Review Article

Effects of Vitamin D Supplementation on Serum 25-Hydroxy Cholecalciferol in Inflammatory Bowel Diseases: A Meta-Analysis of Randomized Clinical Trials

Abstract

Background: Earlier studies about the influence of vitamin D (Vit D) supplementation on patients with inflammatory bowel disease (IBD) reported inconsistent results. Current comprehensive systematic review and meta-analysis was conducted to assess the effect of Vit D supplementation on clinical and subclinical factors in patients with IBD. **Methods:** PubMed, Scopus, and Web of Science databases were searched for relevant randomized controlled trials (RCTs) on the effect of Vit D supplementation in IBD patients, published up to March 2023. Data were analyzed by the random-effect model. Heterogeneity was assessed by Cochran's Q test and I-square (I^2) statistic. The mean differences (MDs) were calculated as the summary effect size. **Results:** We included nine related articles, and our findings indicated that vitamin D administration increased serum vitamin D levels compared to placebo (weighted mean difference (WMD): 12.08; 95% confidence interval (95% CI): 9.06, 15.09; I^2 = 97.01%; P < 0.001) in IBD patients. However, it had no significant influence on disease activity (standardized mean difference (SMD): 0.27; 95% CI: -0.42, 0.95; I^2 = 91.7%; P < 0.001) or serum levels of C-reactive protein (CRP) (WMD: -1.42; 95% CI: -3.90, 1.06; I^2 = 41.9%; P = 0.262). **Conclusions:** Current meta-analysis showed a significant effect of Vit D supplementation on increasing serum cholecalciferol. However, no significant effects of Vit D supplementation on the disease activity and serum levels of CRP were seen. Further studies are needed to expand current knowledge in this issue and found a significant increment in serum 25-hydroxy cholecalciferol concentrations following Vit D supplementation in IBD patients.

Keywords: *Cholecalciferol, inflammatory bowel diseases, meta-analysis, vitamin D*

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Introduction

Inflammatory bowel disease (IBD) is an idiopathic chronic gastrointestinal disease that has two main types: Crohn's disease (CD) and ulcerative colitis (UC).[1] IBD is characterized by recurrent periods of remission followed by episodes of clinical recurrence.[2] Due to the westernization of lifestyle in many nations, the prevalence of IBD has been increased throughout the world.[3] The incidence and prevalence of IBD have been increased globally in the twenty-first century.[4,5] Epidemiologic studies of IBD have been conducted in Asian countries, and the incidence and prevalence of IBD in Asia have increased over time.[4] Epidemiological studies have estimated that IBD affects about 2.5–3 million people in Europe.[6] IBD annually costs about 4.6–5.6 billion in Europe and six billion in the USA for healthcare systems.[6,7] The rate of IBDs has increased significantly in Asian countries during the last decade.[8]

Dietary intake is considered an important contributing factor in the pathogenesis of IBD; deficiencies of some micronutrients such as Vit D that is common among patients with IBD have been associated with the increased risk of IBD[9] and individuals with IBD are recognized to have an increased susceptibility to developing vitamin D deficiency.[10] Some epidemiological studies have shown higher risk of IBD among patients with Vit D deficiency.[11-13] In addition to the modulatory role in calcium and phosphate metabolism, Vit D has been found to improve innate immune system.[14] It can also minimize and regulate excessive immune responses by affecting T lymphocytes, dendritic cells (DCs), and macrophages.[15] Earlier studies reported controversial findings

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for the effects of Vit D supplementation on clinical and subclinical factors in patients with IBD. A meta-analysis by Li *et al*.[16] showed significant increase in serum 25-hydroxy cholecalciferol concentrations after treatment with Vit D in those patients; however, it had no significant influence on serum C-reactive protein (CRP) levels in that study.[16] In contrast, a systematic review and meta-analysis found that Vit D supplementation significantly decreased hs-CRP levels in IBD patients.[17] IBD management with supplementation of Vit D in those who are deficient offers an important strategy in improving clinical outcomes.[18] In addition to its role in modulating the inflammatory immune response and the composition of the gut microbiota, vitamin D is also crucial for maintaining intestinal homeostasis and preserving the integrity of the mucosal barrier.[19]

Given discrepancies between earlier studies, a comprehensive systematic review and meta-analysis is needed to summarize earlier studies on the effects of Vit D supplementation in IBD patients. This study aimed to summarize findings from available randomized clinical trials (RCTs) on the effects of Vit D supplementation on clinical and subclinical factors in patients with IBD.

Methods

Search strategy

This meta-analysis was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[20] PubMed, Scopus, and Web of Science databases were searched for relevant studies published from inception to March 2023 using these MESH and non-MESH terms: ((“Cholecalciferol”[Mesh] OR “Calcitriol”[Mesh] OR “Vitamin D”[Mesh] OR “Ergocalciferols”[Mesh] OR “vitamin D3”[tiab] OR “Vitamin D2”[tiab] OR “25-hydroxyvitamin D”[tiab] OR “25(OH) D”[tiab] OR “Cholecalciferol”[tiab] OR “Calcitriol”[tiab] OR “Vitamin D”[tiab] OR “Ergocalciferols”[tiab]) AND (“Inflammatory Bowel Diseases”[Mesh] OR “Crohn Disease”[Mesh] OR “Colitis, Ulcerative”[Mesh] OR “IBD”[tiab] OR “ulcerative colitis”[tiab] OR “Colitis, Ulcerative”[tiab] OR “Crohn Disease”[tiab] OR “Inflammatory Bowel Diseases”[tiab])). Moreover, a manual search of the reference lists of relevant original and review publications was conducted to avoid missing any eligible study. Gray literatures, such as dissertations, letters, and congress abstracts, were not included. Details of our search strategy are available in Supplementary Table 1.

Eligibility criteria

Three trained independent reviewers (RR, PGh, and AM) separately assessed the eligibility of included studies. Studies were included if they met the following criteria: (a) RCT study design; (b) population: involved adults with IBD; (c): reported mean values and standard deviations (SDs) for serum Vit D, CRP level, and disease activity at baseline and end of study or changes throughout the study in both intervention and control groups; and (d) published in English.

Studies were excluded if they were as follows: animal or *in vitro* studies, books, case reports, letters, unpublished data, dissertations, comments, conference papers, observational studies, non-interventional studies, and review articles. We also excluded studies in which Vit D was administrated along with another intervention or a low dose of Vit D was considered as a control group. Studies conducted on pregnant or lactating women or subjects under 18 years old were also excluded.

Data extraction and quality assessment

Three independent reviewers (RR, PGh, and ME) extracted necessary data from included studies. Any disagreements were resolved by the third independent researcher (AM). The following data were extracted from eligible articles: first author’s name, year of publication, study design, the sample size in each group, intervention type and dosage, placebo type, participants’ gender and age, duration of intervention, outcome assessment method, and adjustment or matching. The variables dose, duration, age, and total sample have been considered for subgroup analysis. We also extracted the mean values and SDs for outcomes of interest at study beginning and end. The quality of the selected RCTs was assessed using the Cochrane Collaboration risk-of-bias tool.[21]

Statistical analysis

Pooled weighted mean differences (WMDs), standardized mean differences (SMDs), and 95% confidence intervals (CIs) for the effects of Vit D supplementation on outcomes of interest were calculated using the random-effect model. Between-study heterogeneity was assessed using Cochran’s Q test (with significance P value lower than 0.1) and the I-square statistics (I^2 more than 50% considered as statistically significant). Subgroup analyses were conducted to identify potential sources of heterogeneity. All analyses were conducted on mean and SDs; therefore, if a study had reported other statistics than SD, we converted them to SDs using suitable formula. Plotdigitizer software was used to obtain data when it was reported in figures. All statistical analyses were conducted using the Comprehensive Meta-Analysis software, version 3. P values of <0.05 were considered to be statistically significant. We considered variables age, dose, duration, and total sample for subgroup analysis.

Results

Search results

The flowchart of the selection process in meta-analysis is shown in Figure 1. A total of 1844 reports were initially identified; after removing duplicate articles and studies that did not meet our inclusion criteria (n = 1500), 344 articles

Table 1: Demographic characteristics of the included studies

Code/Author (year)	Subjects and gender	Age range (y) and mean	Design	Intervention type		Duration (wk/d)	Outcomes	Outcome assessment method	Outcome		Adjustment or matching*
				Intervention (name and composition)	Control (name and composition)				Intervention Mean±SD and number	Control Mean±SD and number	
1. Jørgensen *et al.* (2010)	F: 62 M: 32 B: 94 I: 46 C: 48	I: 36±11 C: 38±14	Parallel	1200 IU/d Vit D	Placebo	48	25-OH vitamin D (nmol/L)	NR	B: 69±31 A: 96±27	B: 76±33 A: 76±33	No
2. Arihiro *et al.* (2019)	F: 87 M: 136 B: 223 I: 115 C: 108	I: 44.1±1.2 C: 45.4±1.4	Parallel	500 IU/d Vit D	Placebo	24	25-OH vitamin D (ng/mL)	Radioimmunoassay	B: 22.9±7.7 A: 32.2±10.2	B: 23.4±9 A: 21.1±8.2	No
							CAI	Lichtiger Clinical Activity Index for patients with UC	B: 2.55±0.21 A: 3.24±0.16	B: 2.49±0.19 A: 2.75±1.18	
							CDAI	The Crohn's Disease Activity Index (CDAI) for patients with CD	B: 97.9±77.7 A: 78.8±65.3	B: 68.1±43.9 A: 65.3±44.6	
3. Emami *et al.* (2020)	F: 37 M: 49 B: 86 I: 46 C: 40	I: 38±9 C: 35±9	Parallel	300000/(IU. IM)/90d Vit D	1 mL normal saline	13	Serum 25(OH) D (ng/ml)	ELISA	B: 33.3±7.0 A: 40.8±5.2	B: 32.9±9.6 A: 33.9±10.6	Age and BMI
4. Sharifi *et al.* (2016)	F: 37 M: 49 B: 86 I: 46 C: 40	I: 37.5±9 C: 35±9.2	Parallel	300000/(IU. IM)/90d Vit D	1 mL normal saline	13	Serum 25-hydroxyvitamin D (ng/ml)	Commercial ELISA kit	B: 33.3±7 A: 40.8±5.2	B: 32.9±9.6 A: 33.9±10.6	Age and BMI
							CRP (mg/L)	ELISA kit	B: 3.43±3.47 A: 2.31±2.25	B: 3.86±3.55 A: 3.90±3.97	
5. Raftery *et al.* (2015)	F: 14 M: 13 B: 27 I: 13 C: 14	I: 36.5±11.8 C: 36.7±12.1	Parallel	2000IU/d Vit D	Placebo	12	Vitamin D, nmol/L	Liquid chromatography–-tandem mass spectrometry	B: 69.2 (7.0) A: (91.6 (75.5–107.6)	B: 51.8 (20.7) A: (40.4 (30.4–50.4)	No

Contd...

Table 1: Contd...

Code/Author (year)	Subjects and gender	Age range (y) and mean	Design	Intervention type		Duration (wk/d)	Outcomes	Outcome assessment method	Outcome		Adjustment or matching*
				Intervention (name and composition)	Control (name and composition)				Intervention Mean±SD and number	Control Mean±SD and number	
6. Bendix *et al.* (2015)	F: 12 M: 6 B: 18 I: 9 C: 9	I: 36±9.25 C: 42±10.75	Parallel	1200 IU/d Vit D	Placebo	26	hs-CRP (nmol/l) 25-OH vitamin D nmol/l CDAI	NR	B: 61 (6–247) A: 17 (6–166) B: 36 (16–66) A: 111 (62–154) B: 35 (8–111) A: 33 (23–53)	B: 20 (12–276) A: 18 (0–83) B: 66 (22–105) A: 45 (27-97) B: 22 (0–187) A: 27 (0–273)	No
7. Dadaei *et al.* (2015)	F: 59 M: 49 B: 108 I: 53 C: 55	I: 37.3±14.7 C: 38.7±15.7	Parallel	50,000 IU/ weekly Vit D	Placebo	12	25-OH vitamin D (nmol/L)	Radioimmunoassay commercial kit (nmol/L)	B: 15.54 (S.D. 7.7) A: 67.89 (S.D. 33.7)	B: 21.70 (S.D. 7.8) A: 23.90 (S.D. 8.3)	No
8. Tan *et al.* (2018)	F: 34 M: 46 B: 80 I: 47 C: 33	I: 38.95±14.29 C: 42.7±14.4	Parallel	150,000 IU/3 months Vit D + calcium 600 mg	Calcium 600 mg	48	25-OH vitamin D (ng/ml)	25-(OH) vitamin D: a radioimmunoassay commercial kit (25 hydroxyvitamin D (ng/ml) Serum 25(OH) D levels were assayed by enzyme-linked immunosorbent kits Hercules, CA, USA	UC 25(OH) D: B: 10.62±4.11 A: 28.09±11.60 CRP: (mg/dL) B: 0.94±1.15 A: 1.02±0.94 CD 25(OH) D: B: 10.58±3.82 A: 23.04±9.66 CRP: (mg/dL) B: 5.36±12.04 A: 3.84±5.88	UC 25(OH) D: B: 12.53±3.77 A: 17.83±6.62 CRP: (mg/dL) B: 1.30±1.32 A: 1.36±1.68 CD 25(OH) D: B: 11.21±3.84 A: 15.94±7.87 CRP: (mg/dL) B: 8.16±8.04 A: 3.11±4.57	No
9. Bruyn *et al.* (2021)	F: 86 M: 57 B: 143 I: 72 C: 71	I: 31±15.55 C: 33±15.55	Parallel	20000 IU/d Vit D	placebo	4	25,000 IU/ weekly	NR	B: 39.7±23.0 A: 121.4±43.2	B: 29.6±6.3 A: 143.0±25.2	No

remained. Of them, 258 were excluded because they were non-relevant articles to our meta-analysis. Therefore, 86 potentially relevant articles were selected for full-text evaluation. Then, 77 articles were excluded for one or more of the following reasons: Supplementation was conducted with other types of intervention (n = 9), subjects <18 years old (n = 4), had no RCT design (n = 16), and did not measure outcomes of interest (n = 26). After the final assessment, nine eligible randomized controlled studies met the inclusion criteria and were considered for the final meta-analysis.

Sensitivity analysis revealed that excluding any studies did not change our findings in the current meta-analysis.

Characteristics of included studies

Table 1 shows general characteristics of the included studies. All selected studies were randomized, double-blind clinical trials, which enrolled 865 participants (445 subjects in the intervention group and 418 in the placebo group). The sample size of included studies ranged from 18 to 223. The mean age of participants ranged from 31 to 44.1 and 33 to 45.4 years in the intervention and control groups, respectively. All studies had parallel designs and were conducted on both genders. They were published between 2010 and 2023 and were conducted in Denmark (two studies),[22,23] Iran (three studies),[24-26] Japan,[27] China,[28] Ireland,[29] the Netherlands, and Belgium.[30] The duration of supplementation varied from 12 to 48 weeks in these studies. As a control group, participants in two studies received 1 mL of normal saline and in one study they used 600 mg of calcium. Intervention and control groups in two studies were matched for age and BMI, while the others had no adjustment.

Data quality

The Cochrane Collaboration risk-of-bias tool was used to assess the methodological quality of studies by the following domains: "randomization generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data, and selective outcome reporting, and the other sources of bias." We assigned low risk (+), unclear risk (?), and high risk (-) of bias for every eight items in Tables 2 and 3.

Meta-analysis: Forest plots containing effect sizes for the influence of vit D supplementation in IBD markers are presented in Figure 1. Pooled results from the random-effect model showed no significant effect of vit D supplementation on disease activity (SMD: 0.27; 95% CI: -0.42, 0.95; I^2 = 91.7%; P < 0.001) and serum concentrations of CRP (WMD: -1.42; 95% CI: -3.90, 1.06; I^2 = 74.11%; P = 0.262) [Figures 2 and 3]. However, as shown in Figure 1, vit D supplementation significantly increased serum vit D level in comparison with placebo (WMD: 12.08; 95% CI: 9.06, 15.09; I^2 = 97.5%; P < 0.001).

Subgroup analysis

Subgroup analyses were applicable only for the effect of Vit D supplementation on serum concentrations of cholecalciferol [Figure 4]. Stratifications were conducted by participants' age (<40 and ≥40), intervention duration (12< week and >12 weeks), supplementation

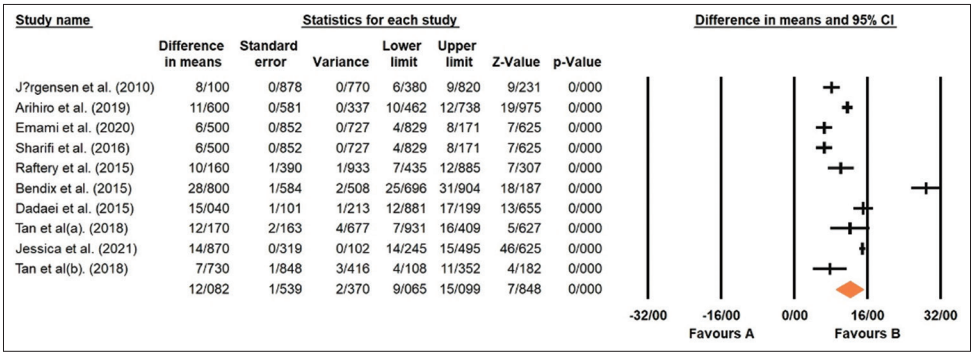

Figure 1: Forest plot detailing WMD and 95% CI for the effect of Vit D supplementation on serum Vit D level

Table 2: Results of subgroup analysis of included randomized controlled trials in meta-analysis of vitamin D and IBD

Variables	Dose (g/d)		Duration (weeks)		Age		Total sample		Study quality	
Vitamin D	**≥50**	**<50**	**≥12**	**<12**	**≥40**	**<40**	**≥50**	**<50**	**High**	**Low**
Number of comparisons	6	4	6	4	2	8	6	4	6	4
WMD (95% CI)	10.47 (6.44, 14.51	14.54 (8.03, 21.06)	13.85 (10.02, 17.76)	9.49 (5.54, 13.45)	11.63 (10.53, 12.73)	12.15 (8.22, 16.08)	10.44 (7.18, 13.71)	14.73 (4.82, 24.65)	12.41 (7.50, 17.32)	11.67 (7.24, 16.09)
P	0.00	0.00	0.001>	0.001>	0.001>	0.001>	0.001>	0.001>	0.001>	0.001>
I^2 (%)	96.92	97.76	97.03	93.96	0.00	97.64	97.32	97.14	97.04	96.76
P-heterogeneity	0.001>	0.001>	0.001>	0.001>	0.799	0.001>	0.001>	0.001>	0.001>	0.001>

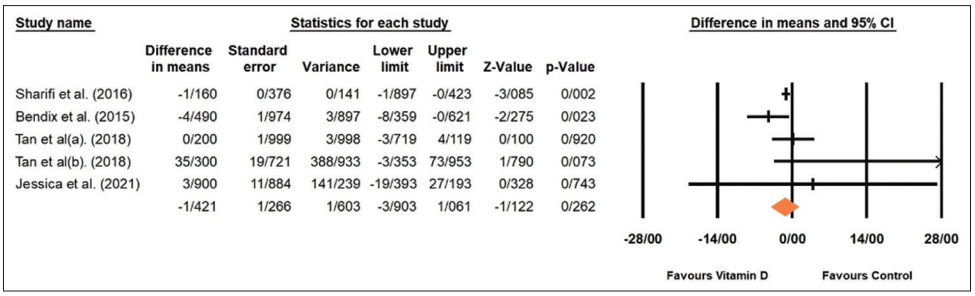

Figure 2: Forest plot detailing WMD and 95% CI for CRP

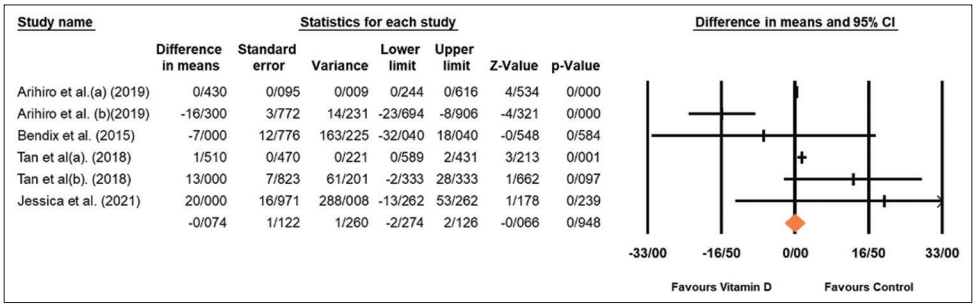

Figure 3: Forest plot detailing WMD and 95% CI for CDAI

Table 3: Quality assessment of clinical trials (according to the Cochrane guideline) and effects of vitamin D supplementation on serum concentrations of 25-hydroxy cholecalciferol and indicators of disease activity among patients with IBD

Study	Sequence generation	Allocation concealment	Blinding of participant and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity	General risk of bias
Jørgensen *et al*. (2010)	L	L	L	U	L	H	L	High
Arihiro *et al*. (2019)	L	L	L	U	L	H	L	High
Emami *et al*. (2020)	L	U	L	U	L	H	L	High
Sharifi *et al*. (2016)	L	U	L	U	L	H	L	Low
Raftery *et al*. (2015)	L	L	L	U	L	L	L	Low
Bendix *et al*. (2015)	L	U	U	U	L	H	L	High
Dadaei *et al*. (2015)	L	U	U	U	L	L	L	Low
Tan *et al*. (2018)	L	U	H	U	L	L	L	High
Bruyn *et al*. (2021)	L	U	L	U	L	L	L	Low

L=Low risk of bias; H=High risk of bias; U=Unclear risk of bias

doses (low concurrent dosage and high single dosage), and study sample size (n <50 and n ≥50). Overall finding remained unchanged in all subgroups.

Publication bias

Based on Egger's regression test, there was no evidence of publication bias for studies examining the effect of vitamin D on CRP (P = 0.765) and the Crohn's Disease Activity Index (CDAI) (P = 0.618). Furthermore, based on Begg's rank correlation test, there was no significant publication bias for CRP (P = 0.999) and CDAI (P = 0.850). The funnel plot of CRP is illustrated in Figure 5. Using the "trim and fill" method, 0 and 1 potentially missing studies were imputed for the meta-analyses of CRP and CDAI, respectively, to adjust for publication bias. Furthermore, 0 and 2 studies would be needed to bring the effect size of CRP and CDAI, respectively, to non-significant (P > 0.05), based on the analysis of the "fail-safe N" test.

Discussion

Current systematic review and meta-analysis showed a significant increase in serum levels of cholecalciferol following supplementation with Vit D in patients with IBD, which was also significant in all subgroups. However, Vit D supplementation had no significant influence on disease activity and serum levels of CRP.

Our meta-analysis showed that Vit D supplementation significantly increased serum levels of 25-hydroxy cholecalciferol in IBD patients. In line with our study,

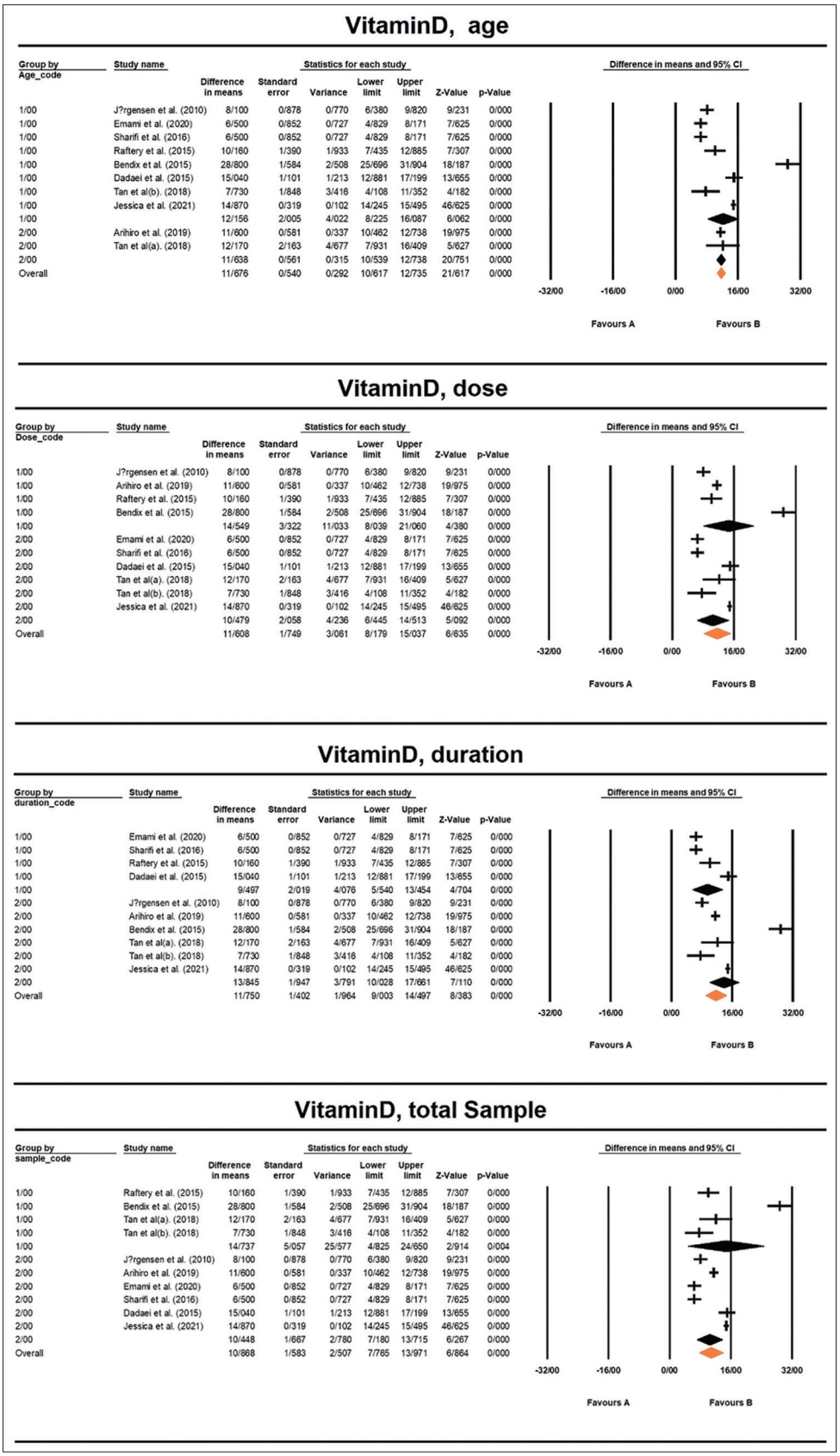

Figure 4: Subgroup analyses were applicable only for the effect of Vit D supplementation on serum

a randomized double-blind placebo-controlled study showed that oral supplementation with 1200 IU vitamin D3 significantly increased serum Vit D levels.[22] A meta-analysis conducted by Li *et al.*[16] showed significant

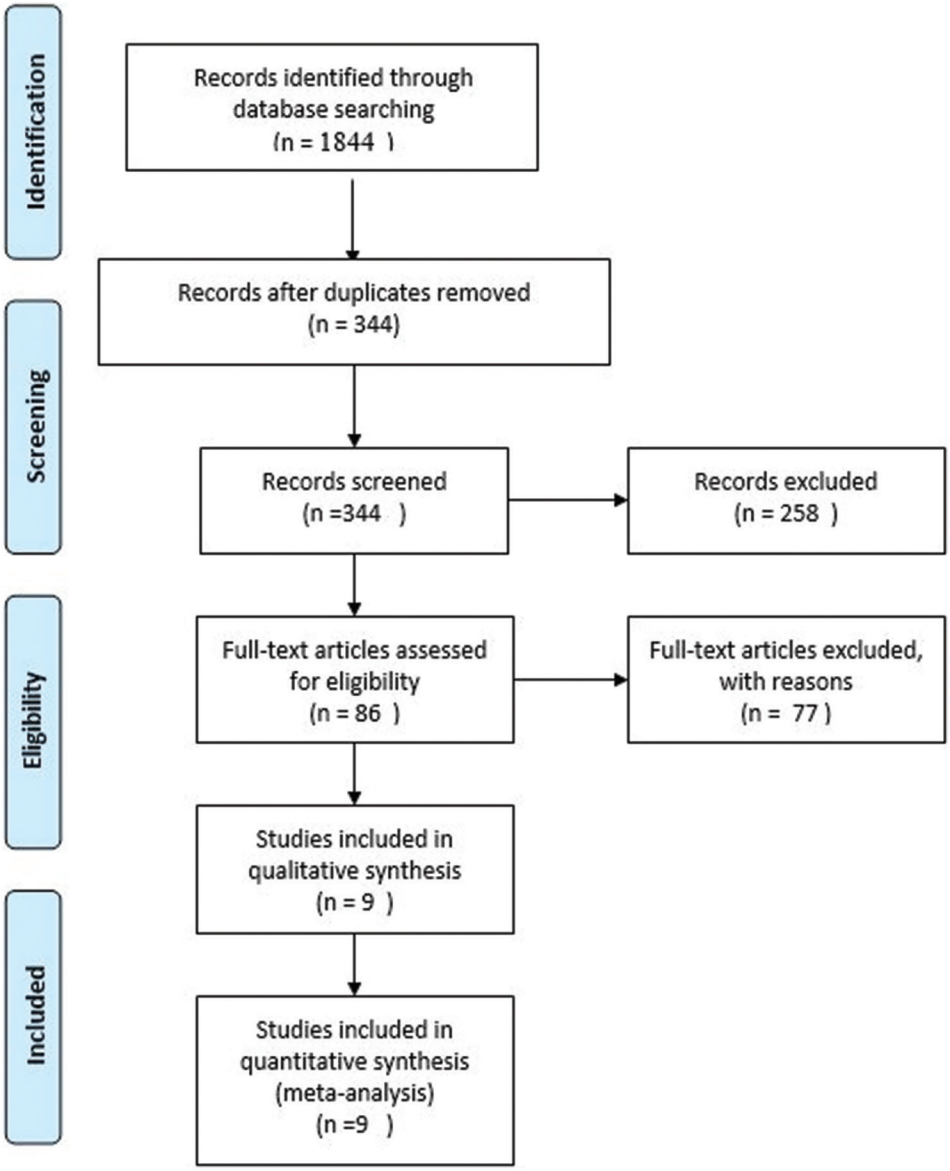

Figure 5: Flow diagram of the study selection procedure showing the number of eligible randomized controlled trials for the meta-analysis of effects of vitamin D supplementation on serum concentrations of 25-hydroxy cholecalciferol and indicators of disease activity among patients with IBD

elevation in serum 25-hydroxy cholecalciferol concentrations after treatment with Vit D in patients with IBD, which was more considerable in those with a treatment duration of ≥6 months and high doses of Vit D. All included studies in our meta-analysis also showed significant increment of serum cholecalciferol concentrations following Vit D supplementation. Our subgroup analyses showed that supplementation with lower doses of Vit D in longer duration might cause better results. Further studies are needed to determine the best supplementation dosage and duration for patients with IBD. Moreover, insufficient data are available about children and more researches are recommended for the future.

Our study failed to find a significant effect of Vit D supplementation on disease activity among patients suffered from IBD. An earlier RCT among patients with CD also showed no significant changes in the disease activity score after intervention with Vit D (27). A cross-sectional prospective study conducted by Hassan *et al.*[31] also found no significant association between Vit D deficiency and disease activity in a relatively small number of IBD patients. However, in contrast with our findings, Yang's RCT in 2013 found that 24-week supplementation with up to 5,000 IU/d Vit D significantly reduced disease activity score in a group of patients with CD.[32] In another RCT by Miheller *et al.*,[33] 6-week supplementation with Vit D in CD patients significantly reduced disease activity score. Differences in supplementation dosage and study duration might be responsible for these discrepancies. Considering earlier findings, one might think that acute supplementation

with high doses of Vit D might be the better choice. We tried to discuss these points by different subgroup analyses, but the number of included studies in each category was limited; so, further studies are needed to expand our knowledge in this area.

This study showed that Vit D supplementation did not significantly affect serum CRP levels. In consistent with our results, Tan *et al*.[28] found that CRP levels were not significantly changed in the Vit D supplement group compared to the control group. Moreover, a meta-analysis by Li *et al*.[16] in 2018 reported that Vit D supplementation in patients with IBD had no significant influence on serum CRP levels. However, a systematic review and meta-analysis found that Vit D supplementation significantly decreased hs-CRP levels in IBD patients.[17] In addition, Sharifi *et al*.[26] reported that hs-CRP levels were lower in the Vit D group after the intervention group, as compared with those in the control group. It seems that baseline concentration of CRP is a crucial factor in the association of Vit D supplementation with changes in CRP concentrations. Most included studies did not adjust their findings for this important confounder. Moreover, disease stage is another important factor in this regard. As IBD is an inflammation-based disease, those in the final stages might have more inflammation than those at the beginning. Therefore, effects of Vit D supplementation on serum CRP levels should be separately studied in patients at different stages of IBD. Finally, CRP is a serum indicator of general inflammation; so, studying effects of Vit D supplementation on gut inflammatory responses will help to reach best conclusions in patients who are suffering from IBD.

Vit D supplementation might influence IBD prognosis in several ways. Antimicrobial and anti-inflammatory properties of Vit D might help to repair intestinal mucosal barriers in these patients.[34] Initially, 1,25(OH) 2D3 binds to the Vit D receptor (VDR) and activates it, then enhances the bactericidal effect by acting directly on the locus of monocyte-induced antibacterial protein expression.[35] Reducing pathogenic bacteria will be associated with significant improvements in disease prognosis for patients with IBD. Besides, Vit D can increase expression of nucleotide-binding oligomerization domain protein 2 (NOD2) by inducing multiple types of cells, through which it activates key downstream signaling to induce expression of some genes encoding antimicrobial peptide defensin beta2 (DEFB2/HBD2) by stimulation of nuclear factor kappa B (NF-kB) transcription factor.[36] In addition, Vit D directly acts with the CD4+T cells to promote the proliferation and differentiation of Th2 cells while inhibiting the proliferation of Th1 cells by acting on DCs to reduce inflammation.[37] Vit D also shows its anti-inflammatory properties by increments in serum levels of IL-10 and decreases in IL-12 levels. Vit D also can reduce the production of TNF-α by upregulating mitogen-activated protein kinase phosphatase-1 and inhibiting activation of mitogen-activated protein kinase (MAPK).[38] These antimicrobial and anti-inflammatory actions of Vit D might result in significant reductions in the gut barrier damages in IBD patient. Moreover, Vit D enhances tight junctions between intestinal epithelial cells, thereby maintaining mucosal barrier function by promoting the expression of tight junction proteins ZO-1, claudin-1, and occluding.[39] Parathyroid hormone, vitamin D supplementation in patients undergoing bariatric surgery modestly improves vitamin D status and vitamin D supplementation was associated with prevention of raising of the PTH serum concentration and without impact on serum calcium levels.[40] Reductions in pathogenic bacteria will be associated with significant improvements in the prognosis of IBD patients. Our study has several strengths. To the best of our knowledge, this research is the first comprehensive systematic review and meta-analysis about the efficacy of Vit D in IBD patients. In addition, the search strategy was precise and we performed subgroup analysis when applicable. Along with these strengths, some limitations of this meta-analysis also should be noted. The limited number of included studies is a great concern. Moreover, we found significant heterogeneity among the included studies mainly due to the different dosages and duration of intervention and also because of differences in patient ethnicity, age, country, and comorbidities. We tried to explore the heterogeneity by doing several subgroup analyses, but limited number of included studies made it impossible in some cases. Further studies on different populations are needed to reach a firm conclusion. Moreover, data about several important outcomes including the disease activity, disease progression, and disease severity were not enough for a separate meta-analysis. Finally, most included studies did not adjust their final results for the baseline levels of Vit D in serum.

Conclusions

In this study, we found a significant increment in serum 25-hydroxy cholecalciferol concentrations following Vit D supplementation in IBD patients. However, we failed to find the influence of Vit D on serum CRP and disease activity in these patients. To confirm our findings and improve the knowledge for reducing the complications of IBD patients, further well-designed RCTs with appropriate methodology and larger populations are needed.

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Conflicts of interest

There are no conflicts of interest.

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