Research Article

Efficacy and Safety of Vitamin D Adjuvant Therapy for Ulcerative Colitis: A Meta-Analysis

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1. Introduction

Ulcerative colitis (UC) is an inflammatory colonic disease with unknown etiology, characterized by continuous and diffuse colonic mucosal inflammation, commonly manifested as abdominal pain, mucus, pus, blood and stool, etc.[1]. This disease has the characteristics of long course, easy recurrence, and difficult to cure. About 20% of patients with chronic UC have the risk of developing colorectal cancer, and the number of UC cases in China is increasing at present[2]. Western medicine treatment mainly adopts protection and repair of intestinal mucosa, reduction of inflammatory factors, and prevention and treatment of complications. Aminosalicylic acid preparation is the most commonly used drug. If aminosalicylic acid treatment effect is not good, glucocorticoids and immunosuppressants can be added[3].

Mesalazine is the most generally prescribed amino salicylic acid preparation for the treatment of UC, and it helps to protect the mucosa of the intestine. However, mesalazine alone has a low efficacy and a significant rate of side effects in some people[4]. As one of the sterols, Vitamin D is a recognized new immune factor, which exists in the form of 1, 25-dihydroxyvitaminD3 (1,25-(OH) D3) in the human body and participates in various autoimmune regulations[5]. Relevant studies have shown that Vitamin D level is negatively...
correlated with the risk of UC [6], but rigorous and standard-
ized clinical evidence is still lacking. As a result, by examining
domestic and international clinical randomized controlled
studies on the treatment of UC, this research analyzed the
efficacy of Vitamin D on UC and presented evidence-based
evidence for the selection of UC treatment plans.

The paper is organized as follows: the data and methods
are presented in Section 2. Section 3 discusses the experi-
ments and results. Section 4 consists of the discussion, and
finally, in Section 5, the research work is concluded.

2. Data and Methods

2.1. Retrieval Strategy. Figure 1 depicts the article screening
procedure. PubMed, Cochrane Library, and Web of Science
databases were searched for the “randomised controlled
study” using terms like “inflammatory disease”, “Vitamin
D”, “mesalazine”, and “Ulcerative colitis”, linked with
“AND”/“OR” operators. Chinese search terms such as “ulcer-
ative colitis”, “vitamin D”, “mesalazine”, and “clinical con-
trolled trial” were searched in CKNI, and Wanfang databases.

2.2. Inclusion and Exclusion Criteria

2.2.1. Literature Inclusion Criteria. The literature should be a
clinical randomized controlled study (RCT study).

2.2.2. Intervention Measures. Vitamin D and mesalazine
were given orally to the treatment group, while mesalazine
was given alone to the control group.

2.2.3. Efficacy Evaluation Indicators. Refering to Consensus
on Diagnosis and Treatment of Ulcerative Colitis by Inte-
grated Chinese and Western Medicine(2017) [7], clinical
curative effect is the main indicator.

Secondary indicators are Mayo score, intestinal mucosal
function (serum MDA and DAO), inflammatory factors (IL-
6, CRP, and TNF-α), and incidence of adverse reactions.

2.2.4. Exclusion Criteria. Animal studies, pharmacological
studies, or literature with repeated discussions, reviews,
and conference summaries and incomplete outcome indica-
tors was excluded.

2.3. Data Collection and Extraction. According to the inclu-
sion and exclusion criteria, the two researchers indepen-
dently screen the title, abstract, and full text of the paper.
If there is a dispute on the inclusion or exclusion of the
research, all the research members participate in the discus-
sion and make a decision together. Data were extracted from
a uniform data extraction table, including first author,
publication year, number of cases, sex, evaluation age, inter-
vention, outcome measures, and randomization. A total of
10 RCT studies were included [8–17], with a total of 1077
patients. The basic characteristics are shown in Table 1.

2.4. Quality Analysis of Included Literature. The methodo-
logical quality of all included RCTs was evaluated using the
risk bias assessment tool in the Cochrane Review Manual
[18], including (1) whether to use random numbers or
computer randomization, (2) whether to implement the
allocation hiding scheme, (3) whether blind method is used
correctly, (4) data integrity, (5) selective outcome report,
and (6) other sources of bias. The risk of bias from included
studies is shown in Figure 2.

2.5. Statistical Methods. Meta-analysis was conducted using
RevMan 5.4 software, and the main effect values were as
follows: weighted standard deviation (WMD), standard mean
difference (SMD), and 95% credibility interval (CI). If \( P > 0.05 \)
and \( I^2 \leq 50\% \), the fixed effects model could be selected, indi-
cating statistical homogeneity of subjects. On the contrary, if
\( P < 0.05 \) and \( I^2 > 50\% \), it indicates that there is heterogeneity
in the selected research object, and sensitivity analysis should
be conducted step by step by eliminating all studies [19].

3. Results

3.1. Outcome Index Analysis

3.1.1. Clinical Efficacy Indicators. A total of 8 RCTs were
included [8–13, 15,16], including 393 patients in the treatment
group and 396 patients in the control group. After the hetero-
geney test \( (I^2 = 0\% < 50\%) \) and \( Q \) test \( (P = 0.94 > 0.1) \),
indicating that there was no significant heterogeneity among
the selected literatures, the fixed effects model was selected for
meta-analysis: the clinical efficacy of the observation group
was higher than that of the control group \( (OR = 4.07, 95\% CI
2.64-6.27) \), and the difference was statistically significant
\( (Z = 6.38, P < 0.00001) \), as shown in Figure 3.

3.1.2. The Mayo Score. Four literatures [8–10, 13] were
included to report the Mayo score, including 385 patients.
Meta-analysis was performed to compare the improvement of
the Mayo score between the oral vitamin D group and the con-
trol group. The MD value was used as the e
fect scale, and there
was no statistical heterogeneity between studies \( (I^2 = 0\%, P =
0.82) \). Our study reveals: \( (MD: -0.41, 95\% CI [-0.595,0.98]) \), \( Z =
13.09, P < 0.00001 \). The difference was statistically significant,
indicating that oral vitamin D significantly reduced the Mayo
score, as shown in Figure 4.

3.1.3. Levels of Inflammatory Factors. A total of 4 literatures
[8, 12, 14, 17] were used to measure the levels of inflammatory
colitis by the levels of inflammatory factors (IL-6, TNF-α,
and CRP). Two literatures [8, 14] included IL-6 and TNF-
α indicators, and 4 literatures [8, 12, 14, 17] included CRP
indicators. Using the MD value as the effect scale, the sub-
group analysis showed that the \( I^2 \) of the three groups was
all less than 50\%, showing homogeneity. Using fixed effects
model analysis, in the IL-6 group \( (MD = -4.50, 95\% CI
(-5.13-3.87), P < 0.00001) \), TNF-α group \( (MD = -7.27, 95\%
CI (18.96-5.58), P < 0.00001) \), and CRP group \( (MD = -1.49,
95\% CI (-1.76~-1.23), P < 0.00001) \), the differences in the
three groups were statistically significant, suggesting that oral
vitamin D can effectively reduce the levels of inflammatory
factors, as shown in Figure 5.

3.1.4. Intestinal Barrier Function. Four of the included liter-
atures [9, 11, 13, 14] used serum MDA or DAO indicators
to describe intestinal barrier function, and MD was used as the
Retrieval database (n = 436)  
Elimination of duplicate literature (n = 231)  
The initial screening (n = 81)  
Eliminate by reading the questions and abstracts (n = 150)  
Exclusion does not meet inclusion criteria (n = 52)  
Full text reading meets inclusion criteria (n = 29)  
The design type does not meet requirements (n = 13)  
Outcome indicators were incomplete (n = 12)  
Conference summary (n = 4)  
Final inclusion (n = 10)

**Figure 1:** Specific process of literature screening.

**Table 1: Baseline characterization of included literatures.**

| Author and year | Case load (T/C) | Gender (male/female) | Age (T/C, year) | Intervening measure | Time (w) | Outcome | Random method |
|----------------|----------------|----------------------|----------------|---------------------|----------|---------|---------------|
| Yu Xia 2020 [9] | 60/60         | 61/59                | 38.4 ± 3.3     | C: mesalazine       | 8        | ①②④⑥     | —             |
|                 |               |                      | 38.2 ± 3.1     | T: mesalazine+VD    |          |         |               |
| Senyuan Zheng 2021 [10] | 52/51 | 51/52                | 39.95 ± 6.5    | C: mesalazine       | 8        | ①②⑥      | —             |
|                 |               |                      | T: mesalazine+VD |                     |          |         |               |
| Haipeng Dou 2021 [11] | 44/44 | 58/30                | 46.1 ± 10.7    | C: sulfasalazine    | 4        | ①②③④⑥⑧⑨ | Random number table |
|                 |               |                      | 44.7 ± 8.9     | T: sulfasalazine+VD |          |         |               |
| Ningning Yue 2020 [8] | 40/40 | 38/44                | 41.30 ± 11.16  | C: mesalazine+placebo | 8        | ①②③④⑥⑧⑨ | Computer stochastic method |
|                 |               |                      | 40.98 ± 10.94  | T: mesalazine+VD    |          |         |               |
| Hongliang Gao 2021 [12] | 57/59 | 59/57                | 40.2 ± 6.30    | C: mesalazine       | 24       | ①②③④⑥⑧⑨ | —             |
|                 |               |                      | 39.6 ± 6.90    | T: mesalazine+VD    |          |         |               |
| Fenghui Chen 2018 [13] | 40/42 | 44/38                | 42.30 ± 10.48  | C: mesalazine       | 6        | ①②③④⑥⑧⑨ | Random number table |
|                 |               |                      | 43.45 ± 12.5   | T: mesalazine+VD    |          |         |               |
| Rong Yang 2017 [15] | 40/40         | 51/39                | 41.19 ± 10.23  | C: mesalazine       | 12       | ①②③④⑥⑧⑨ | —             |
|                 |               |                      | 43.07 ± 11.87  | T: mesalazine+VD    |          |         |               |
| Yang Jing 2019 [14] | 99/99         | 104/94               | 41.38 ± 5.34   | C: mesalazine       | 4        | ①②③④⑥⑧⑨ | —             |
|                 |               |                      | 42.35 ± 5.09   | T: mesalazine+VD    |          |         |               |
| Shusheng Zhu 2015 [16] | 60/60 | 60/60                | 34.6 ± 3.6     | C: mesalazine       | 4        | ①②③④⑥⑧⑨ | —             |
|                 |               |                      | T: mesalazine+VD |                     |          |         |               |
| Vahedi 2016 [17] | 45/45         | 49/41                | 37.5 ± 9.0     | C: mesalazine+NS    | 6        | ①②③④⑥⑧⑨ | Random number table |
|                 |               |                      | 35.0 ± 9.2     | T: mesalazine+VD    |          |         |               |

T: treatment group; C: control group. Clinical observation indicators: ①—effective rate, ②—Mayo risk score, ③—serum MDA, ④—serum DAO, ⑤—IL-6, ⑥—CRP, ⑦—TNF-α, and ⑧—incidence of adverse reactions.
The results showed that the serum MDA group had homogeneity ($I^2 = 0\%$, $P = 0.76$). The fixed effects model was used for analysis (MD = $-0.75$, 95% CI (-0.96 to $-0.53$), $P < 0.00001$), and the difference was statistically significant. Heterogeneity was observed in the serum DAO group ($I^2 = 81\%$, $P = 0.001$), and the random effects model was used for analysis (MD = $-1.17$, 95% CI (-1.39 to $-0.95$), $P < 0.00001$). The difference was statistically significant, as shown in Figure 6. Due to the heterogeneity of the 4 studies in the serum DAO group, the remaining 3 studies show homogeneity ($I^2 = 26\%$, $P = 0.26$) after sensitivity analysis and were analyzed using the fixed effects model (MD = $-1.00$, 95% CI (-1.08 to $-0.92$), $P < 0.00001$), as shown in Figure 7. The difference was statistically significant, suggesting that oral vitamin D improved the repair function of intestinal mucosa in both serum MDA and DAO indexes.

### 3.1.5. Incidence of Adverse Reactions

A total of 4 studies [8, 11, 12, 16] described the incidence of adverse events, and the heterogeneity test ($I^2 = 30\% < 50\%$, $P = 0.23 > 0.1$) suggested...
3.1.1 1L-6

| Study or subgroup | Experimental | Control | Mean difference | Mean difference |
|------------------|--------------|---------|-----------------|----------------|
|                  | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| Ningning Yue 2020 | 19.04 | 5.22 | 40 | 22.68 | 5.75 | 40 | 1.0% | -3.64 (-6.05, -1.23) |              |
| Yang Jing 2019    | 15.33 | 2.27 | 99 | 19.89 | 2.41 | 99 | 13.8% | -4.56 (-5.21, -3.91) |              |
| Subtotal (95% CI) | 139  | 139 |     | 149.4 | 14.9% | 149.4 | 14.9% | -4.50 (-5.31, -3.67) |              |
| Heterogeneity: Chi² = 0.52, df = 1 (P = 0.47); I² = 0% |              |              |
| Test for overall effect: Z = 14.00 (P < 0.00001) |              |              |

3.1.2 TNF-α

| Study or subgroup | Experimental | Control | Mean difference | Mean difference |
|------------------|--------------|---------|-----------------|----------------|
|                  | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| Ningning Yue 2020 | 24.23 | 6.59 | 40 | 30.26 | 7.88 | 40 | 0.6% | -6.03 (-9.21, -2.85) |              |
| Yang Jing 2019    | 23.51 | 6.9 | 99 | 31.27 | 7.43 | 99 | 1.5% | -7.76 (-9.76, -5.76) |              |
| Subtotal (95% CI) | 139  | 139 |     | 159.3 | 2.1% | 159.3 | 2.1% | -7.27 (-8.96, -5.58) |              |
| Heterogeneity: Chi² = 0.81, df = 1 (P = 0.37); I² = 0% |              |              |
| Test for overall effect: Z = 8.42 (P < 0.00001) |              |              |

3.1.3 CRP

| Study or subgroup | Experimental | Control | Mean difference | Mean difference |
|------------------|--------------|---------|-----------------|----------------|
|                  | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| Hongliang Gao 2021 | 4.63 | 2.35 | 57 | 7.56 | 6.63 | 57 | 1.8% | -2.93 (-4.73, -1.13) |              |
| Vahedi 2016       | 2.31 | 2.25 | 45 | 3.86 | 3.55 | 45 | 3.9% | -1.55 (-2.78, -0.32) |              |
| Yang Jing 2019    | 5.55 | 1.11 | 99 | 7.04 | 0.95 | 99 | 71.0% | -1.49 (-1.78, -1.20) |              |
| Subtotal (95% CI) | 241  | 243 |     | 227.2 | 13.8% | 227.2 | 13.8% | -1.49 (-1.76, -1.23) |              |
| Heterogeneity: Chi² = 3.10, df = 3 (P = 0.38); I² = 3% |              |              |
| Test for overall effect: Z = 11.01 (P < 0.00001) |              |              |

Total (95% CI)

| Study or subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
|------------------|------|---|------|------|---|------|--------|-----------------|-----------------|
|                  | 519  | 521 | 100% | -2.06 | (-2.30, -1.82) | |              |              |

Test for overall effect: Z = 16.64 (P < 0.00001)

Test for subgroup differences: Chi² = 115.80, df = 7 (P < 0.00001); I² = 94%

3.2. Risk Analysis of Bias. The funnel plot was drawn based on the influence of the included literature on the cure rate of UC, and the results showed that the circle was located around both sides of the midline, presenting an incomplete symmetrical distribution, suggesting a large possibility of publication bias in this study, as shown in Figure 9.

4. Discussion

4.1. Mechanism of Vitamin D Adjuvant Treatment of UC. Vitamin D is a fat-soluble steroid hormone that is mainly
present in the human body in two forms: plant-based vitamin D2 and animal-derived vitamin D3, both of which can be ingested through food [20]. Vitamin D is linked to biological processes such as regulating intestinal mucosal immunity and intestinal integrity, in addition to regulating calcium and phosphate metabolism and skeletal homeostasis [21]. Vitamin D insufficiency has thus been linked to immune-mediated illnesses, such as inflammatory bowel disease. Inflammatory response, intestinal microflora disorder, and mucosal barrier damage play an important role in the occurrence and development of ulcerative colitis, and vitamin D can induce and maintain UC remission through reducing inflammatory factors and promoting the repair of intestinal mucosal barrier [22, 23]. In previous systematic reviews, no study evaluated vitamin D as a supplement to adjuvant therapy for UC. In this study, through quantitative synthesis, it was found that compared with the control group, UC patients treated with vitamin D as adjuvant therapy had beneficial effects on the Mayo score, intestinal barrier function, IL-6, TNF-α, CRP, and other inflammatory factors. There was no significant difference in safety.

Vitamin D can reduce the levels of inflammatory factors. First, 1,25(OH)2D3 combined with vitamin D receptor (VDR) can induce the expression of anti-inflammatory factors in monocytes to reduce inflammatory factors [24]. Second, vitamin D can act directly on CD4 and T lymphocytes to enhance Th2 cell proliferation and differentiation while inhibiting Th1 cell proliferation in DC cells [25]. Vitamin D can upregulate mitogen-activated protein kinase phosphatase-1 and inhibit the activity of mitogen-activated protein kinase (MAPK) and reduce the production of TNF-α while inhibiting HIF-1α or progression of inflammatory bowel disease (IBD) and inflammatory outcome index was consistent with Xue et al. [26]. Multiple studies included in this study showed that vitamin D supplementation effectively reduced the levels of inflammatory factors (IL-6, TNF-α, and CRP) in patients with ulcerative colitis. The proposed inflammatory outcome index was consistent with Xue et al. [27]. Xue et al. collected biopsy samples from 103 patients with UC and found that vitamin D/vitamin D receptor (VDR) signaling has a protective effect on the onset or progression of inflammatory bowel disease (IBD) and proved that the activation of hypoxia-inducible factor 1α (HIF-1α) is closely related to inflammatory factors. HIF-1α inhibitors inhibit the expression of TNF-α, IL-6, and IL-17, thereby reducing the inflammatory response.

Furthermore, the most prominent pathogenesis of UC is mucosal barrier degradation, which can be separated into
mechanical, immunological, chemical, and biological barriers. The four are self-contained and interact with one another, forming a massive defense system against foreign pathogenic pathogens [28]. Vitamin D enhances the connection between intestinal epithelial cells by promoting the expression of transmembrane proteins such as occludin and claudin and mucosal tight junction proteins such as zo-1, zo-2, and zo-3, thus constituting the mechanical barrier of intestinal mucosa [29, 30]. Based on mouse modeling, Wibowo et al. [31] gave different doses of vitamin D on the basis of blank control. By observing the intestinal brush-like margin component protein and the DAO level in peripheral blood under a microscope, it was concluded that vitamin D3 could activate the Wnt protein pathway, thus leading to cell differentiation and proliferation through stem cell signal transduction. Increase the proliferation of colonic mucosa cells to repair the colonic mucosa. Four of the literatures included in this study described intestinal barrier function by serum MDA or DAO indicators. After the mucosal cells of UC patients are damaged, DAO located in the mucous villi falls off and enters the blood and intestinal lumen [32]. When an inflammatory reaction occurs, a significant number of germs and endotoxins enter the bloodstream, and the body goes into survival mode, which inhibits SOD activity, weakens disproportionation reaction, and raises MDA levels as a lipid peroxide metabolic degradation product [33]. Therefore, DAO and MDA levels in peripheral blood are helpful to evaluate the degree of mucosal injury.

Recent studies have found that UC patients may be deficient in trace elements due to intestinal symptoms that lead to reduced nutrient intake and intestinal microbiota disorder, resulting in impaired mucosal barrier [34–36]. Vitamin D deficiency is more common [37]. Horta et al. [38] conducted a prospective study of 44 IBD patients living in Los Angeles (73% of whom had UC) and concluded that 75% of the patients had varying degrees of vitamin D deficiency. Vitamin D can improve intestinal microflora imbalance, regulate immunity, and maintain the integrity of intestinal mucosal barrier, so it is recommended for the treatment or adjuvant treatment of UC. Therefore, this study adopted meta-analysis to analyze the efficacy and safety of vitamin D in the treatment of UC, providing evidence-based medical evidence for the clinical application of vitamin D.

4.2. Research Limitations. Studies on vitamin D adjuvant treatment of UC are still in the initial stage. Although meta-analysis showed that vitamin D can improve UC symptoms from repairing the intestinal mucosa and reducing inflammatory factors, there are still many deficiencies. In one thing, the sample size of the literatures included in this study was limited, which was consistent with the small number and low quality of the literatures. This may be because vitamin D has not been unified into the treatment standards in China. In another thing, there were some differences in the measurement, usage, and course of vitamin D in the included literatures. In the future, more rigorous and prospective researches will be needed, such as collaboration between multiple centers.

5. Conclusion

Meta-analysis results show that, compared with the control group, vitamin D supplement is an effective intervention for UC. Vitamin D supplementation can increase intestinal mucosal repair factors and reduce inflammatory factors and Mayo risk score in UC patients. The results showed that there was no significant difference in the incidence of adverse events between the two methods, and it was a relatively safe adjuvant therapy. Moreover, vitamin D adjuvant therapy has the advantages of simplicity, effectiveness,
The datasets used during the current study are available from the corresponding author on reasonable request.

**Conflicts of Interest**

The authors declare that they have no conflict of interest.

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