Effect of Vitamin D Supplementation on Inflammatory Bowel Disease in Children: A Meta-Analysis

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ABSTRACT

Background Apart from its role in bone health, recent developments have shown that vitamin D also has anti-inflammatory properties, and therefore may have a role in inflammatory bowel disease (IBD) in children.

Objectives To determine the effect of vitamin D supplementation on the disease activity of pediatric patients with IBD.

Design Random-effects meta-analysis

Data Sources Studies were searched at Cochrane Library, PubMed, EBSCO Host, ScienceDirect, Google Scholar, and Wiley Online.

Review Methods Experimental studies measuring the effect of vitamin D on the disease activity of pediatric patients with IBD were included. The proportion of disease activity, measured as remission rate or inactivity using Pediatric Crohn's Disease Activity Index (PCDAI) or Pediatric Ulcerative Colitis Activity Index (PUCAI), and the mean and standard deviation of mean serum vitamin D [25(OH)D] level, change in 25(OH)D, and different inflammatory markers [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] were extracted or estimated and recorded in an abstraction form. Standardized mean difference and odds ratio were used as summary effect measures and estimated using Stata/Multiprocessor.

Results The serum 25(OH)D (SMD = 1.75, z = 2.33, p = 0.001) and change in 25(OH)D (SMD = 3.37, z = 2.34, p = 0.019) was significantly higher among those who received a high dose of vitamin D. However, a significantly high heterogeneity was estimated (I^2 >50%). For the disease activity of IBD, the standard mean difference of mean ESR (SMD = –1.10, z = 5.35, p = 0.001) was significantly lower with high-dose vitamin D. The likelihood of remission rate using the Pediatric Crohn's Disease Activity Index or Pediatric Ulcerative Colitis Activity Index, and standardized mean difference of CRP were not significantly different among those who received high-dose and low-dose vitamin D.

Conclusion Cognizant of the functions of vitamin D in enhancing intestinal flora balance, regulating immunologic response, and improving intestinal mucosal barrier, vitamin D can be recommended as a supplementary treatment for IBD among the pediatric population. Nevertheless, there is still insufficient evidence for the cut-off level of adequate levels of serum 25(OH)D among pediatric patients with IBD, thus necessitating further studies.

Key words *Vitamin D therapy, Pediatric Inflammatory Bowel Disease, Vitamin D deficiency*

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Academic editor: Raymond L. Rosales

Submitted date: December 23, 2021

Accepted date: March 30, 2023

INTRODUCTION

Vitamin D, as it is widely known, has an important role in calcium homeostasis. Following the discovery of vitamin D receptors on peripheral blood mononuclear cells,[1] vitamin D was also acknowledged to have a role in regulation of the immune system.[2] It has been shown to have functions including anti-inflammatory, cell differentiation, and apoptotic effects.[3]

Inflammatory bowel disease (IBD), which includes Crohn's Disease (CD) and ulcerative colitis (UC), is a well-known gastrointestinal tract disease with a chronic and relapsing course that requires lifelong treatment.[4] The exact cause remains largely unknown, but it is hypothesized that genetic, environmental, and microbial influences converge and result in a dysregulated mucosal immune response resulting in disease.[5]

Children with IBD are known to be at greater risk for having nutritional consequences than adults. In particular, due to vitamin D deficiency, they are more likely to have decreased bone mineral density. [5] Recent studies have focused on the potential link between vitamin D and severity of IBD in children; proposing that a deficiency state of vitamin D is associated with a more severe course of disease.[6,7]

While there are several studies on vitamin D therapy in children with IBD, there has not yet been a meta-analysis of these published studies. The aim therefore of this study was to determine the effect of vitamin D supplementation on disease activity of IBD in children, by analyzing results of published studies that have evaluated the supplementation of vitamin D in this population.

METHODOLOGY

Search Strategy

Articles were searched on the following search engines and research databases: Cochrane Library, PubMed, EBSCO Host, ScienceDirect, Google Scholar, and Wiley Online. Keyword search and Boolean logic search were used as search techniques. Using these search strategies, the following phrases were searched:

("Vitamin D" OR "25-hydroxy vitamin D" OR "25(OH)D" OR "vitamin D2" OR "vitamin D3") AND ("Inflammatory Bowel Disease" OR "Crohn's" OR "Ulcerative Colitis") AND ("Child") AND ("Treat" OR "Therapy") AND ("Randomized Trial"). The references of included articles were searched for other relevant articles. Duplicates were subsequently removed.

Eligibility Criteria

Trials conducted on pediatric patients with IBD, CD or UC in which vitamin D supplementation was instituted and where serum 25(OH)D concentrations and disease activity parameters such as Pediatric Crohn Disease Activity Index (PCDAI)/Pediatric Ulcerative Colitis Activity Index (PUCAI), and inflammatory markers [ie, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)] reported from baseline and follow-ups were included in this meta-analysis. Studies were excluded if: (a) they included adult patients; (b) they were not in the English language; and (c) they were only available in abstract.

Selection Process

Two reviewers independently screened titles and abstracts of all identified articles and assessed full-text articles of each potentially eligible study for inclusion. Disagreement between the reviewers was resolved by discussion and with a third reviewer. The Cochrane Collaboration's Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessment tool was utilized to identify and categorize the quality of studies as low, unclear, and high risk. The following elements of a randomized controlled trial were appraised: *sequence generation, blinding, allocation concealment, incomplete outcome data, selective outcome reporting,* and *other sources of bias.* Low risk of bias indicates that plausible bias is unlikely to seriously alter results, while unclear bias denotes the presence of plausible bias which raises doubts about results. High risk of bias, on the other hand, implies that there is plausible bias which seriously weakens results.[8]

Data Collection Process

The following information were obtained from each study and encoded in a standardized Excel file: authors, year of publication, country, study design, sample size, demographic characteristics of patients (age, sex), disease of study population (IBD/CD/UC), vitamin D supplementation (generic, dose and

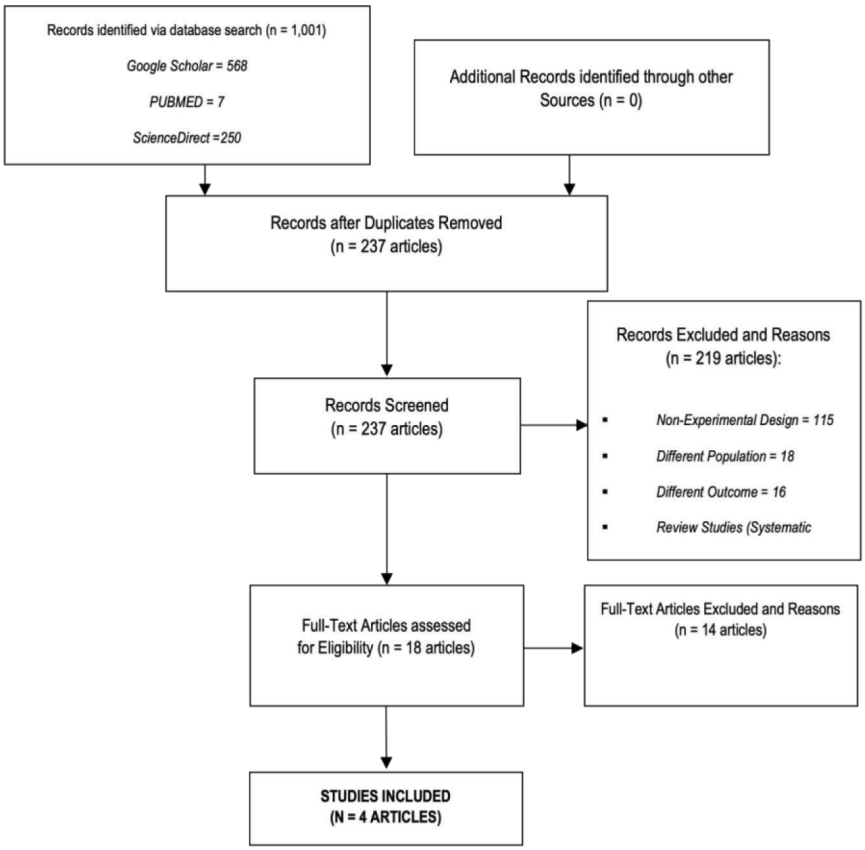

Figure 1 PRISMA Flow Diagram of Study Selection

duration), vitamin D levels (mean, standard deviation, or interquartile range of serum 25-OHD) and vitamin D cut-off points, disease activity of IBD, outcomes of the study, and any conclusions regarding the effect of vitamin D therapy. (ie, risk ratio, odds ratio). Vitamin D levels reported in nmol were adjusted to and reported in ng/mL to allow accurate comparisons.

Data Analysis

Statistical analyses were conducted using STATA MP Statistical Software, Version 13, College Station, TX: StataCorp LP. A *p*–value ≤0.05 was considered statistically significant. Since primary studies did not assume one effect size among all the studies, the overall effect of meta-analysis was derived using a random-effects model (REM), which took within-study and between-study variation into account. Two summary effect measures were utilized according to the type of outcome data: pooled odds ratio for categorical outcomes and standardized mean difference for continuous-level outcomes. Pooled odds ratio was utilized for disease activity between the interventional and control groups, while standardized mean difference was employed for serum 25(OH)D and different inflammatory markers (ESR and CRP). Statistical heterogeneity between studies was evaluated using Q statistics test, I^2 statistics, and tau squared (τ^2) statistics.[9] I^2 values greater than 50% imply substantial heterogeneity.[9] Publication bias was assessed using both graphical and statistical approaches. Graphical approach for publication bias involved contour-enhanced funnel plots, while statistical assessment of funnel plot asymmetry was performed using Egger's test and Begg's asymmetry test.[9]

ETHICAL CONSIDERATIONS

The study involved the use of data from results of previously published studies; thus, no ethical approval and patient consent was needed.

RESULTS

Study Selection

The search strategy retrieved a total of 1,001 articles. Upon initial screening, 764 duplicates were removed leaving 237 papers. The abstract and title of the remaining 237 articles were screened,

Table 1.
Characteristics of the Included Trials in the Meta-Analysis (N = 4)

Study (Year) and Country	Design	Population	Timeframe (Months)	Intervention (Sample Size)		Demographics		Outcome Variables						
				Experimental	Control	Mean Age	Sex Distribution	25(OH)D	Δ25(OH)D	Disease Activity (Inactive)	Serum ESR	ΔESR	Serum CRP	ΔCRP
Pappa et al. (2012) USA	RCT	Children aged 5 – 21 with diagnosis of IBD and with serum 25(OH)D levels of 20ng/mL, or less within 8 weeks of enrollment	1.50 Months	50,000 IU Vitamin D_3 (23)	2,000 IU Vitamin D_3 (24)	Exp: 16.30 (3.20) Con: 15.90 (3.00)	Experimental: • Male: 14 • Female: 9 Control: • Male: 14 • Female: 10	Experimental: 40.80 (2.60) Control: 25.70 (2.20)	Experimental: 25.40 (2.50) Control: 9.30 (1.80)	Experimental: 13 Control: 12	Experimental: 8.50 (2.36) Control: 12.50 (4.21)	Experimental: −2.50 (2.56) Control: −1.50 (1.61)	Experimental: 0.20 (0.40) Control: 0.20 (0.60)	Experimental: 0.00 (0.25) Control: 0.00 (0.23)
Pappa et al. (2014) USA	RCT	Children aged 5 – 21 with diagnosis of IBD and with serum 25(OH)D levels of 20ng/mL, or more within 8 weeks of enrollment	12 Months	1,000 or 2,000 IU Vitamin D_3 (31)	400 IU Vitamin D_3 (32)	Exp: 14.50 (3.10) Con: 15.10 (3.10)	Experimental: • Male: 14 • Female: 17 Control: • Male: 13 • Female: 19	Experimental: 29.90 (8.80) Control: 28.10 (9.40)	Experimental: −5.80 (15.20) Control: −3.70 (10.80)	Experimental: 11 Control: 14	Experimental: 7.00 (2.12) Control: 9.80 (3.11)	Experimental: −1.50 (0.07) Control: −0.80 (0.22)	Experimental: 0.10 (0.21) Control: 0.20 (0.23)	Experimental: 0.00 (0.00) Control: 0.10 (0.01)
Simek et al. (2016) USA	Pilot RCT	Children aged 8 – 21 years old diagnosed with IBD by a pediatric gastroenterologist and have serum 25(OH)D <30ng/mL and weighs >20kg.	3 Months	10,000 per 10kg IU Vitamin D_3 (18)	5,000 per 10kg IU Vitamin D_3 (14)	Exp: 15.80 (3.20) Con: 15.60 (2.50)	Experimental: • Male: 7 • Female: 11 Control: • Male: 5 • Female: 9	Experimental: 35.10 (8.40) Control: 30.80 (4.20)	Experimental: 11.40 (−0.10) Control: 6.80 (−2.80)	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported
Wingate et al. (2014) Canada	RCT	Children and adolescents with quiescent CD ages 8–18 years old	6 Months	2,000 IU Vitamin D_3 (42)	400 IU Vitamin D_3 (40)	Exp: 14.50 (2.10) Con: 14.00 (2.40)	Experimental: • Male: 24 • Female: 19 Control: • Male: 21 • Female: 19	Experimental: 34.40 (10.40) Control: 28.00 (8.80)	Experimental: 12.40 (3.60) Control: 2.00 (−0.40)	Experimental: 32 Control: 29	Not Reported	Not Reported	Not Reported	Not Reported

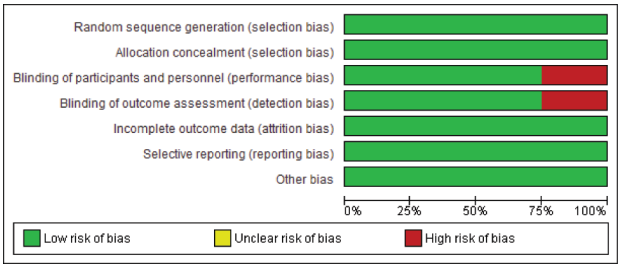

Figure 2 Risk of Bias Analysis Graph of Included Studies

and 219 of these were removed due to reasons enumerated in Figure 1. The full-text articles of the remaining 18 papers were then reviewed and 14 of these were removed as these involved a different population (adult population); hence, a total of four studies were included in the analyses.

Study Characteristics of Individual Studies

Four experimental studies were included in this meta-analysis. Table 1 presents a summary of characteristics and the population of included studies.

Risk of Bias Analysis and Quality of Evidence of Included Studies

The risk of bias analysis and quality of evidence of included studies are depicted in Figure 2. All studies have low risk for random sequence generation, allocation concealment bias, attrition bias, reporting bias, and other biases. However, 25% of the included studies have high risk for performance and detection biases due to the absence of blinding in the studies.

Pooled Estimate of 25-Hydroxyvitamin D [25(OH)D] and Mean Change in 25(OH)D between the Experimental and Control Groups

Figure 3 illustrates the pooled estimate of mean 25(OH)D and change in 25(OH)D between the experimental and control groups. A total of four eligible and complete studies, with a total of 224 respondents were included – 114 in the experimental and 110 in the control group. There was a significant difference in the mean serum 25(OH)D after giving vitamin D (SMD = 1.75, z = 2.33, $p = 0.001$, 95% CI = 0.28–3.22), denoting that the 25(OH)D levels of those in the experimental group was significantly higher. However, there was a significantly high heterogeneity among included studies ($\chi^2 = 63.48$, $p = 0.001$, $I^2 = 95.30\%$, $\tau^2 = 2.08$).

The pooled estimate of mean change in 25(OH)D was significantly different between the control and experimental groups (SMD = 3.37, z = 2.34, $p = 0.019$, 95% CI = 0.55–6.19), favoring the experimental group. However, there was a substantially high heterogeneity among included studies ($\chi^2 = 139.57$, $p = 0.001$, $I^2 = 97.70\%$, $\tau^2 = 8.00$).

Pooled Estimate of Disease Activity between the Experimental and Control Groups

The pooled estimate for disease activity (remission/inactivity), measured using PCDAI or PUCAI, between the experimental and control group are presented in Figure 4. A total of three trials were included, which enrolled 96 respondents in the experimental

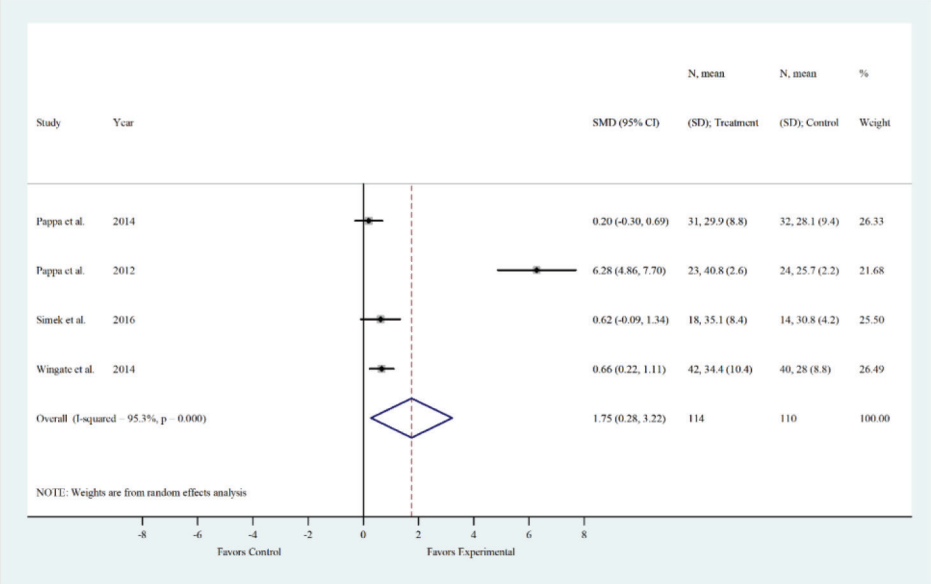

Figure 3 Meta-Analysis for the Comparison of Mean 25-Hydroxyvitamin D [25(OH)D] (Upper Forest Plot) and Mean Change in 25(OH)D (Lower Forest Plot) between the Control and Experimental Groups

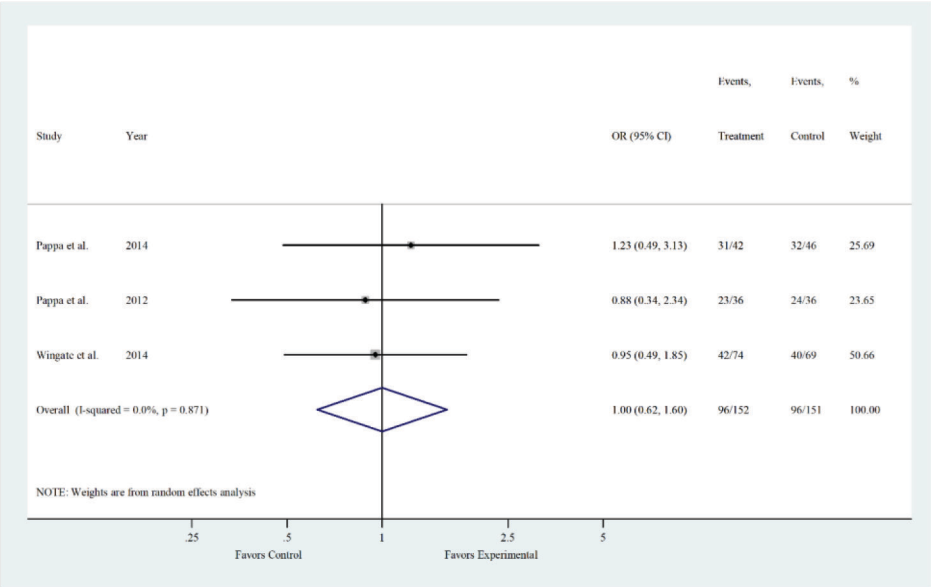

Figure 4 Meta-Analysis for the Comparison of Disease Activity (Inactive) using PCDAI or PUCAI between the Control and Experimental Groups

group and 96 patients in the control group. The pooled or summary effect measure using odds ratio was 1.01, indicating that proportion of those with inactive IBD did not significantly differ between the two groups after their respective treatment regimen (OR = 1.01, z = 0.01, p = 0.998, 95%CI = 0.62–1.60). Analysis also showed that there was no heterogeneity detected among the articles included (χ^2 =0.28, p=0.871, I^2 =0.00%, τ^2 =0.00).

Pooled Estimate of ESR and Mean Change in ESR Between the Experimental and Control Groups

Figure 5 depicts the pooled estimates of mean ESR and change in ESR between the experimental and control groups. The analysis included a total of two studies with a total of 110 respondents, 54 in the experimental and 56 in the control group. The mean ESR between the two groups was statistically different (SMD = –1.10, z = 5.35, p = 0.001, 95% CI = –1.50 to –0.70), suggesting that the mean ESR after vitamin D therapy was lower in the experimental group. Moreover, results also showed no heterogeneity among the studies (χ^2 = 0.08, p = 0.779, I^2 = 0.00%, τ^2 = 0.00).

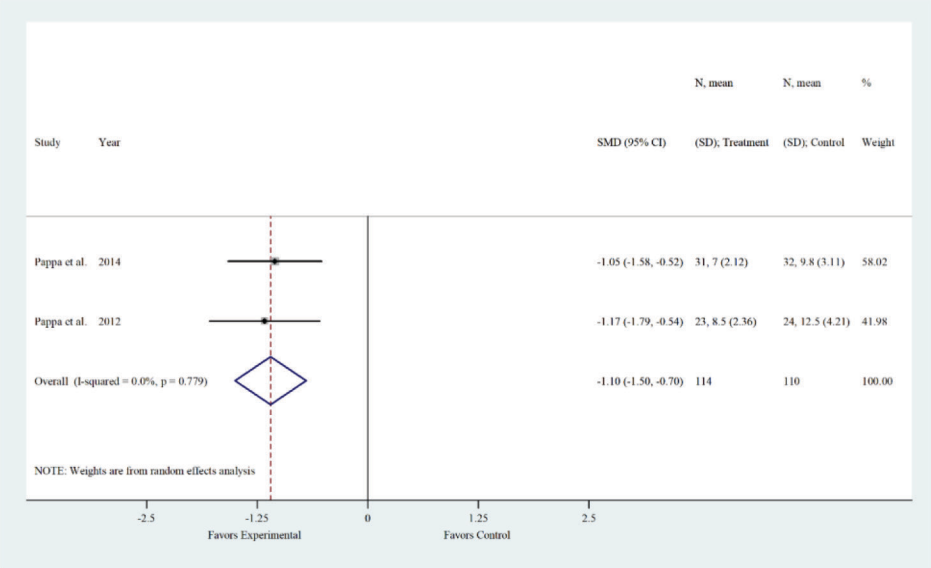

Figure 5 Meta-Analysis for Comparison of Mean Erythrocyte Sedimentation Rate (ESR) (Upper Forest Plot) and Mean Change in ESR (Lower Forest Plot) Between the Control and Experimental Groups

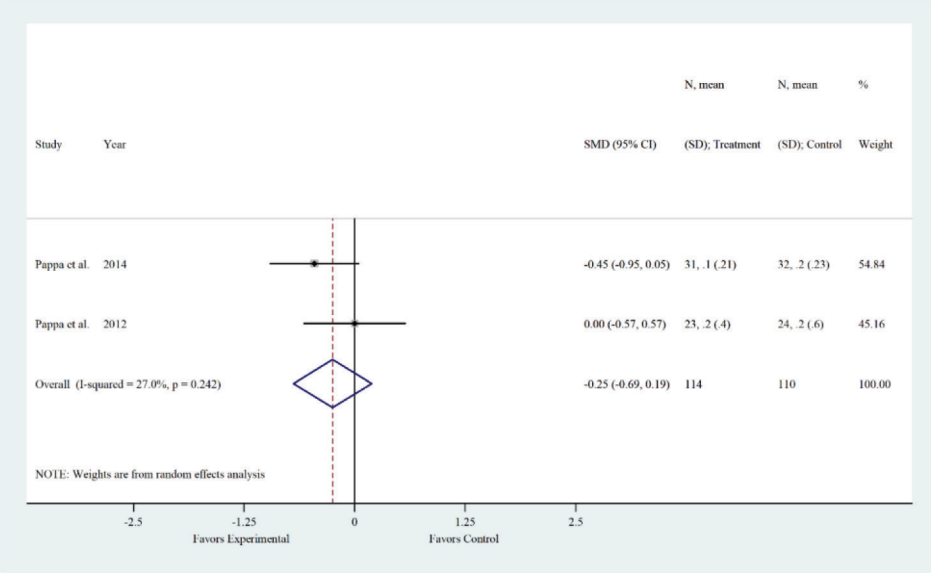

Figure 6 Meta-Analysis for the Comparison of Mean C-Reactive Protein (CRP) (Upper Forest Plot) and Mean Change in CRP (Lower Forest Plot) Between the Control and Experimental Groups

The change in ESR was not different between the two groups (SMD = –2.35, z = 1.24, p = 0.215, 95%CI = –6.06 to 1.37). There was a substantially high heterogeneity among the included studies (χ^2 = 47.90, p = 0.001, I^2 = 97.90%, τ^2 = 7.03).

Pooled Estimate of CRP and Mean Change in CRP Between the Experimental and Control Groups

The pooled estimates of mean CRP and change in CRP between the experimental and control groups, which included two articles and a total of 110 respondents, are presented in Figure 6. There was no evidence that the mean CRP (SMD = –0.25, z = 1.10, p = 0.242, 95%CI = –0.69 to 0.19) and mean change in CRP (SMD = 0.00, z = 0.00, p = 1.000, 95%CI = –0.37 to 0.37) were statistically different. There was also negligible heterogeneity for studies included in the analysis for both mean CRP (χ^2 = 1.37, p = 0.242, I^2 = 27.00%, τ^2 = 0.03) and mean change in CRP (χ^2 = 0.00, p = 1.000, I^2 = 0.00 τ^2 = 0.01).

Publication Bias Assessment

Graphical analysis using contour-enhanced funnel plots indicated the likelihood of funnel asymmetry with a left-side predominance for mean serum

Table 2. Statistical Assessment of Publication Bias of Different Study Outcomes

Study Outcomes	Number of Studies	Egger's Test		Begg's Test	
		Bias Estimate	*p*-value	Estimate	*p*-value
Mean 25-Hydroxyvitamin D [25(OH)D]	4 Studies	9.94	0.121	1.02	0.308
Mean Change in 25-Hydroxyvitamin D [25(OH)D]	4 Studies	13.77	0.121	1.36	0.174
Disease Severity (Inactive)	3 Studies	0.52	0.803	–0.52	0.602
Mean Erythrocyte Sedimentation Rate (ESR)	2 Studies	–	–	–1.00	0.317
Mean Change in Erythrocyte Sedimentation Rate (ESR)	2 Studies	–	–	–1.00	0.317
Mean C-Reactive Protein (CRP)	2 Studies	–	–	–1.00	0.317
Mean Change in C-Reactive Protein (CRP)	2 Studies	–	–	–1.00	0.317

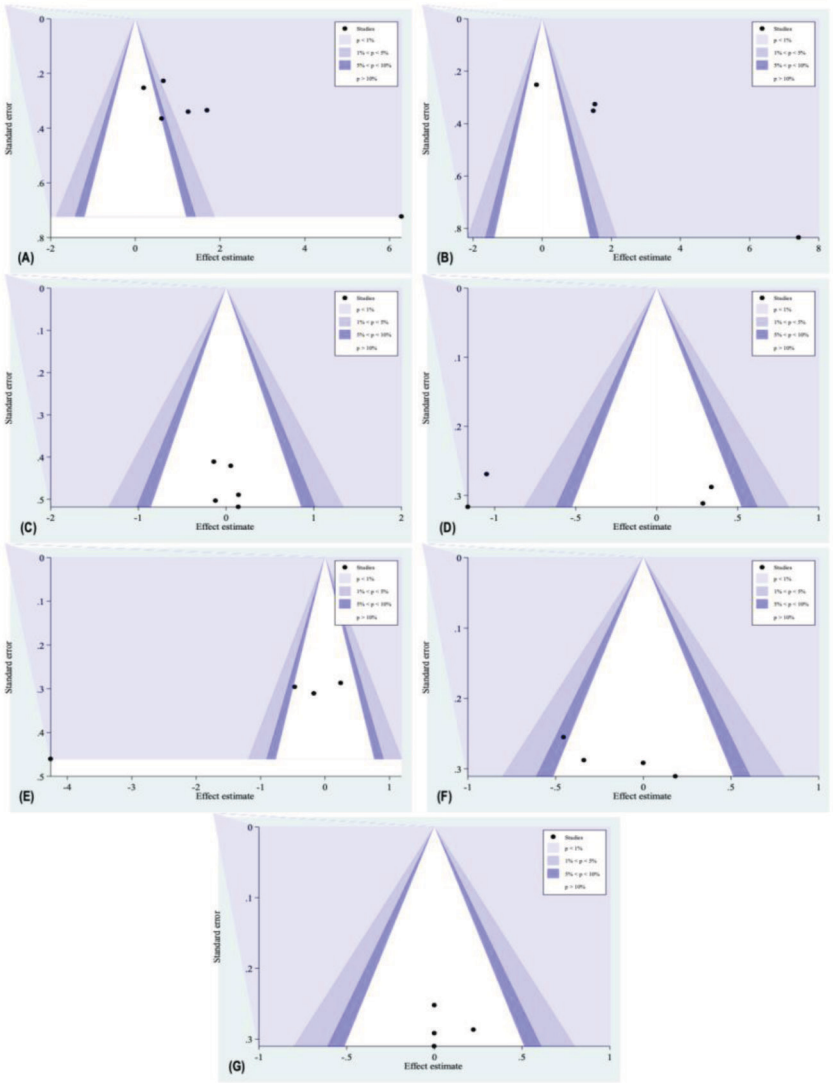

Figure 7 Contour-Enhanced Funnel Plots for the Analysis of Publication Bias for (A) Mean 25(OH)D; (B) Mean Change in 25(OH)D; (C) Disease Severity (Inactive); (D) Mean ESR; (E) Mean Change in ESR; (F) Mean CRP; and, (G) Mean Change in CRP

25(OH)D and mean change in 25(OH)D, suggesting that publication bias was possible (Figure 7). Similarly, contour-enhanced funnel plots indicated the possibility of funnel asymmetry with a right-sided predominance for mean change in ESR. However, formal statistical analyses using Egger's and Begg's

tests indicated no evidence of publication bias in all the study outcomes (p>0.05; See Table 2).

DISCUSSION

IBD is a chronic, relapsing intestinal inflammatory disorder with unidentified causes.[10] However, it is believed to be due to a result of inappropriate and ongoing activation of the immune system against environmental triggers among genetically predisposed individuals.[11] Studies in animal models of colitis and in vitro human studies support the role of vitamin D in regulation of the immune system of the gut and its potential as therapeutic adjuncts in IBD.[12-14] Therefore, this study aimed to analyze the effect of vitamin D supplementation in disease activity of IBD among pediatric patients and also provide evidence-based recommendation for future clinical application.

The serum 25(OH)D levels vary among the IBD population, and the effect of vitamin D supplementation is also not consistent. Currently, the optimal serum 25(OH)D level for children with IBD has not been established, and there is no optimal vitamin D regimen for the maintenance of serum 25(OH)D in children with IBD. In this study, pooled analysis showed that mean serum 25(OH)D concentration post-vitamin D therapy and mean change in serum 25(OH)D concentration from baseline was significantly higher among those who received high doses of vitamin D, a result consistent with previous studies.[15-17] The effect of vitamin D on serum 25(OH)D was more evident among pediatric patients who had received it for at least 6 months.[16]

There are limited studies that have focused on the relationship between vitamin D and disease activity. Some suggested an association of vitamin D deficiency with a more severe course of disease, while other studies do not report the same.[18-20] In this study, remission or inactivity of IBD using PCDAI or PUCAI was not significantly different between those who received high-dose and low-dose or standard recommended dose of vitamin D. Likewise, the change of serum CRP and ESR were not significantly different between those who received high-dose and low-dose or standard recommended dose of vitamin D. Nevertheless, the included articles reported improvement with reduction in inflammatory markers from baseline and a lower incidence of elevated inflammatory markers among participants receiving post-vitamin D treatment.

Strengths and Limitations

A limitation of this study is the low number of included articles and accumulated sample size from the articles, which may have affected the current results. Although an exhaustive search of eligible articles was conducted, there were only a few articles which fit into the study's criteria. Another limitation of this study was the amount of risk for performance and detection biases due to the lack of blinding in approximately 25% of included studies. The high heterogeneity of several study outcomes is also a limitation, which prevented comparison of treatment regimens and making a conclusion for optimal dose. Although further analyses such as subgroup analyses and meta-regression should be conducted to explore the source of heterogeneity, the low number of included articles makes these statistical treatments not feasible. Nevertheless, this study has strengths attributable to high quality of evidence, with low risk of bias in almost all potential sources of bias and meticulous and exhaustive search strategy.

Clinical Implications

The acquired results of this meta-analysis may be attributed to various effects of vitamin D on the immune system and immune response of individuals with IBD. Across literature, several researches have suggested that IBD develops because of three primary mechanisms, namely, imbalance in intestinal flora, excessive inflammatory response of affected individuals, and injury of the intestinal mucosal barrier.[21-23] The antibiosis effect of $1,25(OH)_2$ D is associated with its ability to bind and activate vitamin D receptors of the body, which induces monocyte-induced anti-bacterial protein expression and thus, enhancing the antimicrobial effect.[24] Furthermore, $1,25(OH)_2$ D induces multiple types of cells to express nucleotide-binding oligomerization domain protein 2 (NOD2), which causes the expression of gene-encoding antimicrobial peptide defensin beta 2, which further improves bactericidal effects.[25] The anti-inflammatory activity of vitamin D, on the other hand, is a result of its effect on CD4+ T cells to instigate the proliferation and differentiation

of Th2 cells and to inhibit Th1 cells which act on the dendritic cells of the gastrointestinal tract.[26] Vitamin D also increases the level of interleukin-10 (IL-10), an anti-inflammatory cytokine; decreases the levels of interleukin-12 (IL-12), a pro-inflammatory cytokine which enhances the cytotoxic activity of natural killer cells and cytotoxic T lymphocytes; and reduces the production of tumor necrotic factor-alpha (TNF-a), a mediator of inflammatory functions, by increasing mitogen-activated protein kinase phosphatase-1 (MAPKP-1) and inhibiting activation of mitogen-activated protein kinase (MAPK).[27-29] Finally, vitamin D promotes intestinal mucosal repair by increasing the expression of tight junction proteins such as ZO-1 (zona occludens 1), claudin-1 and occludin between epithelial cells of the intestinal lining, thus maintaining mucosal barrier function. [21-22,30]

CONCLUSION

This meta-analysis highlighted the efficacy of vitamin D supplementation, wherein high doses of vitamin D resulted in a significant change in disease activity among children with IBD as manifested by a lower ESR level and higher serum 25(OH)D concentration at follow-up compared to those who were given vitamin D at low doses.

Cognizant of the functions of vitamin D in enhancing intestinal flora balance, regulating immunologic response and improving intestinal mucosal barrier, vitamin D supplementation can be considered as an adjunct in treatment of IBD among the pediatric population. Nevertheless, it should be noted that there is still insufficient evidence for the cut-off level of adequate levels of serum 25(OH)D among pediatric patients with IBD. Hence, further research should be conducted recognizing the various limitations of this meta-analysis study.

REFERENCES

1. Provvedini DM, Tsoukas CD, Deftos LJ, Manolagas SC. 1,25-dihydroxyvitamin D3 receptors in human leukocytes. *Science* [Internet]. 1983;221(4616):1181–3. Available from: http://dx.doi.org/10.1126/science.6310748
2. Cantorna MT. Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease. *Prog Biophys Mol Biol* [Internet]. 2006;92(1):60–4. Available from: http://dx.doi.org/10.1016/j.pbiomolbio.2006.02.020
3. Hanauer SB. Inflammatory bowel disease: Epidemiology, pathogenesis, and therapeutic opportunities. *Inflamm Bowel Dis* [Internet]. 2006;12:S3–9. Available from: http://dx.doi.org/10.1097/01.mib.0000195385.19268.68
4. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. *Nature* [Internet]. 2011;474(7351):307–17. Available from: http://dx.doi.org/10.1038/nature10209
5. Raman M, Milestone AN, Walters JRF, Hart AL, Ghosh S. Vitamin D and gastrointestinal diseases: inflammatory bowel disease and colorectal cancer. *Therap Adv Gastroenterol* [Internet]. 2011;4(1):49–62. Available from: http://dx.doi.org/10.1177/1756283X10377820
6. Joseph AJ, George B, Pulimood AB, Seshadri MS, Chacko A. 25 (OH) vitamin D level in Crohn's disease: association with sun exposure & disease activity. *Indian J Med Res*. 2009;130(2):133–7.
7. Blanck S, Aberra F. Vitamin D deficiency is associated with ulcerative colitis disease activity. *Dig Dis Sci* [Internet]. 2013;58(6):1698–702. Available from: http://dx.doi.org/10.1007/s10620-012-2531-7
8. Schünemann H, Brożek J, Guyatt G, Oxman A. Introduction to GRADE handbook: Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. The GRADE Working Group; October 2013.
9. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* [Internet]. 2003;327(7414):557–60. Available from: http://dx.doi.org/10.1136/bmj.327.7414.557
10. Park SJ, Kim WH, Cheon JH. Clinical characteristics and treatment of inflammatory bowel disease: a comparison of Eastern and Western perspectives. *World J Gastroenterol* [Internet]. 2014;20(33):11525–37. Available from: http://dx.doi.org/10.3748/wjg.v20.i33.11525
11. Bamias G, Cominelli F. Immunopathogenesis of inflammatory bowel disease: current concepts. *Curr Opin Gastroenterol* [Internet]. 2007;23(4):365–9. Available from: http://dx.doi.org/10.1097/MOG.0b013e3281c55eb2
12. Zhu Y, Mahon BD, Froicu M, Cantorna MT. Calcium and 1 alpha,25 dihydroxyvitamin D3 target the TNF-alpha pathway to suppress experimental inflammatory bowel disease. *Eur J Immunol*. 2005;35(1):217–24.
13. Verlinden L, Leyssens C, Beullens I, Marcelis S, Mathieu C, De Clercq P, et al. The vitamin D analog TX527 ameliorates disease symptoms in a chemically induced model of inflammatory bowel disease. *J Steroid Biochem Mol Biol* [Internet]. 2013;136:107–11. Available from: http://dx.doi.org/10.1016/j.jsbmb.2012.09.017
14. Goff JP, Koszewski NJ, Haynes JS, Horst RL. Targeted delivery of vitamin D to the colon using glucuronides of vitamin D: therapeutic effects in a murine model of inflammatory bowel disease. *Am J Physiol Gastrointest Liver Physiol*. 2012;302:G460-469.
15. Jørgensen SP, Agnholt J, Glerup H, Lyhne S, Villadsen GE, Hvas CL, et al. Clinical trial: vitamin D3 treatment in Crohn's disease - a randomized double-blind placebo-controlled study: Clinical trial: vitamin D and Crohn's disease. *Aliment Pharmacol Ther* [Internet]. 2010;32(3):377–83. Available from: http://dx.doi.org/10.1111/j.1365-2036.2010.04355.x
16. Li J, Chen N, Wang D, Zhang J, Gong X. Efficacy of vitamin D in treatment of inflammatory bowel disease. *Medicine* (Baltimore). 2018;97(46):e12662.
17. Sharifi A, Hosseinzadeh-Attar MJ, Vahedi H, Nedjat S. A randomized controlled trial on the effect of vitamin D3 on inflammation and cathelicidin gene expression in ulcerative colitis patients. *Saudi J Gastroenterol* [Internet]. 2016;22(4):316–23. Available from: http://dx.doi.org/10.4103/1319-3767.187606
18. Mouli VP, Ananthakrishnan AN. Review article: vitamin D and inflammatory bowel diseases. *Aliment Pharmacol Ther* [Internet]. 2014;39(2):125–36. Available from: http://dx.doi.org/10.1111/apt.12553
19. Nicholson I, Dalzell AM, El-Matary W. Vitamin D as therapy for colitis: A systemic review. *J Crohns Colitis*. 2012;6(4):405–11.
20. El-Matary W, Sikora S, Spady D. Bone mineral density, vitamin D, and disease activity in children newly diagnosed with inflammatory bowel disease. *Dig Dis Sci* [Internet]. 2011;56(3):825–9. Available from: http://dx.doi.org/10.1007/s10620-010-1380-5
21. Karimi S, Tabataba-Vakili S, Yari Z, Alborzi F, Hedayati M, Ebrahimi-Daryani N, et al. The effects of two vitamin D regimens on ulcerative colitis activity index, quality of life and oxidant/anti-oxidant status. *Nutr J* [Internet]. 2019;18(1):16. Available from: http://dx.doi.org/10.1186/s12937-019-0441-7
22. Nielsen OH, Hansen TI, Gubatan JM, Jensen KB, Rejnmark L. Managing vitamin D deficiency in inflammatory bowel disease. *Frontline Gastroenterol* [Internet]. 2019;10(4):394–400. Available from: http://dx.doi.org/10.1136/flgastro-2018-101055
23. Simek RZ, Prince J, Syed S, Sauer CG, Martineau B, Hofmekler T, et al. Pilot study evaluating efficacy of two dosing regimens for repletion of hypovitaminosis D in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2016;62(2):252–8.
24. Gombart AF, Borregaard N, Koeffler HP. Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. *FASEB J* [Internet]. 2005;19(9):1067–77. Available from: http://dx.doi.org/10.1096/fj.04-3284com
25. Wang TT, Dabbas B, Laperriere D, Bitton AJ, Soualhine H, Tavera-Mendoza LE. Direct and indirect induction by 1,25-dihydroxyvitamin D3 of the NOD2/CARD15-defensin β^2 innate immune pathway defective in Crohn disease. *J Biol Chem*. 2010;285(4):2227–31.
26. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. *Nat Rev Immunol* [Internet]. 2008;8(9):685–98. Available from: http://dx.doi.org/10.1038/nri2378
27. Feng YJ, Li YY. The role of p38 mitogen-activated protein kinase in the pathogenesis of inflammatory bowel disease: Role of p38 MAPK in IBD. *J Dig Dis* [Internet]. 2011;12(5):327–32. Available from: http://dx.doi.org/10.1111/j.1751-2980.2011.00525.x

28. Mannon PJ, Fuss IJ, Mayer L, Elson CO, Sandborn WJ, Present D, et al. Anti-interleukin-12 antibody for active Crohn's disease. *N Engl J Med* [Internet]. 2004;351(20):2069–79. Available from: http://dx.doi.org/10.1056/NEJMoa033402
29. Zhang Y, Leung D, Richers BN, Liu Y, Remigio LK, Riches DW. Vitamin D inhibits monocyte/macrophage pro-inflammatory cytokine production by targeting MAPK phosphatase-1. *J Immunol*. 2012;188(5):2127–35.
30. Zhao H, Zhang H, Wu H, Li H, Liu L, Guo J. Protective role of 1,25(OH)2 vitamin D3 in the mucosal injury and epithelial barrier disruption in DSS-induced acute colitis in mice. *BMC Gastroenterol*. 2012;12:57.