise conclusions.[33] The most trustworthy study designs are well-randomized and well-allocated experimental trials. However, the few existent randomized clinical trials that have investigated vitamin D and its analogs supplementation on the activity of immune-mediated rheumatic diseases were never analyzed systematically. No assertive conclusions exist on the clinical outcomes of vitamin D supplementation on such conditions.

Given this gap in the literature, this study aims to systematically analyze the results of such trials and to develop a meta-analysis in order to identify rheumatic conditions in which vitamin D supplementation could be an appropriate therapeutic strategy.

2. Materials and methods

2.1. Ethics disclosure

According to the policies of the authors' institution, as no human patients or animal models were required in order to conceive this study, an ethics statement was not required. No funding bodies played a role in the design, writing, or decision to submit this work.

3. Eligibility criteria

3.1. Types of studies

Only randomized controlled trials, double-blinded or not, that studied the effect of vitamin D supplementation or its analogs were included.

3.2. Types of participants

Trials conducted on participants with any of the following diseases were eligible: Behçet Syndrome, Dermatomyositis, Juvenile Arthritis, Mixed Connective Tissue Disease, Polymyalgia Rheumatica, Rheumatic Fever, Rheumatoid Arthritis, Sjogren's Syndrome, Ankylosing Spondylitis, Systemic Lupus Erythematosus, Systemic Sclerosis, and Vasculitis.

3.3. Types of intervention

Selected manuscripts were required to include studies investigating the supplementation of vitamin D or its analogs for at least 3 months. This supplementation was compared with a matching placebo or no drugs. We considered that additional supplementation with calcium and/or use of other medications to control disease progression, if matched between groups, would not interfere with established outcomes.

3.4. Types of outcome measures

This review included trials that studied appropriate clinical and/or laboratory outcomes related to disease activity for each disease before and after vitamin D supplementation (Table 1).

Table 1

Diseases included with its appropriate clinical and/or laboratorial outcomes.

Disease	Outcome
Behçet syndrome	BDCAF, IBDDAM, BDAI, number of systems affected
Dermatomyositis	Physician and Patient/Parent Global Activity, MMT, CMAS, MDAAT, DAS, physician global damage, MDI, QMT, FI-2, MAP, CDASI, CAT, DSSI
Juvenile idiopathic arthritis	VAS or equivalent modified scales for pain, JADAS, DAS-28, CDAI, ACR paediatric; CHAQ
Polymyalgia rheumatica	PMR-AS
Rheumatoid arthritis	DAS-28, VAS or equivalent modified scales for pain, fatigue scales, ACR-EULAR and dose reduction of drugs
Sjogren's syndrome	ESSDAI, SCAI
Ankylosing spondylitis	ASDAS, BASDAI
Systemic lupus erythematosus	SLEDAI, ECLAM, FSS and variations, anti-dsDNA, C3 and C4 serum levels
Systemic sclerosis	EUSTAR Systemic Sclerosis Activity Score, skin scores
Vasculitis	VAI, BVAS, BVAS/GPA

ANCA = anti-neutrophil cytoplasmic antibodies, ASDAS = Ankylosing Spondylitis Disease Activity Score, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BDAI = Behçet's Disease Activity Index, BDCAF = Behçet's Disease Current Activity Form, BVAS = Birmingham vasculitis activity score, BVAS/GPA = Birmingham vasculitis activity score for granulomatosis with polyangiitis, CAT = Cutaneous Assessment Tool, CDAI = Clinical Disease Activity Index, CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index, CHAQ = Childhood Assessment Score, CMAS = Childhood Myositis Assessment Scale, CNS = Central Nervous System, CRP = C-reactive Protein, DSSI = Dermatomyositis Skin Severity Index, ESR = Erythrocyte Sedimentation Rate, ESSDAI = EULAR Sjogren's Syndrome Disease Activity Index, FI-2 = Myositis Functional Index-2, IBDDAM = Iranian Behçet's Disease Dynamic Measure, JADAS = Juvenile Arthritis Disease Activity Score, MAP = Myositis Activities Profile, MDAAT = Myositis Disease Activity Assessment Tool, MDI = Myositis Damage Index, MMT = Manual Muscle Testing, PMR-AS = Polymyalgia Rheumatica Activity Score, QMT = Quantitative Muscle Testing, SCAI = Sjogren's Systemic Clinical Activity Index, VAI = Vasculitis Activity Index.

3.5. Exclusion criteria

Trials with endpoints related solely to bone metabolism and/or cardiovascular events were excluded from the present study.

3.6. Information sources and search strategy

Manuscripts containing the following MeSH keywords and terms were identified by surveying MEDLINE, EMBASE, LILACS, COCHRANE, and CINAHL databases: rheumatic diseases, Behçet Syndrome, spondylitis, vasculitis, juvenile arthritis, rheumatoid arthritis, Sjogren's Syndrome, polymyalgia rheumatica, systemic lupus erythematosus, systemic sclerosis, dermatomyositis, vitamin D, cholecalciferol, hydroxycholecalciferols, ergocalciferols, 25-hydroxyvitamin D. Depending on the search mechanisms of each database, our strategy was adapted (supplementary File, http://links.lww.com/MD/B725). Additional searches were performed using selected study references. There were no time or language restrictions, and the last search dates back to June/2016 for all databases.

3.7. Study selection

Identification, screening, and eligibility assessments were performed independently in an unblinded standardized manner by 2 reviewers. Disagreements between reviewers were discussed with a third researcher.

3.8. Data collection process

Two reviewers collectively developed a data extraction sheet. After extracting and checking the information, disagreements were resolved by discussion between the 2 review authors. If no agreement could be reached, a third author decided between the disagreement. After reading the full texts, 4 of the authors from the selected trials were contacted in order to retrieve further details. Only 1 author responded and provided numeric data that we previously could not access.

3.9. Data items

Initially, of all the data from the selected articles, we sought (I) the rheumatic disease(s) each of article studied; (II) the type of intervention; that is, what type of vitamin D was administered (cholecalciferol, calcitriol, alfacalcidol) and its corresponding doses and frequency of administration; (III) the comparison groups; that is, what type of treatment was compared to supplementation with vitamin D (other type or dose of vitamin D, placebo or no treatment); and (IV) the endpoints (described separately in the "types of outcome measures" section).

Subsequently, to simplify our further analyses, we expanded our data extraction to include numbers on (V) the total study population, (VI) the intervention and comparison group populations and (VII) the length of each trial (Table 2).

3.10. Risk of bias in individual studies

To ascertain the validity of eligible trials, 2 authors extracted and checked the adequacy of the (I) query of the study, (II) randomization, (III) concealment of allocation, (IV) blinding, (V) number of patients lost to follow-up, (VI) homogeneity between groups after randomization, (VII) outcome measures, and (VIII) an intention-to-treat analysis (Table 3).

Regarding the study queries, we considered a study to have a low risk of bias whenever its objectives were clear. Randomization had to be generated by computer software or regulated by a pharmacy to be considered adequate. Unbiased allocation was defined as a sequence that was generated using computer random number generation or a random number table. Whenever the sequence generation method was not specified or was not random, allocation was considered inadequate (a high risk of bias). Double-blinding was recognized as the only adequate blinding. A high risk of bias was granted whenever more than 20% of any study branches were lost to follow-up. Homogeneity between groups after randomization was adequate if statistical

Table 2

Study characteristics of the 9 studies included in the systematic review.

Disease	Study	Population*	Intervention		Comparison		Outcome	Follow-up (mo)
			Type	N	Type	N		
RA	Dehghan et al[38]	80	Cholecalciferol 50,000 IU/wk	40	Placebo	40	Recurrence (DAS-28); dose reduction of drugs	6
	Gopinath and Danda et al[39]	204 identified → 121 randomized → 110 completed	Calcitriol 500 IU + 1000 mg CaCO3/day	59 → 55	1000 mg CaCO3 per day	62 → 55	VAS	3
	Hansen et al[40]	711 contacted → 98 eligible → 22 randomized	Ergocalciferol 50,000 IU 3 times/wk for 4 weeks then 50,000 IU twice monthly for 11 months	11	placebo	11	DAS-28, VAS	12
	Salesi and Farajzadegan[41]	117 eligible → 98 completed treatment	Cholecalciferol 50,000 IU/wk	50	Placebo	48	DAS-28, VAS	3
	Yang et al[42]	377 eligible → 340 completed treatment and follow-up	alfacalcidol 0.25 mcg twice a day	93 → 84	No vitamin D (normal vitamin D levels) no vitamin D (control)	185 → 168 / 99 → 88	Recurrence (DAS-28 > 3.1)	24
SLE	Abou-Raya et al[43]	325 screened → 267 eligible → 236 completed treatment + 175 controls	Cholecalciferol 2000 IU/day	178 → 158	Placebo	89 → 78	Anti-dsDNA, C4, SLEDAI reduction	12
	Aranow et al[44]	127 screened → 57 randomized → 54 modified intention to treat analysis	Cholecalciferol 2000 IU/day	17 → 10	Placebo	19 → 9	Anti-dsDNA	3
			Cholecalciferol 4000 IU/day	18 → 12				
	Lima et al[45]	45 selected → 40 analysed after losses	Cholecalciferol 50,000 IU/wk	22 → 20	Placebo	23 → 20	SLEDAI, ECLAM, K-FSS, anti-dsDNA	6
SSc	Hulshof et al[46]	7 selected → 6 completed study	Calcitriol 0.75 mcg/day for 6 months plus 1.25 mcg/day for 3 months	3 → 2	Placebo	4	Skin score	15

Table 3

Risk of bias in individual studies.

Disease	Study	Query	Randomization	Allocation	Blinding	Losses	Prognosis	Outcomes	ITT[*]
RA	Dehghan et al[38]	Yes	No	No	Yes	Yes	Yes	Yes	No
	Gopinath and Danda et al[39]	Yes	Yes	No	No	Yes	Yes	Yes	Yes
	Hansen et al[40]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Salesi and Farajzadegan et al[41]	Yes	No	No	Yes	No	Yes	Yes	Yes
	Yang et al[42]	Yes	Yes	No	No	Yes	Yes	Yes	No
SLE	Abou-Raya et al[43]	Yes	No	No	Yes	Yes	Yes	Yes	Yes
	Aranow et al[44]	Yes	No	No	Yes	No	Yes	Yes	No
	Lima et al[45]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
SSc	Hulshof et al[46]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes

significance between groups was not found. Whenever the proposed outcomes were adequate and the clinical and/or laboratory criteria used to assess the outcomes were relevant and followed up for at least 3 months, the outcomes were considered unbiased. Measurement of treatment effect was obtained using an intention-to-treat basis whenever possible. Whenever any of these items were poorly or not described, the said item was considered inadequate.

3.11. Summary measures

For every selected study, absolute risk reduction of clinical and/or laboratory parameters was the primary measure of treatment effect for each disease and outcome. Quantitative analyses were performed on an intention-to-treat basis and were confined to data derived from the period of end of treatment or follow-up. The number needed to treat (NNT), absolute risk reduction and 95% confidence intervals (95% CI) for each outcome measure

were obtained from the articles when possible or were calculated using OpenEpi software.[47] When absolute risk reduction and 95%CI were not statistically significant, NNT was not calculated (shown as NA) (Table 4).

Whenever studies presented continuous variables, we (I) depicted data as the mean or median, with its respective standard deviation (SD), (II) calculated a ratio between the means of each group, and (III) specified the significance of their differences (Table 5).

CI 95% = 95% confidence interval, DAS-28 = Disease Activity Score-28 for Rheumatoid Arthritis, N = absolute number, NNT = number needed to treat, NR = not reported, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus.

CI 95% = 95% confidence interval, DAS-28 = Disease Activity Score-28 for Rheumatoid Arthritis, ECLAM = European Consensus Lupus Activity Measurement, NNT = number needed to treat, NR = not reported, RA = rheumatoid arthritis, SD = standard deviation, SLE = systemic lupus erythematosus, SLE-

Table 4

Study results sorted by disease (absolute variables).

Disease	Study	Outcome	Intervention Events (N)	Intervention Population (N)	Comparison Events (N)	Comparison Population (N)	Risk Intervention	Risk Comparison	Absolute risk reduction	CI 95%	NNT
RA	Dehghan et al[38]	Recurrence (DAS-28)	7	40	11	40	0.175	0.275	−0.1	−28.17 to 8.168	NR
		Prednisolone dose reduction	17	40	23	40	0.425	0.575	−0.15	−36.66 to 6.664	NR
		Methotrexate dose reduction	25	40	31	40	0.625	0.775	−0.15	−34.81 to 4.812	NR
		Chloroquine dose reduction	35	40	37	40	0.875	0.925	−0.05	−18.1 to 8.101	NR
	Yang et al[46]	Recurrence (DAS-28 ≥ 3.2)	16	84	26	88	0.1905	0.2955	−0.105	−23.2 to 2.205	NR
SLE	Abou-Raya et al[43]	Anti-dsDNA (positive)	119	178	73	89	0.6685	0.8202	−0.1517	−25.73 to -4.61	6.59
	Aranow et al[44]	Anti-dsDNA (positive)	33	35	19	19	0.9429	1	−0.5714	−13.4 to 1.975	NR
	Lima et al[45]	Anti-dsDNA (positive)	6	20	8	20	0.3	0.4	−0.10	−39.4 to 19.4	NR

Table 5

Study results sorted by disease (continuous variables).

Disease	Study	Outcome	Intervention—Mean or Median (SD)	Comparison—Mean or Median (SD)	Ratio	Significance
RA	Hansen et al[39]	DAS-28	3.03 (1.13)	2.96 (1.14)	1.02	0.96
		VAS	3.87 (1.9)	2.42 (1.9)	1.59	0.03
	Salesi and Farajzadegan et al[42]	DAS-28	4.2 (1.2)	4.7 (2.1)	0.89	>0.05
		VAS	45.7 (19.9)	38.7 (20.4)	1.18	>0.05
SLE	Abou-Raya et al[38]	Anti-dsDNA (U/mL)	32.8 (12.7)	44.8 (13.9)	0.73	0.05
		C4 (mg/L)	0.270 (0.071)	0.179 (0.079)	1.51	0.05
	Lima et al[40]	SLEDAI	3.00 (3.22)	5.4 (4.5)	0.56	0.06
		ECLAM	1.80 (1.64)	2.75 (2.12)	0.65	0.121
SSc	Hulshof et al[43]	Skin Score	3.66 (5.51)	21.75 (8.18)	0.17	NR

DAI = Systemic Lupus Erythmatosus Disease Activity Index, SSc = systemic sclerosis, VAS = visual analog scale.

3.12. Planned methods of analysis

Meta-analyses were performed separately for each disease using Review Manager (version 5.3; The Nordic Cochrane Centre).[48] The results were expressed as a risk difference for categorical variables or as the mean difference for continuous variables. We measured the inconsistency (the percentage of total variation across studies due to heterogeneity) of effects across interventions using I^2. In order to obtain adequate confidence intervals, we used a random-effects model if $I^2 > 40\%$ and a fixed-effect model if $I^2 \leq 40\%$. Statistically significant P values were considered as higher than $P = .05$.

3.13. Risk of bias across studies

The possibility of publication bias was assessed by evaluating a funnel plot of the trial mean differences for asymmetry, which can result from the non-publication of small trials with negative results. Nonetheless, other factors, such as differences in trial quality or true study heterogeneity, can produce asymmetry in funnel plots.

4. Results

4.1. Study selection

The MEDLINE, EMBASE, LILACS, COCHRANE, and CINAHL database searches identified 661 studies. An additional 7 studies that met the inclusion criteria were identified by reviewing the references of other relevant papers and by searching for studies that had cited these papers. Of these, 638 studies were discarded because after reviewing the abstracts, they clearly did not meet the inclusion criteria: other study types that did not involve clinical trials (reviews, commentary, letters, cross-sectional studies); interventions in nonrheumatic diseases or in non-autoimmune rheumatic conditions; interventions without vitamin D supplementation (calcium supplementation, bisphosphonates) or comparisons with other strategies as bisphosphonates or other vitamin D supplementation scheme; and cardiovascular, bone, genetic or molecular outcomes. Twenty-one studies were duplicated and therefore discarded. The full texts of the remaining 9 citations were examined in more detail and were included in this systematic review. Two studies did not have sufficient data and were excluded from the quantitative analysis. Therefore, 7 studies were meta-analyzed. No unpublished relevant studies were obtained (Fig. 1).

4.2. Study characteristics

Because only studies conducted on patients with RA, SLE, and SSc met our eligibility criteria, only these 3 rheumatic diseases are reported in this systematic review and meta-analysis. Five trials were conducted on patients with RA, 3 trials on patients with SLE and only 1 trial on SSc. Characteristics of each study are summarized (Table 2) according to methods, participants, interventions, and outcomes.

4.3. Methods

All 9 studies selected for the review were randomized controlled trials published in English. However, 2 of the trials,[39,42] both on RA, were not double-blind. The length of follow-up ranged from
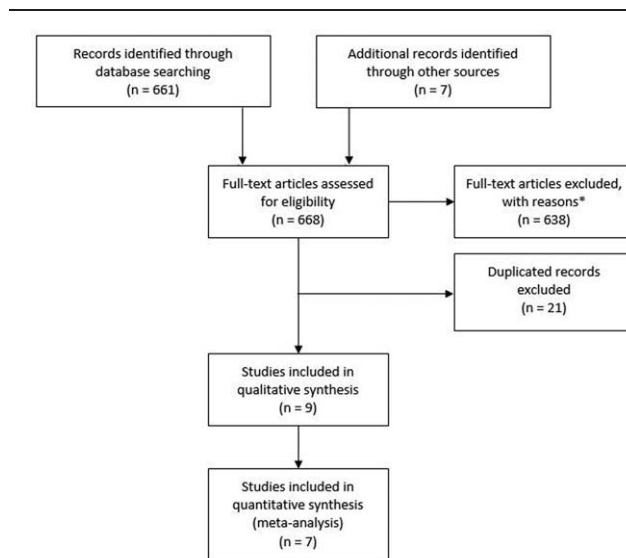

Figure 1. Flow diagram of study selection. *See the text for details.

3 to 24 months, in which 1 month was defined as 4 weeks when the period in months was not explicit.

4.4. Participants

The included studies involved 1161 participants, 640 with RA, 505 with SLE, and 6 with SSc.

The main inclusion criteria for patients with RA were its diagnosis according to the 2010 American College of Rheumatology and European League Against Rheumatism (ACR-EULAR) or the 1987 ACR criteria. For patients with SLE, the ACR criteria updated in 1997 were used by the 3 trials. For SSc, the diagnosis was "according to the criteria in the literature."[46] All trials excluded patients with multiple comorbidities and polypharmacy.

4.5. Intervention

In RA studies, the intervention group used the following: cholecalciferol 50,000 IU/wk in 2 studies[38,41]; ergocalciferol 50,000 IU 3 times/wk for 4 weeks, then 50,000 IU twice monthly for 11 months in 1 study[40]; calcitriol 500 IU in 1 study[39]; and alfacalcidol 0.25 mcg twice a day in 1 study.[42] In all studies, the comparison group used placebo, and Gopinath and Danda[39] used calcium supplementation in both intervention and placebo groups.

For SLE, all 3 studies used cholecalciferol in the intervention group and compared to placebo. Administered vitamin D doses were different: 2000 IU/day in 1 study[43]; 2000 IU/day and 4000 IU/day in 1 study[44]; and 50,000 IU/wk in another study.[45]

For SSc, the only study[46] used calcitriol 0.75 mcg/day for 6 months, then 1.25 mcg/day for 3 months, compared to the placebo.

4.6. Outcomes

The outcomes for RA were recurrence, based on DAS-28[38]; dose reduction of methotrexate, chloroquine and glucocorticoid[38]; reduction in Visual Analog Scale (VAS) and Disease Activity Score for RA (DAS-28)[39–41]; and recurrence of disease, defined as an increase of 3.6 in DAS-28.[42]

For SLE, the Disease Activity Index (SLEDAI),[43,45] European Consensus Lupus Activity Measurement (ECLAM),[45] K-FSS (Fatigue Severity Scale/children version),[45] positivity of anti-dsDNA[43–45] and serum C4 levels[43] were considered outcomes. Skin scores were the preferred outcome for SSc.[46]

All of these studies featured other outcomes that were considered unrelated or impertinent to our review and are not depicted here.

4.7. Risk of bias within studies

Risk of bias in all 9 works was analyzed. Every study was classified as having a high risk of bias for at least 1 parameter. The highest risk of bias was found in the trial on SLE by Aranow et al,[44] and the lowest was described in the trial on RA by Hansen et al.[40] The assessment of the different domains of risk of bias in each trial are shown in Table 3.

4.8. Results of individual studies

Outcomes considered for each study are summarized in Table 4 with data of each intervention group and intervention effect. One study had to be removed from this analysis because the data were insufficient; even though the author was contacted, we did not receive a response.[39]

In all studies, considering the 3 diseases, there was a risk reduction for all outcomes described as absolute variables, with no statistical significance. Nonetheless, Abou-Raya et al[43] reported that the reduction in anti-dsDNA positivity was statistically significant in SLE, with a NNT of 7.

Regarding continuous variables, VAS in RA[40] was found worse after vitamin D supplementation. Differently, fatigue in SLE was improved after 6 months of vitamin D supplementation using K-FSS for the following conditions: fatigue when performing exercise ($P=.03$), fatigue easily ($P=.003$), fatigue to medium efforts ($P=.02$), fatigue considered a problem ($P=.03$), and fatigue interfering with social life ($P=.01$).[45] Hulshof et al[46] did not find significant differences for skin scores after vitamin D supplementation for 9 months (Table 5), nor after another 6 months of follow-up after treatment (not shown).

4.9. Synthesis of results

Meta-analysis was performed for RA and SLE because we only found 1 study about SSc.[46] Therefore, 7 trials were included in this meta-analysis: 4 studies on RA and 3 studies on SLE.

For RA, 3 analyses were performed based on the following outcomes: VAS reduction, DAS-28 reduction, and recurrence (Fig. 2A–C). VAS reduction was meta-analyzed using 2 studies,[40,41] with 61 patients receiving vitamin D supplementation and 59 in the placebo group. Vitamin D was not associated with significant VAS reduction (mean difference=2.79, 95% CI=−1.87, 7.44, $P=.24$), with a calculated medium heterogeneity between studies for this analysis ($I^2=44\%$). DAS-28 reduction was meta-analyzed using the same 2 studies[40,41] with low heterogeneity ($I^2=0\%$ for this analysis), and vitamin D was not associated with significant DAS-28 reduction (mean difference=−0.31, 95%CI=−0.86, 0.25, $P=.28$). Recurrence was meta-analyzed using 2 other studies,[38,42] with 124 patients in the intervention group and 128 in the placebo group; vitamin D supplementation produced an insignificant reduction in recurrence (risk difference=−0.10, 95%CI=−0.21, 0.00, $P=.05$). Heterogeneity was, again, low ($I^2=0\%$).

For SLE, only 1 analysis was performed based on the reduction of anti-dsDNA positivity that was reported by 3 studies[43–45] (Fig. 2D). Overall, 233 patients in the intervention group and 128 patients in the placebo group were analyzed, and vitamin D supplementation was significantly associated with a reduction in anti-dsDNA positivity (risk difference=−0.10, 95%CI=−0.18, −0.03; $P=.005$), and no evidence of heterogeneity was found ($I^2=0\%$).

4.10. Risk of bias across studies

Even though all meta-analyses that were performed had no evidence of heterogeneity, a funnel plot was drawn for every outcome analyzed. No considerable asymmetry was observed in any of the plots (data not shown).

5. Discussion

5.1. Summary of evidence

Few randomized clinical trials have investigated the clinical benefits of vitamin D supplementation on rheumatic diseases. RA, SLE, SSc were the only 3 rheumatic diseases studied by eligible clinical trials. Therefore, the evidence is, overall, not sufficiently robust to determine the effectiveness of vitamin D supplementation on immune-mediated rheumatic diseases.

Five randomized trials on RA were eligible for systematic review, and 4 were meta-analyzed. However, as vitamin D supplementation schemes and clinical or laboratory outcomes were different across studies, few conclusions could be drawn from the meta-analysis.

Despite analyzing only 2 studies[38,42] that used different methods to assess recurrence in remitted patients, this meta-analysis showed a tendency of reduction in recurrence ($P=.06$) after vitamin D supplementation. Individually, Yang et al[42] concluded that low vitamin D levels are a risk factor for RA recurrence but that treatment with alfacalcidol for 24 months did not change recurrence rates significantly ($P=.11$). Dehghan et al[38] also described non-significant differences in frequency of recurrence after cholecalciferol supplementation for 6 months ($P=.42$). Notably, the study[42] with the bigger population showed results that were closer to statistical significance. A pathophysiological explanation for this finding is that active vitamin D decreases IL-17-expressing CD4$^+$ T cells, and consequently reduces proinflammatory cytokines such as IL-1β, IL-6, and TNF. It also decreases Th$_{17}$-induced osteoclast activity and RA-associated bone resorption by inducing expression of RANK ligand on fibroblast-like synoviocytes and osteoblasts.[7] Articular damage is further prevented by vitamin D because it inhibits interleukin 1A-mediated production of matrix metalloproteinases.[49] Moreover, vitamin D also increases regulatory T cells, wich are impaired in RA.[7]

Furthermore, a recent meta-analysis that evaluated only serum vitamin D levels in RA showed a negative relationship between 25-hydroxyvitamin D serum concentrations and C-reactive protein and DAS-28, further increasing evidence that vitamin D deficiency is correlated to inflammatory biomarkers and disease activity.[50]

Regarding SLE, all 3 studies also had different supplementation schemes but shared 1 outcome of anti-dsDNA positivity, which rendered a reduction on the autoantibody positivity. Two studies[43,45] reported a statistically significant reduction in anti-dsDNA levels after 12 months[43] ($P=.05$) and after 6 months[45]
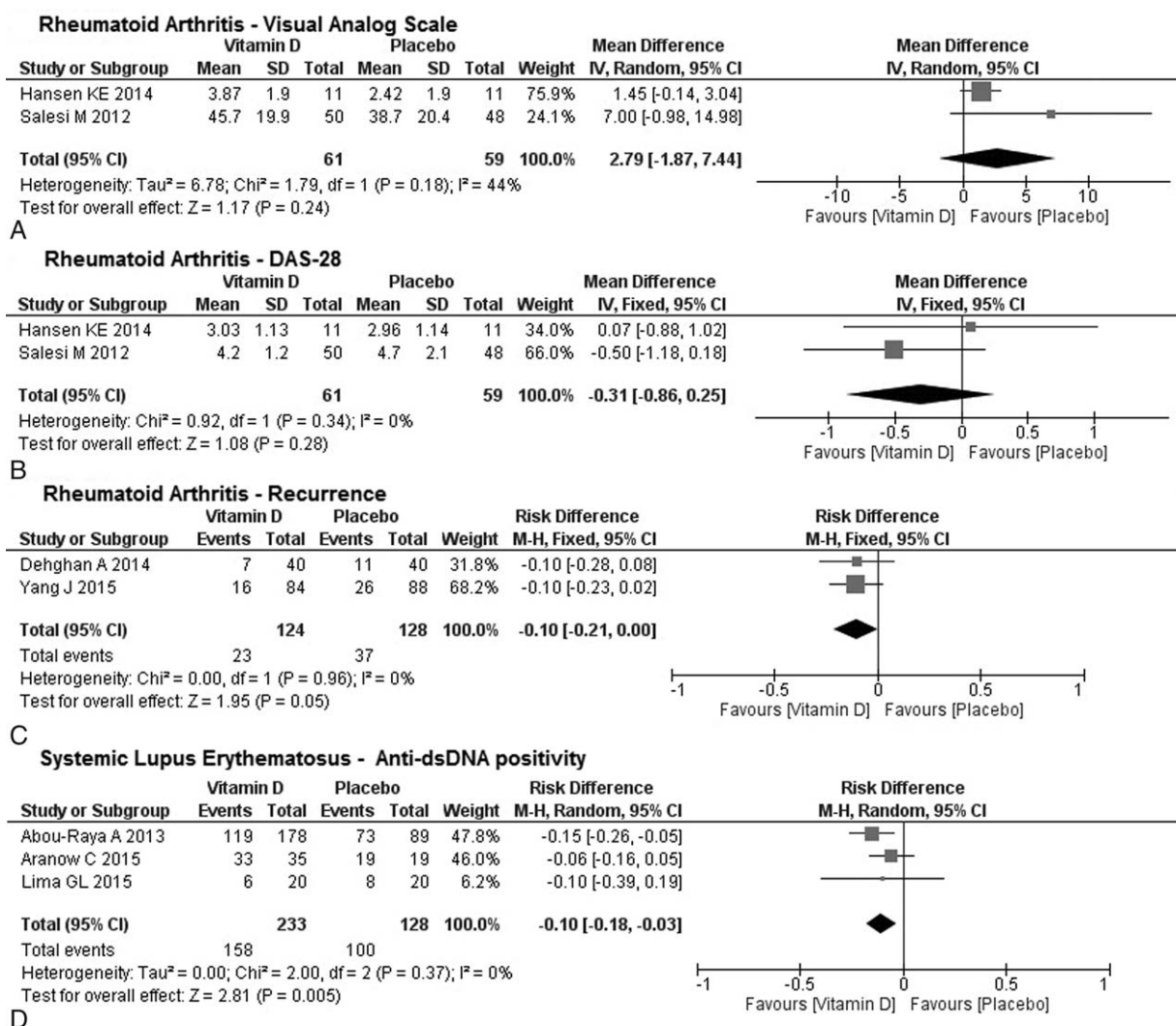
Figure 2. Mean difference of (A) VAS reduction and (B) DAS-28 reduction; and (C) risk difference of recurrence between studies on rheumatoid arthritis. No statistical significance was obtained. (D) Risk difference of anti-dsDNA positivity between studies on Systemic Lupus Erythematosus. Statistical significance was obtained (P = .005). DAS-28 = Disease Activity Score for Rheumatoid Arthritis, VAS = Visual Analog Scale.

(P = .03) of supplementation. However, 1 trial[44] reported fairly stable anti-dsDNA levels throughout 3 months of follow-up, and this difference may be explained by study length. Additionally, Lima et al[45] administered higher cholecalciferol doses than the other 2 studies.

Vitamin D deficiency has been associated with higher antinuclear antibodies levels in healthy subjects and in treatment-naive SLE patients, suggesting it might be a trigger for autoantibody production.[51,52] Moreover, elevated anti-dsDNA titers have been associated with moderate-to-severe SLE flares,[53] especially when its clinical presentation depends pathophysiologically on anti-dsDNA immune complex deposition as in renal impairment.[54–56] However, this correlation is controversial and other studies describe, with more consistent results, increases in anti-dsDNA titers as predictive biomarkers of clinical SLE flare.[57,58] Moreover, in patients with more than a 50% increase in anti-dsDNA titers, precautionary treatment prevents flares.[57] Thus, vitamin D supplementation may be beneficial to patients with high anti-dsDNA positivity, possibly reducing clinical flares.

Other less robust conclusions such as improvements to fatigue severity[45] can be drawn based solely on single trials due to the lack of comparable outcomes between studies.

Evidence on SSc is even poorer because the only identifiable trial was also not able to draw significant conclusions on its own, despite not finding any difference in skin scores after vitamin D supplementation.

6. Limitations

6.1. Outcome level

This meta-analysis, as any other, combines data from studies and estimates treatment effects with more precision than is possible with 1 study only. Thus, its main limitation, as with any overview, is that the patient population, the vitamin D supplementation schemes and the outcome definitions are not the same across studies. Moreover, a limited number of randomized controlled trials on vitamin D supplementation have been conducted in rheumatic diseases, and 2 of these studies

were excluded because important data could not be extracted.[39,46]

Notably, despite having positive statistical significance between groups after supplementation, several outcomes were not associated with clinical results such as anti-dsDNA in SLE. Additionally, new clinical trials should have a follow-up longer than 6 or 12 months, as shorter times may be insufficient to determine this correlation.

Studies on RA were highly heterogeneous primarily regarding intervention schemes and comparison groups. Also, 1 study[40] had a small sample size (N=22).

6.2. Study and review level

This review also has several limitations as the quality of trials varied. Randomization was inadequate in 4 of 9 trials, and allocation was inadequate in 6 of the trials, compromising the reliability of these data. Four of the trials did not analyze the data according to the intention-to-treat principle, which could lead to overestimation of the treatment effect in these trials.

7. Conclusion

Few randomized clinical trials investigated vitamin D supplementation on the activity of immune-mediated rheumatic diseases, and no assertive conclusions were drawn regarding its clinical outcomes. This work demonstrated a trend of reduction in rheumatic disease activity using vitamin D supplementation in RA, with a possible reduction in its recurrence, and in SLE, with a significant reduction in anti-dsDNA positivity, which is a biomarker of clinical flares. Nonetheless, novel randomized clinical trials are needed in order to increase the evidence level on vitamin D supplementation for immune-mediated rheumatic diseases, especially SLE and RA.

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