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Efficacy of vitamin D in treatment of inflammatory bowel disease

A meta-analysis

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Abstract

Background: Vitamin D (VitD) deficiency is prevalent in patient with inflammatory bowel disease (IBD). Recent studies have found that VitD can induce and maintain IBD remission through antibiosis, anti-inflammatory, and repair of intestinal mucosal barriers, thus improving the patient's disease activity and quality-of-life. The purpose of this meta-analysis is to evaluate the therapeutic effect and safety of VitD in the treatment of IBD.

Methods: Published randomized controlled trials (RCTs) were included from electronic databases (PubMed, Embase, Cochrane library, Web of Science, and so forth). Cochrane handbook was applied to evaluate the methodological quality. The levels of 25(OH)D3, relapse rate, inflammation index, and adverse events were compared between the experimental group and the control group (placebo group). All statistical analyses were directed by Revman 5.3 software and statistical significance was defined as $P < .05$.

Results: Eighteen RCTs involved 908 patients were included. Meta-analysis showed that VitD improved the 25(OH)D3 levels more significantly than the control group (ng/mL, weighted mean deviation [WMD] = 7.85, 95% CI (5.52, 10.18), $P < .000001$), and compared with lower doses, there were significant differences increasing 25(OH)D3 levels (WMD = 11.19, 95% CI [4.73, 17.65], $P = .0007$) in high-dose VitD treatment while there was no significant difference in the adverse events between 2 groups (WMD = 1.56, 95% CI [0.74, 3.29], $P = .24$). VitD reduced the relapse rate more significantly than the control group, but there were no significant differences between the low-dose and high-dose vitamin D treatment. The erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hsCRP) of the VitD and the control group showed no statistically significant difference (ESR [mm/h]: WMD = –0.22, 95% CI [–5.73, 5.29], $P = .94$; hsCRP (mg/dL): WMD = –0.53, 95% CI [–1.68, 0.62], $P = .37$).

Conclusions: The treatment of VitD in patients with IBD can improve the level of 25(OH)D3 and control the relapse rate of the disease, whose clinical curative effect is more accurate. Thus VitD should be recommended for the treatment of IBD, at least as an adjunctive treatment.

Abbreviations: CD = Crohn disease, DCs = dendritic cells, ESR = erythrocyte sedimentation rate, hsCRP = high-sensitivity C-reactive protein, IBD = inflammatory bowel disease, NF-*k*B = nuclear factor kappa B, NOD2 = nucleotide-binding oligomerization domain protein 2, RCTs = randomized controlled trials, TNF-*a* = tumor necrosis factor-*a*, UC = ulcerative disease, VDR = vitamin D receptor, VitD = Vitamin D.

Keywords: Crohn disease, inflammatory bowel disease, meta-analysis, systematic review, ulcerative colitis

1. Introduction

Inflammatory bowel disease (IBD), including Crohn disease (CD) and ulcerative disease (UC), is a chronic, relapsing intestinal inflammatory disorder with unidentified causes.[1] The prevalence of IBD is increasing worldwide, with approximately 3 million people in Europe and 1.5 million people in the United States affected and rapidly increasing trends observed in Asia recently.[1,2] IBD is thought to result from an inappropriate and ongoing activation of the immune system against environmental triggers in genetically predisposed individuals.[3] Risk factors associated with IBD include altered intestinal flora, foods rich in carbohydrates and fats, oral contraceptives and living in urban areas,[4–6] and stressful lifestyles are thought to exacerbate the disease.[7] Impaired mucosal barrier function promotes an aberrant innate immune response to gut luminal agents under these circumstances, results in stimulation of dendritic cells and activation of the inflammatory cascade, leading to intestinal inflammation.[8] In addition to regulating calcium and phosphate metabolism, VitD, a pleiotropic hormone, has been found to exert antibiosis by enhancing aberrant innate immune functions.[9,10] It can also modulate immune responses by directly or indirectly affecting T lymphocytes, dendritic cells (DCs) and macrophages, avoiding excessive immune responses.[11,12] In addition, VitD has the function of repairing the intestinal mucosal barrier.[13] VitD deficiency is prevalent in the patient with IBD. Due to low 25(OH)D3 levels, long-term illness, and repeated use of hormones, IBD patients have a significant increase in the risk of

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bone loss and fractures. Lots of clinical trials have been conducted to verify the efficacy of VitD in treatment of IBD. However, these studies provided controversial conclusions of VitD's efficacy and safety. In view of the feasibility and prospect of adjuvant treatment of vitamin D in IBD, this meta-analysis evaluated the efficacy and safety by analyzing eligible studies and statistics, relevant indices to provide guidelines for clinical decisions and further researches.

2. Materials and methods

This study was approved by the Ethics Committee of First Hospital of Jinan University. This meta-analysis was performed as listed steps: planed search strategy, selected study according to inclusion and exclusion criteria, assessed the quality of studies included, extracted the data, defined the outcomes, and analyzed the data.

2.1. Search strategy and selection criteria

The process of article selection is shown in Fig. 1. The Cochrane Library, PubMed, Medline, EMBase, CNKI, CBM, VIP, and Wanfang Data Knowledge Service Platform were searched up from 1978 to 2018 to collect the English and Chinese literatures about randomized controlled trials (RCTs) that compared the levels of 25(OH)D3, relapse rate, inflammation index or adverse events between the experimental group and the control group (placebo group). The search query is limited to the combination of the Mesh and the free word. The following search Mesh were used: inflammatory bowel disease, Crohn disease, ulcerative colitis, randomized controlled trial, and controlled clinical trial. We also performed the manual search of the reference lists of the obtained studies.

Inclusion criteria: the study subjects were confirmed diagnosis of IBD (either CD or UC) by a gastroenterologist. The experimental group was given VitD; the control group was placebo or low-dose VitD; the research indicators mainly included 25(OH)D3 level (ng/mL) and relapse rate, adverse events, inflammation indicators (ESR [mm/h], hsCRP [mg/dL]). The type of study was a randomized controlled trial (RCTs). Exclusion criteria included: pregnant women or women considering pregnancy during the study period, short-gut syndrome, and any condition which could predispose to VitD toxicity, including renal insufficiency (creatinine clearance <60 mL/min), sarcoidosis, hyperparathyroidism, or malignancy. Concomitant therapy with thiazide diuretics, barbiturates, digitalis, or supplemental products containing VitD was not permitted. Review, case reports, and empirical summary articles; documents that cannot be obtained in full; no control group; rats and other animals.

2.2. Data extraction and quality assessment

All of the data were extracted independently by 2 reviewers according to the selection criteria (JL and NC), any disagreements were discussed and documented. When the extracted data were not uniform, consults were needed to settle the disagreements and to make a final determination. All trials included in this study contained the following data: first author's name, published year, the number of patients, interventions, and outcomes. And the risk of bias (selection, detection, attrition, and reporting bias) of each study was assessed independently by 2 researchers by using the tools from the Cochrane Handbook for Systematic Reviews of Interventions (Figs. 2 and 3).

2.3. Statistical analysis

Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to assess pooled weighted mean deviation (WMD) and standard deviation (SD) for continuous

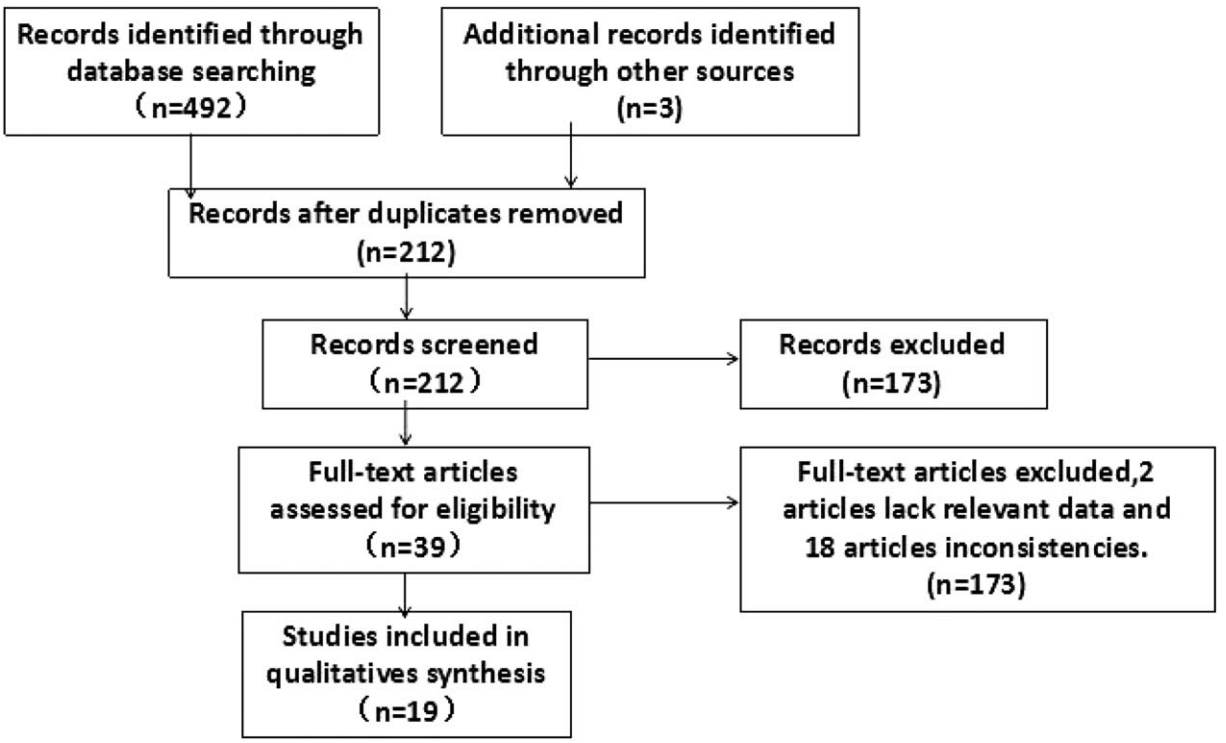

Figure 1. Flowchart of study selection.

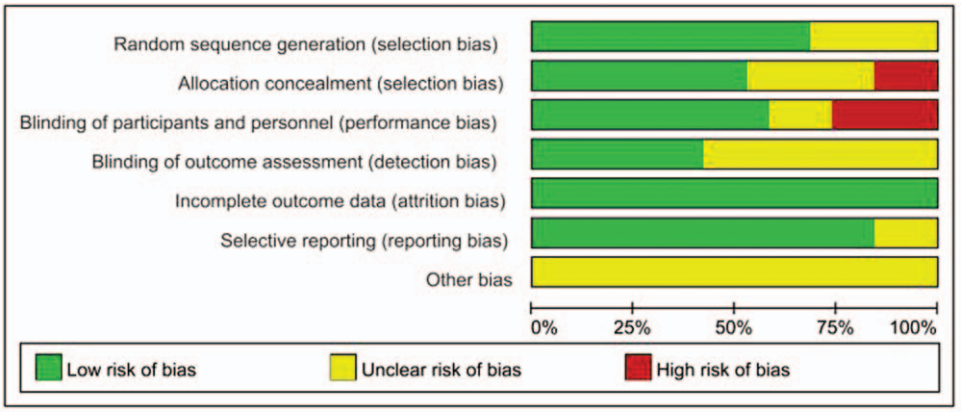

Figure 2. Judgment of the percentage of projects that included the risk of bias in the study.

outcomes. 95% confidence interval (95% CI) was regarded as effective size in the combined analysis. Chi-square and I^2 tests were performed to assess the heterogeneity. If $P > .1$ or $I^2 < 50\%$ indicated substantial heterogeneity among studies, the randomized-effects model was used. Otherwise, the fixed-effects model was used. Statistical significance was defined as $P < .05$.

3. Result

3.1. General characteristics of included studies

The characteristics of studies included are clarified in Table 1. After eligibility assessment, we finally obtained 18 trials with a total of 908 patients: 15 in English and 3 in Chinese.[14–31] Among these records, the study of Tan et al[18] included 2 control groups: CD group and UC group, thus, we divided this study into 2 parts: Tan, B(CD) 2017 and Tan, B(UC). The basic characteristics of the studies included in the meta-analysis are summarized in Table 1. One of the included trials with design limitations have lower study quality due to high risk for blinding of participants and researchers, and Random sequence generation.[31]

3.2. Meta-analysis

3.2.1. Serum 25(OH)D3 levels. Six trials[14–19] reported changes in 25(OH)D3 levels in patients with IBD after vitamin D and placebo treatment. The $P < .00001$ and $I^2 = 93\%$ indicated indispensable heterogeneity. The selected random-effects model showed that the increase of 25(OH)D3 levels in VitD treating group was more significant than that of placebo in control group (25(OH)D3 ng/mL: WMD = 10.44, 95% CI (5.39, 15.48), $P < .0001$) (Fig. 4A). Raftery et al[19] did not directly give the standard deviation of 25(OH)D3 after treatment, which was calculated indirectly according to the quartile spacing; meanwhile, the 25(OH)D3 results of Tan et al[18] were significantly lower in both the experimental group and the control group than those of other included studies; and there were differences in the 25(OH)D3 before treatment in the Dadaei et al,[17] and the difference of 25(OH)D3 between the experimental group and the control group after treatment was too great, considering the error, they were excluded in the meta-analysis. Meta-analysis was conducted again as followed: four trials[14–15,18] reported changes in 25(OH)D3 levels in patients with IBD after vitamin D and placebo treatment. The $P = .78$ and $I^2 = 0\%$ indicated dispensable heterogeneity. The selected Fixed-effects model showed that the increase of 25(OH)D3 levels in VitD treating

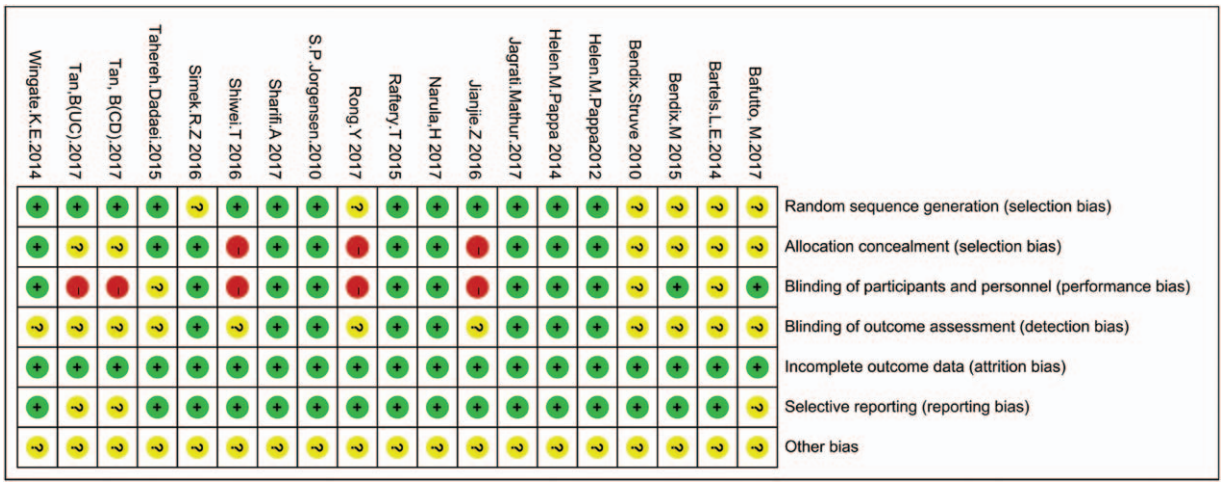

Figure 3. The author's judgment on each risk-biased item included in the study.

Table 1

Characteristics of the studies included in the meta-analysis.

Refs	Patients enrolled (E/C)	Race	Gender (female%)		Age		Case group intervention	Control group intervention	Duration
			E	C	E	C			
Jørgensen et al [14]	94 (48/46)	Dane	72	60	36±11	38±14	1200 IU/d VitD	Placebo	12 mo
Sharifi et al[15]	86 (46/40)	Iranian	43	43	37.5±9	35±9.2	300000/(IU.IM)/90d VitD	1 ml NaCl IM	90 d
Tang et al [16]	90 (45/45)	Chinese	44	49	32.5±10.5	32.5±10.5	800 IU/d VitD	Vehicle control	60 d
Dadaei et al [17]	108 (53/55)	Iranian	51	58	37.3±14.7	38.7±15.73	50,000 IU/wkly VitD	Placebo	26 wks
Tan et al, [18]	40 (23/17)	Chinese	-	-	-	-	150,000 IU/3 mo VitD	Vehicle control	12 mo
Tan et al,[18]	40 (24/16)	Chinese					150,000 IU/3 mo VitD	Vehicle control	12 mo
Raftery et al[19]	27 (13/14)	Iranian	57	53	36.5±11.8	36.7±12.1	2000 IU/d VitD	Placebo	3 mo
Bafutto et al, [20]	20 (10/10)	Dutch	-	-	-	-	50,000 IU/wkly VitD	10,000 IU/wkly	8 wk
Pappa et al [21]	47 (23/24)	American	39	58	16.3±3.2	14.7±3.5	50,000 IU/wkly VitD	2000 IU/d	6 wks
Pappa et al[22]	63 (31/32)	American	55	59	14.5±3.1	15.1±3.1	1000or2000 IU/d VitD	400 IU/d	12 mo
Mathur et al[23]	18 (10/8)	American (Mixed)	40	13	40.2±16.2	41.1±13.7	4000 IU/d VitD	2000 IU/d	90 d
Narula et al,[24]	34 (18/16)	Canadian	56	63	33±3	35±3	10,000 IU/d VitD	1000 IU/d	12 mo
Simek et al[25]	32 (18/14)	American (Mixed)	39	36	15.6±2.5	15.8±3.2	10,000 IU/10 kg. weekly VitD	5000IU/10 kg.weekly	6 wk
Wingateet al[26]	83 (43/40)	Canadian	44	46	14.5±2.1	14±2.4	2000 IU/d VitD	400 IU/dqd	6 mo
Bartels et al [27]	19 (10/9)	Dane	70	56	-	-	1200 IU/d VitD	Placebo	26 wk
Bendix et al[28]	18 (9/9)	Dane	67	67	-	-	1200 IU/d VitD	Placebo	26 wk
Bendix et al[29]	20 (10/10)	Dane	70	60	-	-	1200 IU/d VitD	Placebo	12 mo
Zhao et al[30]	89 (46/43)	Chinese	41	42	46.3±2.5	42.8±3.7	800 IU/d VitD	Vehicle control	3 mo
Yang and Yang [31]	80 (40/40)	Chinese	33	40	41.2±10.2	43.1±11.9	800 IU/d VitD	Vehicle control	12 mo

group was more significant than that of placebo in control group (25(OH)D3 ng/mL: WMD=7.85, 95% CI (5.52, 10.18), $P<.000001$) (Fig. 4B).

Seven trials[20–26] reported changes in 25(OH)D3 levels after different doses of vitamin D treatment, the heterogeneity was high ($P<.00001$, $I^2=94\%$). It revealed that there was significant difference in increasing 25(OH)D3 level between the high-doses vitamin D treating group and lower doses group (25(OH)D3 ng/mL: WMD=11.19, 95% CI [4.73, 17.65], $P=.0007$) (Fig. 5).

3.2.2. Relapse rate. Seven trials[14,19,27–31] reported the relapse rate of IBD patients after treatment with vitamin D and placebo, Raftery et al[19] and Zhao and Zhu[30] were followed up for 3 months. The follow-up time of Bendix et al[28] and Bartles et al[27] was 26 weeks, while that of Jørgensen et al,[14] Bendix-Struve et al,[29] and Yang and Yang[31] was 1 year. As shown in Fig. 6, the heterogeneity was low ($P=1.00$, $I^2=0\%$). The selected fix-effects model showed that the reduction of relapse rate in VitD treating group was more significant than that of placebo in control group (relapse rate: WMD=0.36, 95% CI [0.21, 0.62], $P=.0002$). And the relapse rate of the experimental group and the control group was not statistically significant at 26week, but that of the experimental group was significantly lower than that of the placebo group at 3 months and 1 year.

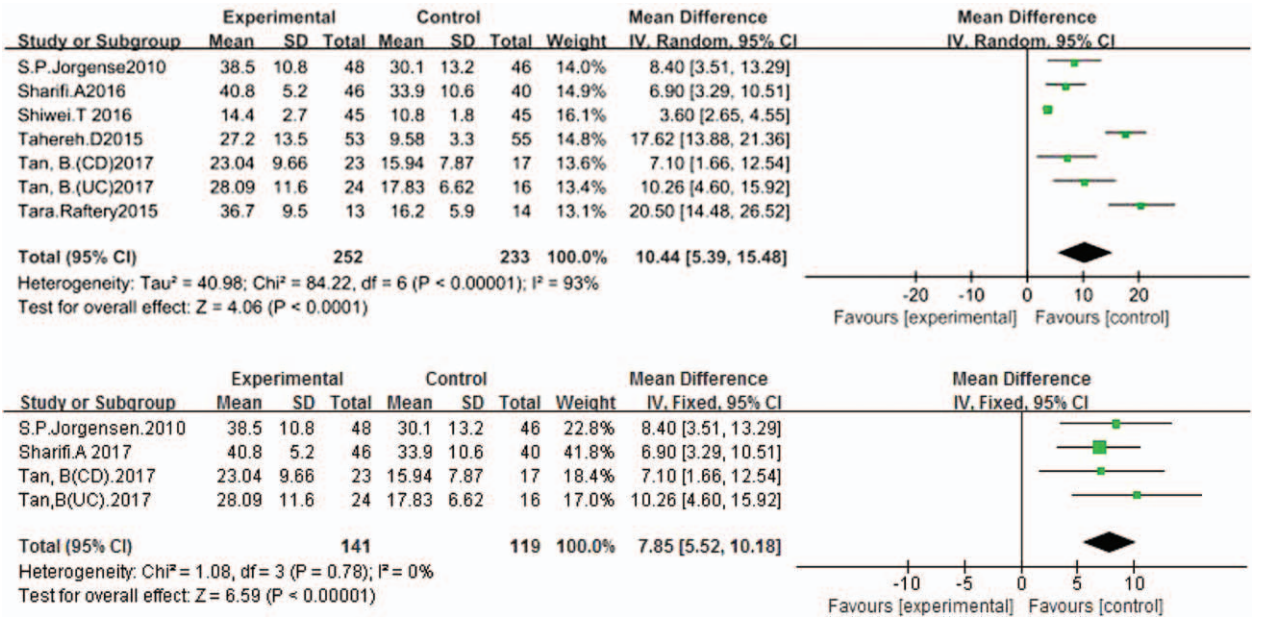

Figure 4. Forest plot for comparison of 25(OH)D3 levels in patient with IBD treated by VitD and the control group. IBD=inflammatory bowel disease, VitD=Vitamin D.

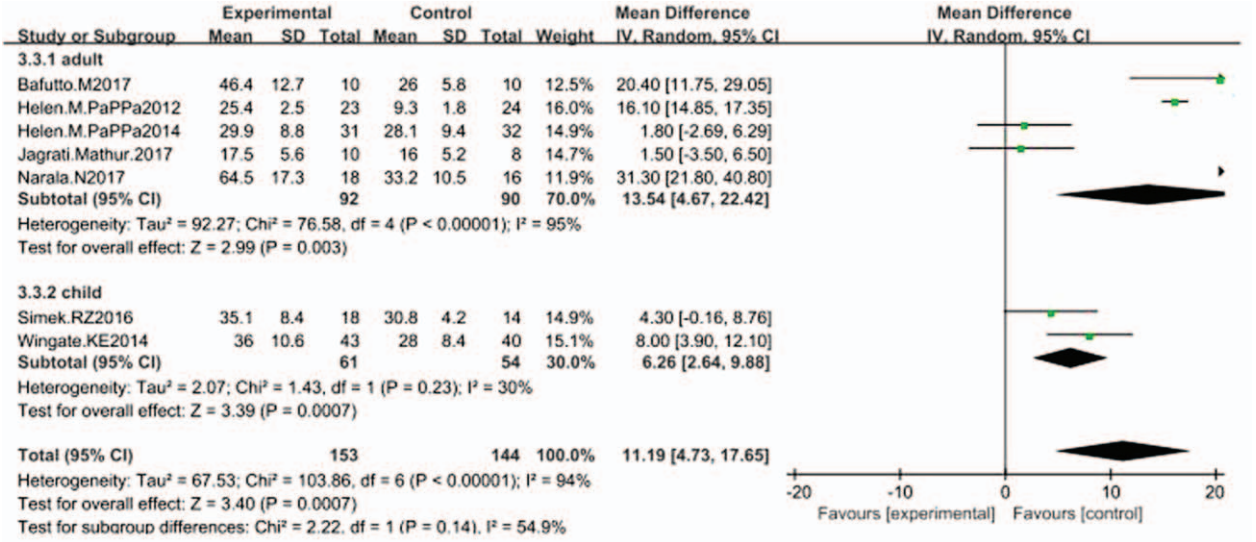

Figure 5. Forest plot for comparison of 25(OH)D3 levels in patient with IBD treated by VitD with different doses. IBD = inflammatory bowel disease, VitD = Vitamin D.

Three trials[21,24,26] reported the relapse rate of IBD patients after treatment with different doses of VitD, the follow-up time of Helen. Pappa et al,[21] Narula et al,[24] and Wingate et al[26] was 6 weeks, 1 year, and 6 months, respectively. The heterogeneity was not evident ($P = .20$, $I^2 = 38\%$), but there was no statistical significances between the high-doses VitD group and the lower doses group ($P = .38$) (Fig. 7)

3.2.3. Inflammation indicators. Two trials[15,18] reported ESR and hsCRP of IBD patients after treatment with Vit D and placebo. The heterogeneity was evident ($P = .001$, $I^2 = 85\%$) in ESR trials, but there was no statistical significances between the VitD group and the placebo group ($P = .94$) (Fig. 8). And, there was no heterogeneity ($P = .15$, $I^2 = 48\%$) and the statistical significance did not exist either ($P = .18$) (Fig. 9). In conclusion,

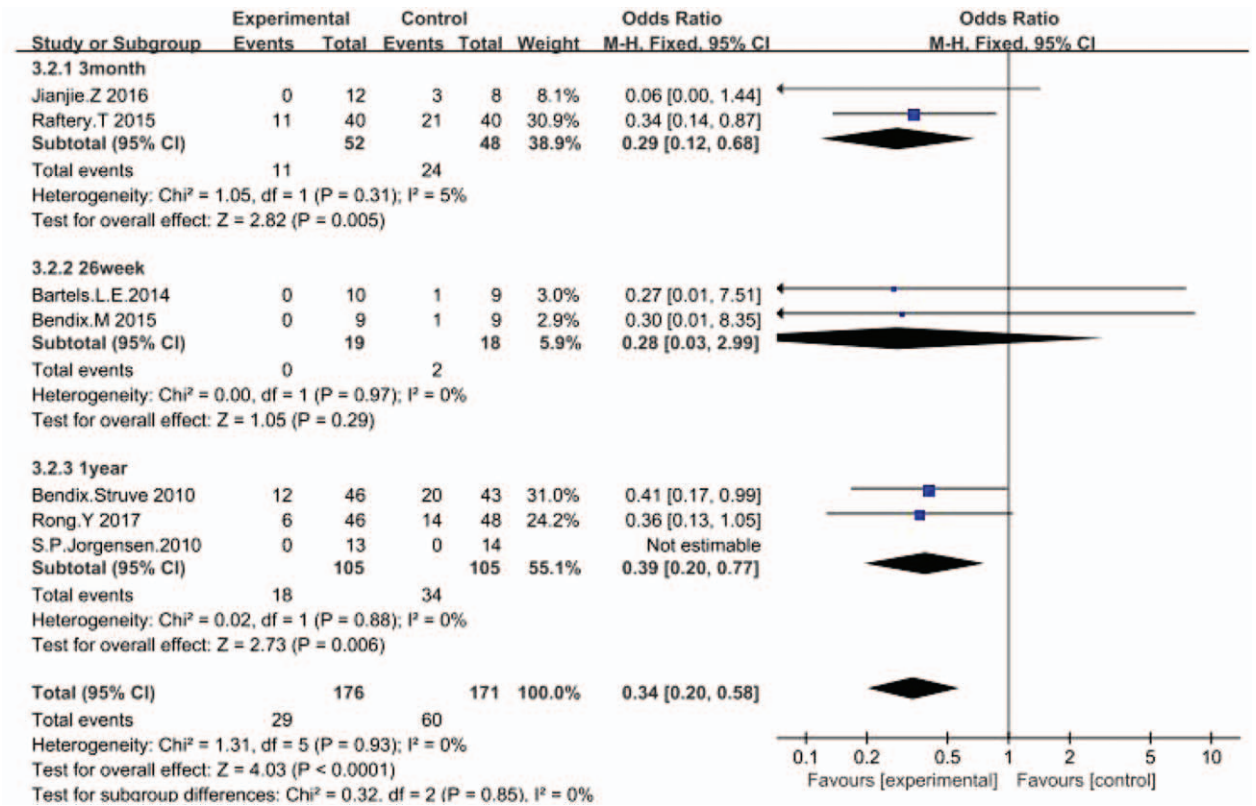

Figure 6. Forest plot for comparison of relapse rate in patient with IBD treated by VitD and the control group. IBD = inflammatory bowel disease, VitD = Vitamin D.

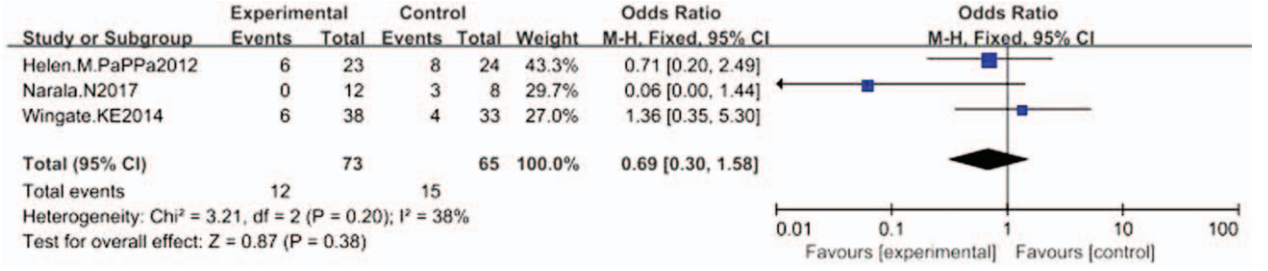

Figure 7. Forest plot for comparison of relapse rate in patient with IBD treated by VitD with different doses. IBD = inflammatory bowel disease, VitD = Vitamin D.

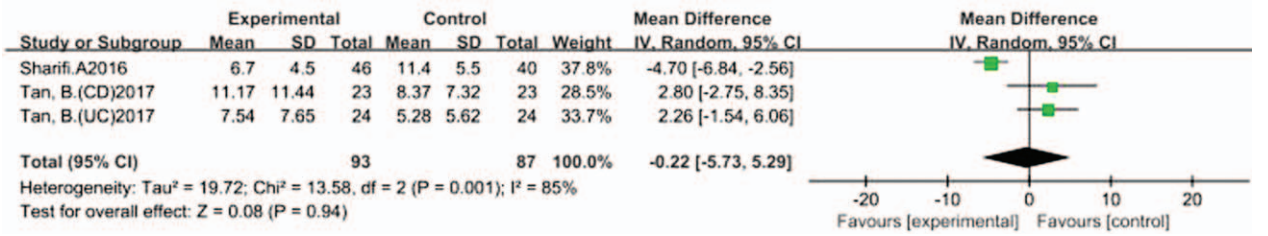

Figure 8. Forest plot for comparison of ESR in patient with IBD treated by VitD and the control group. ESR = erythrocyte sedimentation rate, IBD = inflammatory bowel disease, VitD = Vitamin D.

neither ESR nor hsCRP dropped obviously after VitD treatments in comparison with the placebo.

3.2.4. Adverse events. The above meta-analysis suggests that high-dose VitD therapy can bring higher levels of 25(OH)D3 and lower disease relapse in IBD patients, but it is unclear whether high-level dose supplementation also causes corresponding adverse reactions. Six trials[21–26] reported adverse events after different doses of VitD supplementation, which mainly including drowsiness, thirst, nausea, dry mouth, headache (persistent), unusual fatigue or weakness, and mild gastrointestinal events. As shown in Fig. 10, there was no heterogeneity ($P = .95$, $I^2 = 0\%$), the results showed that the incidence of adverse events of VitD supplementation at different doses was lower, otherwise, there

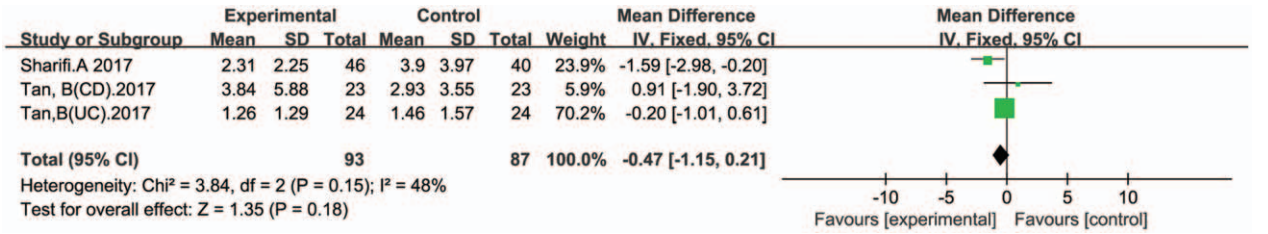

Figure 9. Forest plot for comparison of hsCRP in patient with IBD treated by VitD and the control group. hsCRP = high-sensitivity C-reactive protein, IBD = inflammatory bowel disease, VitD = Vitamin D.

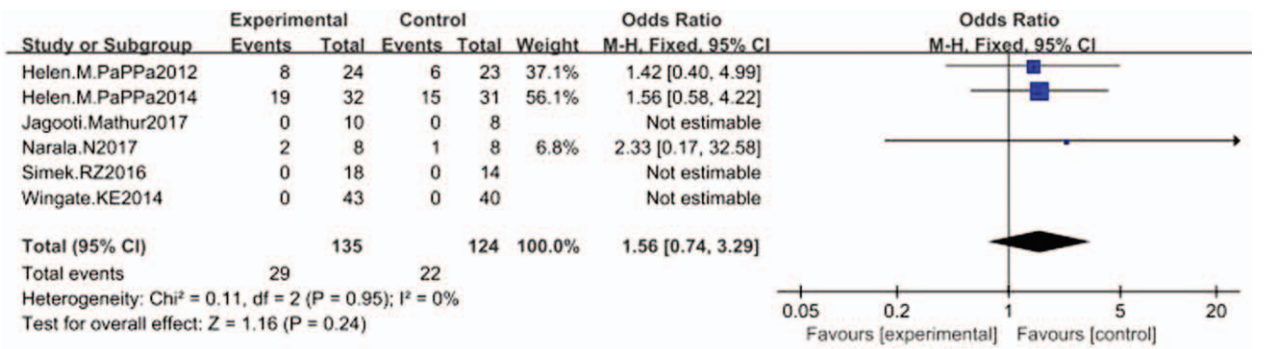

Figure 10. Forest plot for comparison of adverse events in patient with IBD treated by VitD with different doses. IBD = inflammatory bowel disease, VitD = Vitamin D.

was no statistical significances between different doses of VitD supplementation ($P = .24$).

3.2.5. Subgroup analysis. In addition, 25(OH)D3 levels of IBD patients that treated with different doses of VitD was divided into adults with a course of treatment ≥6 months and children with a course of treatment <6 months. The heterogeneity was evident ($P = .001$, $I^2 = 85\%$) in adult group, but there was statistical significances between the high-doses VitD group and the lower doses group (WMD = 13.54, 95% CI [4.67, 22.42]) (Fig. 5). And there was no heterogeneity ($P = .23$, $I^2 = 30\%$) in child group, and the statistical significance did exist either (WMD = 6.26, 95% CI [2.64, 9.88], $P = .0007$) (Fig. 5).

3.2.6. Sensitivity analysis. We excluded each study individually to verify the reliability of our conclusions. None of the significance altered in 25(OH)D3, relapse rate, inflammation index, and adverse events.

4. Discussion

Intestinal flora imbalance, excessive inflammatory response, and injury of the intestinal mucosal barrier play an important role in the occurrence and development of IBD, and VitD can induce and maintain IBD remission through antibiosis, anti-inflammatory, and repair of intestinal mucosal barriers. First, binding and activating the vitamin D receptor (VDR), $1,25(OH)_2D3$ acts directly on the locus of monocyte-induced antibacterial protein expression, thereby enhancing the bactericidal effect[10]; meanwhile, it can also induce multiple types of cells to express nucleotide-binding oligomerization domain protein 2 (NOD2). A key downstream signaling consequence of NOD2 activation by agonist muramyl dipeptide is stimulation of nuclear factor kappa B(NF-*k*B) transcription factor function, which induces expression of the gene encoding antimicrobial peptide defensin beta2 (DEFB2/HBD2).[32] Secondly, VitD acts directly on CD4+T cells to promote the proliferation and differentiation of Th2 cells, while inhibiting the proliferation of Th1 cells by acting on DCs.[33,34] While increasing the level of IL-10 and decreasing IL-12,VitD can reduce the production of TNF-a by upregulating mitogen-activated protein kinase phosphatase-1 and inhibiting activation of mitogen-activated protein kinase (MAPK).[35] In addition, VitD promotes the expression of tight junction proteins ZO-1, claudin-1, and occludin to enhance tight junctions between intestinal epithelial cells, thereby maintaining mucosal barrier function.[36] VitD deficiency is common in patients with IBD, even during periods of remission. Having the function of improving intestinal flora imbalance, regulating immunity, and maintaining the integrity of the intestinal mucosa barrier, VitD should be recommended for the treatment of IBD, at least as a supplementary treatment. Therefore, this study used meta-analysis to analyze the efficacy and safety of VitD in the treatment of IBD, providing evidence for evidence-based medicine for the clinical application of VitD.

According to the results of meta-analysis, the level of 25(OH)D3 in patients with IBD after VitD supplementation was significantly increased, which effect was more pronounced in adults with a course of treatment ≥6 months, and high-dose VitD treatment can relatively achieve higher 25(OH)D3 levels. Adverse events of VitD supplementation is relatively low. Although adverse events caused by high-dose VitD supplementation is relatively higher than the normal dose, the difference, however, was not statistically significant, indicating that the benefits of high-dose VitD treatment far outweighed the risks. The heterogeneity of the adult group was relatively large, considering that there are large differences in area and disease ratio (UC:CD) and the specific doses and methods of VitD usage between trails. However, due to the low number of included trials, subgroup analyses cannot be performed. The US National Institutes of Medicine recommends an intake of 600 IU/d for adults and children, with a maximum limit of 4000 IU/d. However, this upper limit does not apply to people who already have a deficiency.[37] The 25(OH)D3 levels in the IBD population vary widely, and the effect of 25(OH)D3 supplementation is also very different. There is currently no guideline explicitly recommending specific, appropriate supplemental doses, and methods. In the included study, the dose of VitD compared with placebo was between 800 and 7000 IU/d, and compared with low doses of VitD between 700 and 7000 IU/d, high doses could reach 1000 to 10,000 IU/d. Some studies[38] have shown that patients with IBD who maintain a certain serum 25(OH)D3 concentration, in particular higher than 75 nmol/L, can reduce the risk of disease onset while maintaining response to IBD therapy. This study also showed that adjuvant therapy with VitD can reduce the relapse rate of IBD by 64%, but there are not significantly different in reducing the recurrence rate of the disease between high-dose and low-dose VitD, which is, on the one hand, related to the large difference in the specific dose and method of VitD used between the different trials. On the other hand, it also suggests that VitD therapy may only be an auxiliary medium that affects the efficacy of hormones and immunosuppressive agents. Having the greatest effect on IBD patients, VitD will bring greater risks than benefits while exceeding this effect value. As Zator et al[39] showed, patients with serum 25(OH)D3 deficiency (mean 67.5 nmol/L) responded poorly against tumor necrosis factor-*a* (TNF-*a*) treatment, which is more noticeable in CD than UC. Therefore, supplementation with high-dose VitD may be recommended as an adjuvant therapy for IBD, but individualization should be followed and biochemical indicators and adverse reactions should be regularly tested, especially for children. The trial[21] found that the increase in serum 25(OH)D3 concentration was negatively correlated with the weight of participants receiving high-dose VitD ($r = -0.44$; $P = .05$), so the weight-adjusted VitD dose may be more suitable for child.

There are still many deficiencies in the meta, the most obvious of which is the large heterogeneity among the trials. First of all, because the effect of VitD adjuvant therapy on IBD is inaccurate, the dosage, usage, and course of treatment of VitD vary greatly between trials. Secondly, the trial population's racial and regional differences, age composition, and sex ratio all influence the judgment of efficacy. Some studies found that there are 4 VDR gene polymorphisms associated with the risk of IBD: TaqI, BsmI, ApaI, and FokI. TaqI T allele reduces the risk of developing CD and UC in Caucasians, and BsmI B allele increases the risk of developing CD in East Asians; ApaI A allele appears to have a role in preventing CD, while the AA genotype increases the risk of CD; FokI ff genotype is associated with increased Asian UC risk.[40,41] In addition, although the etiology and risk factors of UC and CD are similar, the specific pathological changes and the response to vitamin D are different. In the included Tang et al[16] study, the experimental group used vitamin D and *Saccharomyces boulardii* in combination, while the control group gave *S boulardii*. Vitamin D and *S boulardii* may produce effects such as $1+1>2$, $1+1=2$, or $1+1<2$, which interfere with the opposite observation of the effect of vitamin D on IBD.

In summary, as a new auxiliary treatment method, it makes sense to recommend vitamin D for IBD patients, at least in people with VitD deficiency. So it is worthy of our investigation and

promotion due to its simple, effective, safe, and inexpensive advantages. However, at present, large samples and high-quality RCTs for VitD treatment of IBD are still rare and uneven, thus more high-quality RCTs are still needed for supplementation and evaluation.

Author contributions

Conceptualization: Jinzhong Li.
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Funding acquisition: Xiaobing Gong.
Investigation: Ning Chen.
Methodology: Jie Zhang.
Project administration: Xiaobing Gong.
Software: Ning Chen, Dan Wang.
Supervision: Ning Chen, Xiaobing Gong.
Validation: Dan Wang.
Visualization: Jinzhong Li.
Writing – original draft: Jinzhong Li.
Writing – review & editing: Jinzhong Li, Jie Zhang.

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