Review

The use of vitamin D for patients with inflammatory bowel diseases

A systematic review

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Abstract: As vitamin D (VD) plays an essential role in inflammatory bowel diseases (IBD), this systematic review aimed to update the participation of this vitamin in the prevention or remission of these diseases. This review has included studies in MEDLINE–PubMed, EMBASE, and Cochrane databases. The authors have followed PRISMA (Preferred Reporting Items for a Systematic Review and Meta-analysis) guidelines. According to the inclusion and exclusion criteria, twenty-two randomized clinical trials were selected. In total, 1,209 patients were included in this systematic review: 1034 received only VD and 175 received VD in combination with calcium. The average doses of VD supplementation were from oral 400 IU daily to 10,000 IU per kilogram of body weight. Single injection of 300,000 IU of VD was also used. Several studies have shown the crucial role that VD plays in the therapeutic approach of IBD due to its effects on the immune system. It effectively decreased inflammatory cytokines such as TNF-α and IFN-γ ($p<0.05$) and provided a reduction in disease activity assessed through different scores such as Crohn's Disease Activity Index (CDAI) ($p<0.05$) and Ulcerative Colitis Disease Activity Index (UCDAI) ($p<0.05$). Unfortunately, the available clinical trials are not standardized for doses and routes of administration. Existing meta-analyses are biased because they compare studies using different doses or treatments in combination with different drugs or supplements such as calcium. Even though VD has crucial effects on inflammatory processes, there is still a need for standardized studies to establish how the supplementation should be performed and the doses to be administered.

Keywords: ulcerative colitis, Crohn's disease, inflammatory bowel disease, cholecalciferol, vitamin D

Introduction

Inflammatory Bowel Diseases (IBD) comprise a group of idiopathic gastrointestinal diseases with a multifactorial pathophysiological architecture. The primary forms are Crohn's Disease (CD) and Ulcerative Colitis (UC). These are conditions of substantial prevalence since it reaches about 1.2 million patients and 2.6 million people in Europe [1, 2]. Although the pathogenesis of IBD is still not elucidated, it is known that an inflammatory process resulted from the imbalance of the intestinal microbiota and the immune response in susceptible patients [3, 4], causing changes in the epithelial barrier [5, 6].

CD and UC have anatomopathological differences. The first is manifested as transmural lesions that can occur in the entire length of the gastrointestinal tract. UC is presented only in the colon and rectum, and its lesions are restricted to the mucosa [7, 8, 9]. Clinically, CD and UC share similar manifestations, whose primary complaints are chronic diarrhea, abdominal pain, and hematochezia [10, 11].

The treatment of IBD aims to remission, avoiding recurrences [12, 13]. Conventional clinical management consists of administering medications capable of modulating the inflammatory response to suppress the immune outcomes. Some of these drugs include systemic and topical corticosteroids, aminosalicylates, and antibiotics. Other therapies include immunomodulators, thiopurines, methotrexate, and cyclosporine A. Biologic therapies embrace monoclonal antibodies anti-TNF-α (Tumor Necrosis Factor-alpha) and their related biosimilar such as infliximab and adalimumab. Interleukin-12/Interleukin-23 Antagonist, JAK inhibitors, and Integrin antagonists have been also considered [14, 15, 16, 17, 18, 19]. However, cost, poor

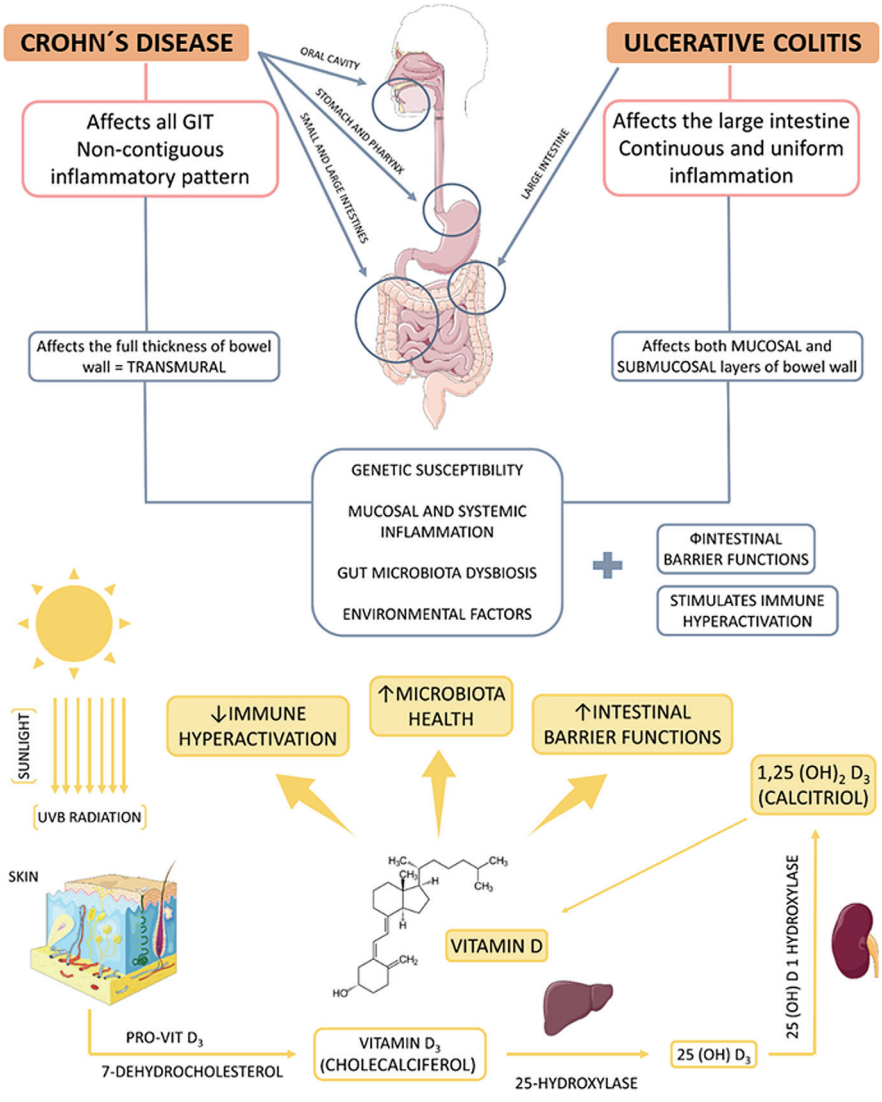

Figure 1. Crohn's Disease, Ulcerative Colitis and vitamin D: pathophysiology and repercussions of Vitamin D use. ↑: increase; ↓: decrease;=: equal; Φ: impairment; 25 (OH) D3: 25-hydroxy vitamin D3; 1,25 (OH)2 D3: 1,25 di-hydroxy vitamin D3; GIT: gastrointestinal tract; PRO-VIT D3: pro-vitamin D3; UVB: ultraviolet B.

compliance, and significant adverse effects in some medications surround these conventional therapies [20, 21].

Recently, the scientific community has turned to the influence of Vitamin D (VD) (1,25(OH)2D3), a fat-soluble hormone from both diet and a photo-dependent skin reaction [22, 23], for regulating the inflammatory process. Such effects have been associated with the immune-regulatory and immune-suppressive potential of this hormone that would help prevent or induce remission in IBD patients. Moreover, authors have shown that the deficiency of VD is common among IBD subjects and is more frequent than in the general population [24–28]. Figure 1 summarizes briefly the main pathological characteristics of CD and UC, as well as the VD actions against these two diseases.

VD, which can also be named cholecalciferol, play endocrine, paracrine, and autocrine actions. The endocrine actions are mainly related to the control of serum calcium homeostasis, and the autocrine and paracrine actions are performed on the cells that express the VD nuclear receptors leading to the downregulation of cell proliferation, the control of differentiation of cells, and apoptosis, influencing several effects such as in the immunity [29–32]. Existing meta-analyses are biased because they compare studies using different doses or treatments to associate different drugs or supplements such as calcium. Therefore, this study aimed to build a Systematic Review to evaluate the role of VD in IBD to suggest or not the use in the IBD treatment.

Materials and methods

Focused question

This review was performed to answer the focused question: What are the effects of vitamin D supplementation on Inflammatory Bowel Disease patients?

Language

Only studies in English were selected.

Databases

This study has included studies in MEDLINE–PubMed (National Library of Medicine, National Institutes of Health), EMBASE, and Cochrane databases. The descriptor used was "Vitamin D or cholecalciferol or 1,25(OH)2D3 and Inflammatory Bowel Disease or Ulcerative colitis or Crohn's Disease or colitis". These descriptors helped identify studies related to VD and its beneficial role in IBD treatment. The authors have followed PRISMA (Preferred Reporting Items for a Systematic Review and Meta-Analysis) guidelines [33, 34].

Study selection

This review included studies that reported the potential role of VD to patients with Inflammatory Bowel Disease. The inclusion criteria for this review were Randomized Clinical Trials (RCTs), prospective, and interventional studies. Full and not full texts were included.

The exclusion criteria were reviews, retrospective studies, studies not in English, case reports, poster presentations, and editorials. Reviews were consulted only to help in the Discussion section.

Data extraction

The search period for this search included December 2011 to January 2022. These studies are described in Table 1. The extraction of the data was performed independently by two authors who used the predefined inclusion and exclusion criteria, as well as the descriptors showed above. A third judge resolved disagreements between these two judges. Data were obtained from eligible articles that included the date, author, study design, sample size, information related to the use of VD, and its relationship with UC and CD. Only original articles were selected for the construction of Table 1.

Quality assessment

To evaluate the risk of biases in the selection, detection, and reporting bias of each RCT we applied the Cochrane Handbook for Systematic Reviews of Interventions [35]. Other risks of biases in the selection of patients, classification of interventions, missing data, and measurement of outcomes were also performed. Descriptive results of the biases found in the included clinical trials are shown in Table 2.

Results

The flow diagram (Figure 2) shows the selection of the articles, as well as the inclusion and exclusion criteria. In line with this, twenty-four studies were selected to build this review. Altogether, 1262 individuals were enrolled in the selected studies, age 5–80 years old (365 men; 317 women). Eight studies did not provide information about the number of men and women enrolled.

Twelve studies investigated the use of VD isolated [36–55] and four studies used VD in association with calcium [56–59]. Three studies were performed in children [46, 53, 57]. One study investigated the effects of VD in Vascular Endothelial Growth Factor (VEGF) and visfatin [45]. Three studies analyzed the levels of TNF-α and Interleukins before and after intervention [36, 56, 58]. One study investigated the effects of VD in the levels of VEGF and visfatin [45]. Two studies evaluated anxiety and depression scores [44, 49]. CDAI (Crohn's Disease Activity Index) and UCDAI (ulcerative colitis disease activity index) were investigated in three studies [41, 47, 52]. SSCAI (simple clinical colitis activity index) was performed by Karimi et al. [38]. IBDQ was evaluated by Karimi et al. [38], De Bruyn et al. [40], Bafutto et al. [42]. Partial Mayo Score was investigated by Mathur et al. [43]. C Reactive Protein and fecal calprotectin were also evaluated by some studies [37, 39, 42, 43, 50].

Discussion

Inflammatory Bowel Disease: general aspects

As an idiopathic disease, there is no determined cause to explain the onset of IBD. It is known that there are genetic factors to make an individual susceptible to developing the disease, as well as numerous environmental factors capable of triggering an exacerbated inflammatory response [60–64].

Table 1. Studies investigating the effects of vitamin D supplementation on inflammatory bowel disease patients

Reference	Country	Type and duration of the study	Patients	Intervention	Comparison	Outcomes
Studies performed with isolated vitamin D on IBD patients						
[55]	Denmark	Double-blind randomized placebo-controlled trial/7 w.	40 patients, 18–80 y with CD.	Bolus of 200,000 IU of VD followed by 7 w of 20,000 IU of VD daily.	Placebo and infliximab.	The high dosage VD treatment was significantly effective to reduce inflammatory biomarkers ($p<0.001$) and calprotectin ($p=0.02$) and the need for later infliximab dose-escalation.
[54]	Denmark	Double-blind randomized placebo-controlled trial/7 w.	40 patients, 18–80 y with CD.	Bolus of 20,0000 IU of VD followed by 7 w of 20,000 IU of VD daily.	Placebo and infliximab.	High-dose treatment with VD reduced IL-17A ($p=0.003$), IFN-γ ($p=0.002$), and IL-10 ($p=0.02$) expression. Alone, VD was not capable to significantly decrease the disease activity, CRP or calprotectin.
[45]	Iran	Double-blind randomized placebo-controlled trial/90 d.	90 patients, 26–47 y with UC.	1 single intramuscular injection of 300,000 IU of VD.	Placebo.	No significant differences in visfatin and VEGF serum levels between groups. Patients with VD insufficiency presented a lower visfatin level and showed an inverse correlation between serum VD and visfatin.
[41]	India	Double-blind randomized parallel placebo-controlled trial/4 w follow-up.	60 patients, 29–37 y (36 men; 24 women) with active UC and VD<40 ng/mL.	Oral nano liquid formulation of VD 60,000 IU daily for 8 days.	Oral placebo.	3-point reduction in UCDAI was observed in VD group ($p<0.001$); reduction of CRP ($p<0.001$), and calprotectin ($p<0.004$). Patients with VD>40 ng/mL more often had a 3-point reduction in UCDAI ($p<0.001$) and grade of severity.
[36]	Iran	Parallel designed double-blind, randomized controlled trial/ 90 days.	90 patients, 28–46 y with mild to moderate UC.	1 single muscular injection of VD (300,000 IU).	Placebo.	A decrease in serum TNF-α, IFN, and IL12p70 levels was observed ($p=0.001$). No significant effect on IL-4 and IL-10 serum levels.
[44]	Iran	Double-blind randomized placebo-controlled trial/ Single-dose/3 m.	90 patients; 28–46 y (51 men; 39 women) with mild to moderate UC.	1 muscular injection of VD (300,000 IU).	Placebo.	Baseline beck depression score was not statistically different between the intervention and placebo group (but scores decreased in the VD group). The scores showed a significant reduction in patients with baseline VD≥30 ng/ml ($p<0.01$).
[38]	Iran	Double-blind randomized clinical trial/12 w.	50 patients (27 men; 23 women; 22–55 y) with mild to moderate UC.	High dose group: 2,000 IU of VD/d.	Low dose group: 1,000 IU/d.	VD supplementation increased serum 25-OHD levels ($p<0.001$). There was no significant change in oxidative and antioxidant markers. Both groups presented a significant increase in the mean score of IBDQ-9, and SSCAI score decreased ($p<0.001$).
[40]	Belgium/ Netherlands	Prospective randomized, placebo-controlled trial.	143 patients with established ileal or ileocolonic CD.	25,000 IU of VD/w for 6 m following first or second ileocolonic resection.	Placebo for 6 m.	Supplementation did not reduce the incidence of postoperative endoscopic and clinical recurrence in CD patients ($p>0.05$). No difference was seen in QoL as measured by SF-36, IBD-Q and EQ-5D despite slight improvement in each group.
[37]	Australia	Prospective pilot study/8 w.	8 patients (30–68 y; 4 men; 4 women) with active UC, 9 patients (28–72 y; 6 men; 3 women) with inactive UC and 8 patients controls.	All patients received 40,000 IU of cholecalciferol.	8 non-IBD patients receiving the same dose of VD.	There was a reduction in FC levels in patients with active UC ($p<0.02$), platelets count reduced ($p<0.03$) and albumin serum increased ($p<0.04$). Those changes were not seen in patients with inactive UC nor in non-IBD patients.
[39]	Australia	Pilot study/2 months	5 patients with mild to moderately active CD and 5 with UC, (24–67 y; 7 men; 3 women).	1,000 to 10,000 IU of VD/d according to serum levels.	None.	There was an increase in VD levels from 10.8–29.2 ng/mL to 35.6–50 ng/mL. There was no improvement on FC and biomarkers of inflammation such as CRP, platelet count and serum albumin. HBI and SSCAI significantly reduced over 12 w in CD, and a trend was seen in UC ($p<0.05$).

Table 1. Studies investigating the effects of vitamin D supplementation on inflammatory bowel disease patients (Continued)

Reference	Country	Type and duration of the study	Patients	Intervention	Comparison	Outcomes
[43]	USA	Prospective double-blinded, randomized trial/90 days.	18 patients with UC (13 men; 5 women; 18–56 y).	2,000 IU of oral VD daily.	4,000 IU daily.	After 90 days, 4,000 IU of VD increased serum levels more than the use of 2,000 IU ($p<0.001$). Only the group receiving 4,000 IU/day showed significant increase in QoL scores. The improvement of the Partial Mayo UC was not significant ($p<0.0017$). CRP levels decreased significantly in both groups.
[42]	Brazil	Prospective double-blinded, randomized trial/8 w.	30 patients with mild-severe CD (18–60 y; men and women NR)	Group 1 (G1): 2,000 IU; G2: 10,000 IU; G3: 50,000 IU.	NR.	Significant augmentation of VD levels (baseline for G1 was 19.5±5.1 ng/mL to 26.0±6.7 at 8 w; G2: 19.1±4.1 to 26.0±5.8 and G3: 19.5±6.4 to 46.4±12.7); improvement of IBDQ were observed in all groups but significance occurred only in G2 and G3 ($p<0.05$). Significant reduction of FC was seen in G3 ($p<0.05$).
[49]	Canada	Randomized, double-blind placebo-controlled trial/12 months.	34 patients, 18–70 y (14 men; 20 women) with CD in remission.	High dose of oral VD at 10,000 IU daily.	Oral VD 1,000 IU daily.	High dose of VD significantly improved VD blood levels ($p<0.05$). The relapse rate showed no significant differences between low- and high-dose groups. Clinical relapse of CD was less observed in patients who received the high dose. Both groups showed improvement in anxiety and depression scores not significant).
[51]	Iran	Double-blind, randomized controlled trial (evaluation of inflammatory biomarkers)/1 single injection.	90 patients, 18–50 y (51 men; 39 women) with UC in remission.	One single muscular injection of 1 mL 300,000 IU VD.	Placebo.	After injection, VD levels increased only in the intervention group ($p<0.001$). CRP levels were lower in the VD group after intervention. Erythrocyte sedimentation rate decreased in the VD group ($p<0.001$). The mean fold modification in hCAP18 gene expression in the VD group was significantly higher ($p<0.001$).
[50]	USA	Randomized, parallel assignment, single Masking (Investigator) – (of VD serum levels, Ca and PTH)/6 w.	32 patients, 8–21 y (20 men; 12 women); Weight > 20 kg with pediatric IBD.	Oral VD 10,000 IU per 10 kg body weight.	Oral VD 5,000 IU per 10 kg body weight.	Serum VD increased in both at 8 w ($p<0.001$). At 12 w, serum VD levels were 35.1±8.4 and 30.8±4.2 ng/mL in the higher and lower dose groups. Mean serum Ca and PTH concentrations did not significantly change.
[47]	Ireland	Double-blind randomized placebo-controlled study/ 3 months.	27 patients with CD in remission.	2,000 IU of VD/day.	Placebo.	Treated group showed significant augmentation of VD levels ($p<0.001$). In the placebo group, small bowel and gastro-duodenal permeability increased from baseline ($p<0.003$). After 3 m, dividing patients between patients with VD≥75 nmol/L and patients with VD<75 nmol/L, the first group had lower CRP ($p<0.019$), higher QoL ($p<0.037$), higher LL-37 ($p<0.001$), and lower CDAI scores ($p<0.082$).
[46]	Canada	Double-blind, randomized controlled study (evaluation of VD levels)/6 months.	83 patients, 8–18 y (45 men; 38 women) with quiescent CD.	Supplementation of 2,000 IU/d of VD orally.	400 IU/d of VD.	2,000 IU/d dose is more effective in raising VD concentrations to >30 ng/mL in children with CD than 400 IU/d ($p<0.001$). Both interventions were effective at achieving 16 or 20 ng/mL.
[52]	USA	Open-labeled, prospective clinical trial/24 w.	18 patients with CD (CDAI: 150–400 and serum levels of VD≤40 ng/mL) (21–55 y; 7 men; 11 women).	1,000 IU/d for 2 w, then it was increased to 5,000 IU/d.	None.	There was a significant increase of serum levels of VD from 16.0±10 to 45±19 ng/mL at the end of the treatment and decreased the mean CDAI scores from 230±74 to 118±66 ($p<0.001$) and improved QoL scores ($p=0.0004$).

Table 1. Studies investigating the effects of vitamin D supplementation on inflammatory bowel disease patients (Continued)

Reference	Country	Type and duration of the study	Patients	Intervention	Comparison	Outcomes
[53]	USA	Randomized, controlled clinical trial (evaluation of VD levels)/6 w.	71 patients, 5–21 y (38 men; 33 women); with serum VD<20 ng/mL and with inactive or mild or moderate/severe IBD (CD and/or UC).	2,000 IU of VD2 orally. (arm A, control); oral VD3 2,000 IU daily (arm B); oral VD2, 50,000 IU weekly (arm C).	–	VD 3 (2,000 IU) daily and VD 2 (50,000 IU) weekly for 6 w are superior to VD 2 (2,000 IU) daily for 6 w in raising serum VD concentration ($p<0.0001$) and are well-tolerated among children and adolescents with IBD.
[48]	USA	Randomized, single-blinded clinical trial/ 26 w.	15 patients within remission, mild and moderate CD (baseline VD<30 ng/ mL).	One group received 1,000 IU/day, and the other received 10,000 IU/day.	None.	At 26 w of treatment, there was a significant increase in HBI levels in the high dose group ($p<0.05$). There was also an increase in VD levels in both groups ($p<0.05$).
Studies performed with vitamin D in association with calcium on IBD patients						
[59]	China	Prospective, randomized, parallel-controlled, open-label pilot clinical trial (evaluation of clinical scores)/12 months.	74 patients with UC and 71 patients with CD, >18 y, diagnosed with IBD and with VD insufficiency.	Oral VD 150,000 IU plus oral Ca 600 mg each 3 months.	Oral Ca 600 mg (daily).	No significant differences in ESR, hsCRP, and Mayo score/CDAI, which remained after a 12-month follow-up ($p>0.05$).
[56]	Denmark	Randomized, placebo-controlled clinical study/ 12 months.	18 patients (23–66 y; 6 men; 12 women) with CD in remission or mild CD.	Each patient was treated with 30 μg/d of VD+1200 mg of calcium.	Placebo+1200 mg of calcium.	VD inhibited the VDR up-regulation expression in previously stimulated T CD4+cells by 30% ($p<0.027$). *In vitro* study showed a decrease in IFN-γ production and a decrease in VDR T cell expression ($p<0.1$).
[57]	USA	Randomized, not blinded, controlled trial. Evaluation of VD serum levels and CRP/12 months.	63 patients, 8–18 y (27 men; 36 women) with inactive or mild or moderate/severe IBD (CD or UC).	400 IU of oral VD/d to group 1+800 mg of Ca^{2+}/d; elemental calcium orally if <11 y and 1,200 mg if ≥11 y.	G 2: 1,000 IU/d in summer and 2,000 IU in the winter.	Three participants in group 1 and three in group 2 achieved maintaining VD of 32 ng/mL or greater in all trimonthly visits for 12 months. More participants in group 1 achieved CRP levels of 1 mg/dL or greater and IL-6 greater than 3 pg/mL.
[58]	Denmark	Randomized placebo-controlled trial (evaluation of cytokines levels)/ 26 w.	20 patients; 19–63 y (8 men; 12 women) with CD in remission.	Oral VD (1,200 IU) and calcium (1,200 mg).	Oral calcium alone (placebo).	LPS-matured monocyte-derived dendritic cells presented reduced expression of CD80 and lower production of IL-10, IL-1β, and IL-6 following 26 w of VD intake ($p=0.04$). The placebo did not affect maturation markers, cytokine production, or the mixed leucocyte reaction.

Ca: Calcium; CD: Crohn's Disease; CD80: Cluster Of Differentiation 80; CDAI: Crohn's Disease Activity Index; CRP: C-Reactive Protein; EQ-5D: EuroQol 5 Dimensions; ESR: Erythrocyte Sedimentation Rate; FC: fecal calprotectin; HBI: Harvey-Bradshaw index; hCAP18: Human Cathelicidin Antimicrobial Protein; HsCRP: High-Sensitivity C-Reactive Protein; IBD: Inflammatory Bowel Disease; IBDQ: Inflammatory Bowel Disease Questionnaire; IFN: Interferon; IL-10: Interleukin 10; IL12p70: Interleukin 12p70; IL-1β: Interleukin 1 β; IL-4: Interleukin 4; IL-6: Interleukin 6; IU: International Unit; PTH: Parathyroid Hormone; QoL: quality of life; SSCAI: Simple Clinical Colitis Activity Index; sf-36: Short Form Health Survey 36; TNF-α: Tumor Necrosis Factor α; UC: Ulcerative Colitis; UCDAI: Ulcerative Colitis Disease Activity Index; VD: Vitamin D; VEGF: vascular endothelial growth factor.

Table 2. Descriptive results of the biases found in the included clinical trials

Study	Question focus	Appropriate randomization	Allocation blinded	Double blind	Losses (<20%)	Prognostics or demographic characteristics	Outcomes	Intention to treat analysis	Sample calculation
[55]	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No
[54]	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No
[45]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
[41]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
[36]	Yes	Yes	Yes	Yes	Yes	No	Yes	NR	Yes
[44]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes
[38]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
[40]	NR	NR	NR	NR	NR	NR	NR	NR	NR
[37]	Yes	No	No	No	NR	Yes	Yes	NR	NR
[39]	Yes	No	No	No	Yes	Yes	Yes	NR	Yes
[43]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
[42]	Yes	NR	NR	Yes	No	No	Yes	NR	NR
[49]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
[51]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
[50]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
[47]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	No
[46]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
[52]	Yes	No	No	No	Yes	Yes	Yes	NR	NR
[53]	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
[48]	Yes	NR	Yes	No	NR	NR	Yes	NR	NR
[59]	Yes	No	No	No	Yes	Yes	Yes	No	NR
[56]	Yes	NR	NR	NR	Yes	Yes	Yes	NR	Yes
[57]	Yes	Yes	No	No	No	No	Yes	Yes	Yes
[58]	Yes	Yes	Yes	No	Yes	No	Yes	NR	No

NR: Not reported.

Concerning genetic factors, changes in alleles of genes encoding proteins and receptors present on the surface of cells of the immune system, such as monocytes, macrophages, and lymphocytes, and of epithelial cells from intestinal lymphoid tissues are observed. These changes are related to the activation of nuclear factors, such as Nuclear Factor kB (NFkB), resulting in the transcription of cytokines and pro-inflammatory factors, such as IFN-γ, TNF-α, IL-12, and IL-1β, as summarized in Figure 3 [65–69].

Several studies suggest that dysbiosis is an important cause of IBD due to an increase in pathogenic bacteria concerning commensals, associated with an exacerbated inflammatory response of the host to these organisms [70–72].

The influence of food habits is also discussed, especially when preservatives and other xenobiotics are present and can trigger inflammation in susceptible individuals with high fat and/or sugar diet and low fiber intake [73–75].

UC is characterized by ulcerative inflammation lesions that necessarily affects the rectum and might reach segments of the colon, with no skipped areas, and is restricted to the mucosa. It is believed that UC is caused by an inflammatory response of a TH2 pattern, whose central cytokines produced are Interleukin-5 (IL-5) and IL-13, which gives the pattern of hemorrhagic injury of the disease. Recent studies have shown a key role for mast cells (also known as a player on the Th2 arm of immunity) in animal models of colonic inflammation, and in human UC [76–80].

On the other hand, CD shows intramural lesions, which can occur from the mouth to the anus. Skipped areas are common because of the discontinuous pattern. Inflammation seems to be determined by a TH1 response due to its granulomatous lesion pattern. Anorectal fistulas and perianal abscesses are also common [78, 81–83].

Vitamin D: remarkable and far-reaching biological effects

VD is a fat-soluble hormone obtained from the diet and absorbed in the small intestine and dietary fat, supplementation, or an exposition of 7-dehydrocholesterol presented in the skin to sunlight. The production of VD occurs due to the activation of 7-dehydrocholesterol, followed by the enzymatic changes in the liver and kidneys [7, 84–87].

In addition to the effects of VD on phosphorus, calcium metabolism, and bone health homeostasis, it has broad functions in the immune system and affects numerous

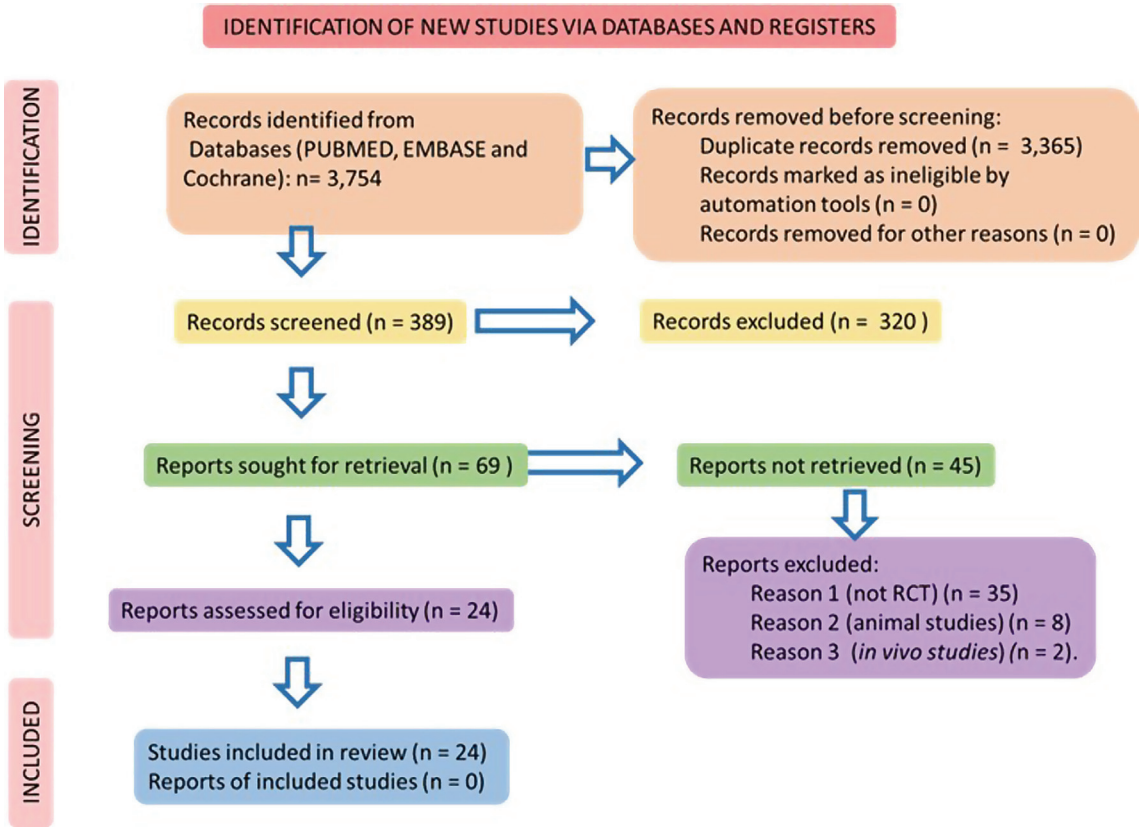

Figure 2. Flow chart showing the study selection [33, 34].

physiologic processes, including damping down inflammation and excessive intracellular oxidative stress [85, 87, 88].

VD acts on immune cells through the vitamin D receptor (VDR). Almost all of them express the VDR at some stage in their development or activation, and the effects occur under different optimal levels of VD. This vitamin participates in macrophages' maturation, antigen presentation and response, gut barrier function, production of antimicrobial peptides, and homeostasis of adaptive and innate immunity. VD has been associated with the pathogenesis of immune-mediated diseases in preventing them and lowering the risk of infections [85, 89–93].

Several studies have shown the relation between VD and systemic inflammation, and that sufficient serum VD levels (>30 ng/mL or 75 nmol/L) substantially inhibit mRNA production of inflammatory cytokines such as IL-1α, IL-6, and TNF-α [84, 94–96].

This hormone improves cell viability, reduces the formation of reactive oxygen species (ROS), and stimulates the expression of IL-33, and stimulating the expression of antioxidant genes. This is one reason to explain how VD can slow down oxidative stress, the aging process, cellular injury, and facilitates balanced mitochondrial activities, preventing lipid peroxidation and DNA damage [88, 94, 97–100].

On the other hand, since VD is a fat-soluble hormone, it can remain in the body for a long time. For these reasons, high doses (plasma levels above 150 ng/mL) are related to toxicity such as hypercalcemia, altered sensorium, nausea, vomiting, pancreatitis, altered sensorium, polyuria, dehydration, and acute kidney injury [101].

The link between IBD and vitamin D

It is known that the deficiency of this VD in patients with IBD is multifactorial, which can be attributed to insufficient sun exposure, to an inadequate diet, intestinal malabsorption, and impaired metabolism and conversion. Thus, it is unclear whether there is a causal or consequence link between IBD and VD deficiency. The therapeutic use of this vitamin was highlighted through an experiment performed with VD-deficient IL-10 knockout mice, which had the development of IBD quickly and with a progressive character. Through a diet with a high content of VD and calcium, attenuation of disease activity was observed [60, 102–107].

VD also affects the production of antimicrobial peptides, such as cathelicidin and b-defensin 2, related to stimulating the transcription of the NOD2 gene, which participates in the release of cytokines as IL-1β, IL-6, and TNF-α, relevant to the inflammatory process. In CD, it is observed that VD

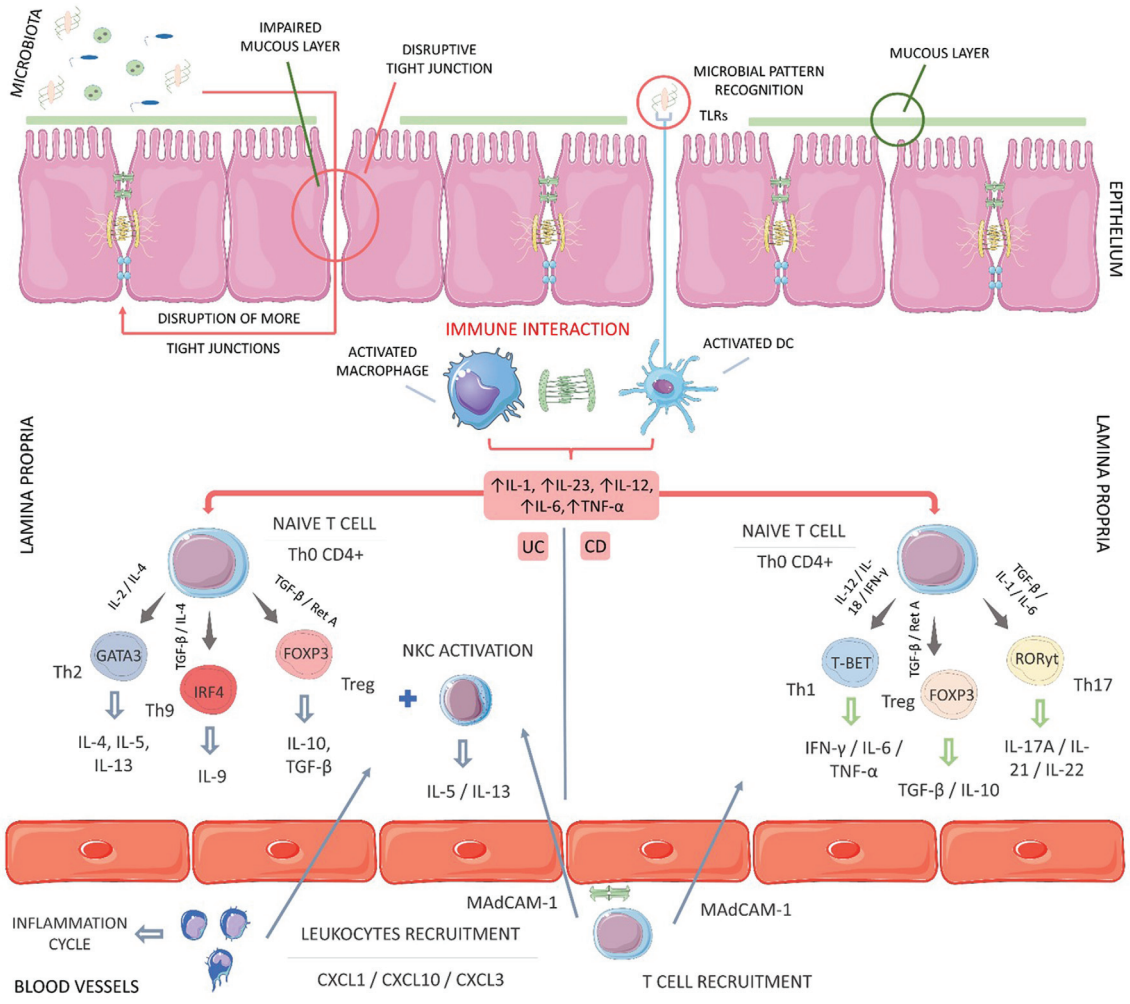

Figure 3. Pathophysiology of inflammatory bowel disease (IBD). The imbalance in the intestinal microbiota, tight junction disruption, and immunological response leads to the release of inflammatory cytokines, resulting in the two major inflammatory patterns. Tight junction disruption promotes the phagocytosis of commensal bacteria of the intestinal lumen by dendritic cells and macrophages, leading to cytokine secretion and modulation of T helper response determinates the granulomatous or ulcerative lesion pattern of IBD. CD: Chron's disease; CXCL1: chemokine (C-X-C motif) ligand 1; CXCL10: chemokine (C-X-C motif) ligand 10; CXCL3: chemokine (C-X-C motif) ligand 3; DC: dendritic cells; FOXP3: forkhead box P3; GATA3: gata binding protein 3; NKC: natural killer cells; TLRs: toll-like receptors; IFN-γ: interferon gama; IL-1: interleukin 1; IL-2: interleukin 2; IL-4: interleukin 4; IL-: interleukin 5; IL-23: interleukin 23; IL-12: interleukin 12; IL-6: interleukin 6; IL-9: interleukin 9; IL-10: interleukin 10; IL-13: interleukin 13; IL-17A: interleukin 17 a; IL-21: interleukin 21; IL-22: interleukin 22; IRF4: interferon regulatory factor 4; MAdCAM-1: MAdCAM-1, mucosal addressing cell adhesion molecule 1; TGF-β: tumor growth factor beta; Ret A: retinoic acid; TNF-α: factor tumor necrosis alfa; T-BET: immune cell transcription factor T-BET; Th1: T helper 1; Th2: T helper 2; Th9: T helper 9; Th17: T helper 17; Treg: T regulator cell; RORγt: retinoid-related orphan receptor gamma t; UC: ulcerative colitis.

activates Treg cells, while suppressing TH1 and TH17 cells. VD also strengthens macrophage response and assists in the maintenance of *Paneth* cells [7, 108–113].

VD also has action on the intestinal microbiota, playing an essential role in maintaining its homeostasis and composition. Moreover, intestinal dysbiosis may be relieved by VD-dependent anti-inflammatory mechanisms. There is evidence that VD participates in the regulation of the integrity of the intestinal mucosal epithelial cells and provides stimuli for their differentiation, further reducing the occurrence of apoptosis of these cells [7, 111, 114–116].

Chronic VD deficiency, associated with well-known damage caused by the intestinal inflammatory process, also leads to malignant neoplastic processes. For this reason, the therapeutic use of VD in the adjuvant treatment of IBD is an important object of study [117–120]. The association between IBD and VD is illustrated in Figure 4.

The articles discussed below present an intervention using Vitamin D alone, in different dosages and routes of administration (Table 1).

In a 1-year follow-up study, Bendix et al. [55] discussed that high dosage VD treatment was significantly effective

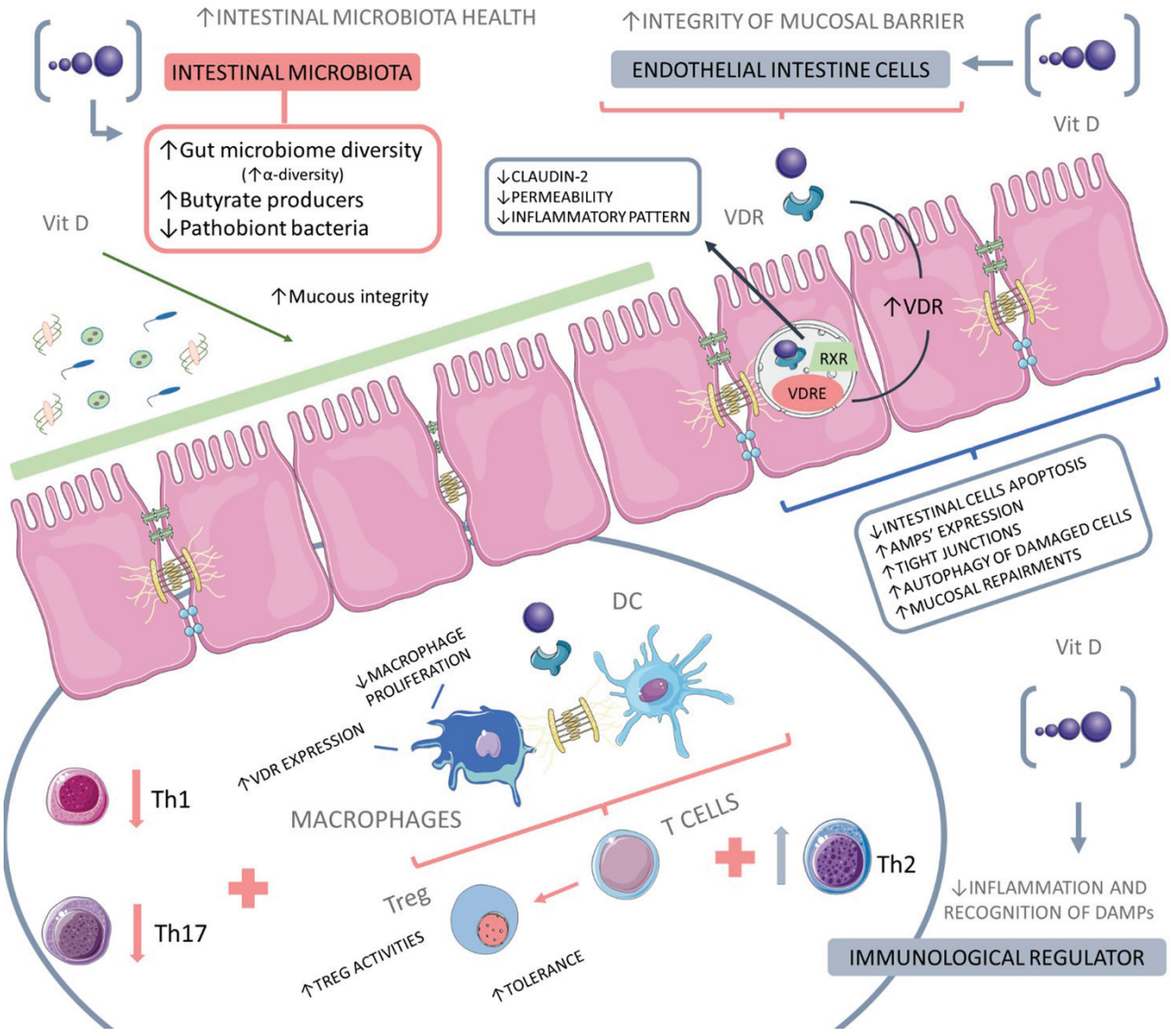

Figure 4. Vitamin D and its effects on epithelial cells, inflammatory cells, and intestinal microbiota. In its active form, VD induces dendritic cells and macrophages to an anti-inflammatory pattern and regulates intestinal microbiota and homeostasis. ↑: increase; ↓: decrease; α: alfa; AMPs: antimicrobial peptides; DAMPs: damage-associated molecular patterns; RXR: retinoic acid receptor; VDR: Vitamin D receptor; VDRE: Vitamin D-response element; Vit D: Vitamin D; Th1: T helper 1; Th2: T helper 2; Th17: T helper 17; Treg: T regulator cell.

to reduce inflammatory biomarkers and the need for later infliximab dose-escalation in CD patients. The original study of Bendix et al. [54] was conducted as a RCT with CD patients to evaluate IL-17A, IFN-γ, and IL-10 expression levels among individuals treated with high dosages of VD alone or combined with infliximab. As an intervention, the investigators administered firstly a bolus of 200,000 IU of VD in the treated groups, followed by 7 weeks of 20,000 IU daily of VD. The results confirm that the use of VD alone can significantly reduce IL-17A, IFN-γ, and IL-10 expressions among VD-treated participants. However, these high dosages of VD were not significantly appropriated to decrease disease activity, CRP, or calprotectin levels. This study does not demonstrate the chronic effects of VD supplementation, although the done measurements of inflammatory biomarkers were interestingly associated with extensive follow-ups. One strength can be the use of endoscopy to assess bowel biopsies and the RNA expression of cytokines of the treated patients at weeks 0 and 7 of treatments.

Emami et al. [45] performed an RCT with UC patients, aiming to assess the levels of proangiogenic factors, visfatin, and vascular endothelial growth factor after intervention with a single intramuscular injection containing 300,000 IU of VD. The outcomes demonstrated that although supplementation with VD generated less increase

in visfatin in patients with insufficiency of this hormone. The study fails to demonstrate the effectiveness of VD supplementation for the outcomes proposed in patients with UC; thus, it is possible to point out the need for studies with chronic administration of the vitamin since its use in a single dose limits the possible effects on an extremely acute and short period. Furthermore, the study does not provide clear information about the participants' gender, which can bring discrepancies between participants and impact the study's result through the generation of bias.

Ahamed et al. [41] performed an RCT with UC and VD deficiency, assessing disease activity, using the UCDAI score, after administering nano liquid formulation of VD 60,000 IU daily, for eight days. The study shows a reduction of 3 points in the score, especially in patients who reached the target of serum VD concentration above 40 ng/mL. However, it is important to note the short administration, for only eight days, limiting the results to an acute use and masking possible adverse effects of the chronic administration. Besides, the small sample also limits the accuracy of the study.

The study of Sharifi et al. [36] used the same cohort of Emami et al. [45] and demonstrated a significant reduction of TNF-α, IFN, and IL12p70 serum levels; however, the IL-4 and IL-10 did not change significantly. The data allow us to infer that VD may exert more relevant inhibitory effects on a TH1 pattern to the detriment of the TH2 response. It is also relevant to note that the study does not provide information about the participants' genders. The single application does not specify a chronic VD administration's effects, limiting the results to a strictly acute supplementation.

In another study, Sharifi et al. [44] investigated the effects of a single intramuscular injection of VD (300,000 IU), evaluating the Beck Depression Score (BDS) at baseline and after application, correlating it with the levels of VD. They observed that the patients, who showed VD levels greater than or equal to 30 ng/mL at the beginning of the study, obtained a significant BDS reduction. This result allows us to conclude that, for the VD supplementation to have a significant antidepressant effect, this hormone's levels must be satisfactory from the baseline. The study did not evaluate other clinical and laboratory data, which does not allow us to know the effects of a possible reduction in the disease's inflammatory activity.

Karimi et al. [38] elaborated a double-blind, randomized clinical trial to investigate the effects of two VD regimens in UC patients with VD deficiency. Patients received 2,000 IU of VD per day for 12 weeks or 1,000 IU of VD per day for the same time. Improvement of VD serum levels was observed in all groups; however, the levels were significantly higher in the high dose group. Regarding QoL, both groups showed a significant increase in the mean score of IBDQ-9 at the end of the study. Besides, the score that assesses the colitis activity decreased in both groups.

In the study of De Bruyn et al. [40], CD patients were treated to receive 25,000 IU of VD weekly for six months following their first or second ileocolonic resection while the other arm received a placebo. The results showed that the higher dose was enough for the normalization of the serum levels of VD, although this supplementation did not reduce the incidence of postoperative endoscopic and clinical recurrence in CD patients. The authors concluded that it is possible that VD deficiency is a consequence of disease activity and does not act as a causative factor in the pathophysiology of CD.

Garg et al. [37] performed a prospective pilot study in which the authors enrolled 25 patients into three groups: eight with active UC, nine with inactive disease, and the other eight had no IBD. All patients received 40,000 IU of cholecalciferol weekly for 8 weeks. There was also a decrease in fecal calprotectin levels in the active UC group. Furthermore, there was a decrease in platelet levels and increased albumin serum levels in this group. It was also reported to increase in abundance of Enterobacteriaceae and a decrease in the mucolytic *Ruminococcus gnavus* species, but no other microbiota alteration was detected. Although this study shows exciting results, it is important to highlight it is not a randomized, placebo-controlled study, which can be led to possible bias. Moreover, the sample size is small.

Garg et al. [39] enrolled five patients with mild to moderately active CD and five patients with active UC and treated them with 1,000–10,000 IU/daily for two months and analyzed stool samples and other serum biomarkers of inflammation. Their results showed improved VD serum levels, but there was no significant improvement in fecal calprotectin, neither on CRP, platelets, serum albumin, and other inflammation biomarkers. After twelve weeks, there was a significant improvement in clinical scores in patients with CD, and a trend was noticed in patients with UC. It is important to notice that this is not a randomized, placebo-controlled, or blinded study and included a small sample size.

In another study, Mathur et al. [43] investigated the effects of VD3 on disease activity and quality of life in UC patients with hypovitaminosis D, evaluating the Short IBD Questionnaire (SIBDQ), the Partial Mayo Score for UC disease activity, and serum laboratory tests. Ninety days after the intervention, VD serum levels increased more on the 4,000 IU group than the 2,000 IU group, although there was a significant increase in both groups. They observed that VD might improve the quality of life, but the effect on the disease activity is still unclear.

Bafutto et al. [42] conducted a prospective double-blinded, randomized trial with patients with mild-severe CD. The trial compared 2,000 IU of VD per week for eight

weeks with two other groups: 10,000 IU of VD and 50,000 IU of VD. The data demonstrated significant augmentation of VD levels and 50,000 IU per week was the best dosage for VD supplementation, and this intervention acts on immunomodulation in patients in the use of anti-TNF. Furthermore, it was seen a significant improvement in the quality of life in the two highest dosages.

In a randomized, double-blind placebo-controlled trial performed by Narula et al. [49] with CD patients in remission, a comparison was made between VD dosages. The subjects were divided into two groups so that one group received oral VD in a dose of 10,000 IU, daily, while the other arm received oral VD in a dose of 1,000 IU, daily for 12 months. The higher dosage of VD was more effective in increasing this hormone's levels in the blood. However, the difference between dosages was not effective in reducing the relapse rate. Furthermore, both groups showed improvement in depression and anxiety scores.

In the same cohort of Emami et al. [45], Sharifi et al. [51] evaluated inflammatory biomarkers in UC patients in remission. C-reactive protein levels were lower in the VD group after an intervention such as Erythrocyte Sedimentation Rate. The mean fold change in cathelicidin hCAP18 gene expression in the VD group was significantly higher. Although there was a significant increase in VD levels in the VD group and decreased inflammatory biomarkers, we cannot say that this dosage of VD in a single injection would promote the disease's clinical improvement.

In a randomized, parallel assignment, a single masking study with IBD patients with 25(OH)D serum level <30 ng/mL of VD, Simek et al. [50] investigated VD as well as calcium and parathormone levels. The patients received VD in a dose of 10,000 IU/10 kg once a week, or 5,000 IU/per 10 kg. Serum VD increased in both groups at eight weeks. At 12 weeks, serum VD levels were 35.1±8.4 and 30.8±4.2 ng/mL in the higher and lower dose groups. Although there was a higher increase in the 10,000 IU group than in the 5,000 IU group, it was not statistically significant. The mean serum of calcium and parathormone concentrations did not significantly change. With the results of this study, it is not clear the impact of the supplementation in improving IBD.

Raftery et al. [47] performed a study with CD patients in remission with an intervention dose of 2,000 IU of VD, daily, for three months. The other arm received only a placebo. The study demonstrated a significant augmentation in VD serum levels in the treatment group. On the other hand, the placebo group showed a reduction. Furthermore, this group had, as a result, small bowel and gastro-duodenal permeability increased from baseline. From the data, it is possible to claim that patients with 25(OH)D≥75 nmol/L after 3 months showed decreased markers of inflammation such as CRP, and plasma cathelicidin concentrations such as LL-37 apart from the non-significantly lower score of disease activity compared to patients with 25(OH)D<75 nmol/L.

Wingate et al. [46] performed an RCT with CD children under supplementation with 2,000 IU/d of VD orally compared to 400 IU/d of VD for six months. The study demonstrated that supplemental dose did not affect the disease activity and showed that both interventions were effective at achieving 16 or 20 ng/mL VD serum levels, although 2,000 IU/d dose was more effective in increasing VD concentrations to >30 ng/mL in children with CD than 400 IU/d doses.

The study performed by Yang et al. [52] enrolled patients with active CD and low VD serum levels at baseline and treated them with 1,000 IU, daily for two weeks and then improved the dose for 5,000 IU for 24 weeks. The results showed an increase in the serum levels at the end of the study and a significant improvement in CD activity according to the CDAI and quality of life scores. A possible bias to be highlighted is the small sample size of the sample and the fact that it is an open-labeled trial, not controlled by placebo.

Pappa et al. [53] performed an RCT with children/adolescents with serum VD<20 ng/mL and IBD (CD and/or UC). The intervention was performed in patients that received 2,000 IU of VD2 orally (control), oral VD3 2,000 IU daily, or oral VD2, 50,000 IU weekly. The study indicated that VD3 (2,000 IU) daily and VD2 (50,000 IU) weekly for 6 weeks is superior to VD2 (2,000 IU) daily for six weeks in raising serum VD concentration and were well-tolerated.

Boothe et al. [48] published a non-complete work of a randomized, single-blinded trial in which they enrolled 15 patients with CD diagnosis with low VD serum levels at baseline. One group received low doses (1,000 IU), and the other group received a higher dose (10,000 IU), daily for 26 weeks. At the end of the study, there was an increase in VD levels in both groups, but there was a significant increase in HBI levels only in the high dose group. Although these are promising data, it is important to observe that the results of this study were not fully published, and the sample size was small.

The studies performed by Tan et al. [59], Bendix et al. [56], Pappa et al. [57], and Bartels et al. [58] carried out an intervention with VD in association with calcium supplementation. Tan et al. [59] conducted a clinical trial where participants had VD insufficiency (10 ng/mL≤VD<20 ng/mL) or deficiency (<10 ng/mL). The trial compared the intervention of oral VD 150,000 IU plus oral Ca 600 mg daily with two other groups: oral Ca 600 mg (daily) and vehicle control group for three months, performing a follow-up over 12 months. The study outcomes did not show significant differences in Erythrocyte Sedimentation Rate, C Reactive Protein, and Mayo score/CDAI, even after the follow-up. It should be noticed that this study does not

provide data on the number of men and women included in the study. Also, VD administration was carried out in association with calcium, leading to a possible bias.

The study performed by Bendix et al. [56] included patients from a previous study in which they were treated with 30 μg of VD, plus 1,200 mg of calcium, daily. They evaluated the CD4+T cells response to the increase of VD in patients' cells that were previously activated. As a result, the authors concluded that VD inhibited the VDR up-regulation expression in previously stimulated T CD4+cells by 30%, with no effect on non-stimulated T cells. There was also a decrease in IFN-γ levels *in vitro* matching VDR expression reduction in those T cells. These results contribute to show the effects of VD supplementation on the regulation of pro-inflammatory cytokines. The small size of the sample may represent a possible bias.

Pappa et al. [57] conducted a trial to evaluate VD serum levels and C Reactive Protein in CD and/or UC patients that received 400 IU or 1,000 IU of oral VD daily in summer and fall and 2000 IU at winter and spring. All patients received 800 mg of calcium supplementation daily and elemental calcium orally if <11 years and 1,200 mg if ≥11 years. Three participants in the first dosage and three in the second achieved VD of 32 ng/mL or higher in all trimonthly visits for 12 months. This shows that VD doses under 2,000 IU are not sufficient to maintain VD serum levels elevated. Since the authors did not observe a significant difference in the groups, it is impossible to postulate if VD supplementation at this dosage could have beneficial clinical outcomes for patients with IBD.

In the study of Bartels et al. [58], CD patients with CDAI below 150 were treated to receive oral VD in a dose of 1,200 IU plus calcium in a dose of 1,200 mg while the other arm received oral calcium alone. The evaluation of cytokine levels exhibited lower production of inflammatory cytokines such as IL-1β and IL-6, and LPS-matured monocyte-derived dendritic cells presented reduced expression of CD80 after 26 weeks of intervention. The data show that the placebo treatment did not affect cytokine production or the mixed leucocyte reaction, while the intervention with oral VD supplementation reduced cytokine levels in these patients.

The recent publication of Guzman-Prado et al. [121] showed a review and meta-analysis of VD in patients with IBD. Although this publication is undoubted of significant scientific contribution, it is essential to point out some elements that may constitute bias to the results of the paper. In the meta-analysis, the authors included patients with different disease stages. Furthermore, they included studies performed with different vitamin D dosages, as well as studies that used an association of vitamin D with calcium supplementation. Our review opted to build the discussion and tables separately, discriminating the isolated use of VD and its use associated with calcium. We believe that this clearer and more systematic form of writing allows a better understanding of the outcomes obtained by each study, culminating in a more assertive conclusion.

Considering the high prevalence of IBD and its potential harm to patients' quality of life, the search for alternative and complementary therapies is imperative. The conventional therapies, such as immunomodulators and corticosteroids, are surrounded by limitations such as high cost and adverse effects. As shown by the studies shown in Table 1, VD is an adjuvant therapy that can help patients and professionals deal with the management of remission induction and prevent relapses. As other authors [122], we can say that VD use helped reduce inflammation markers, reduced the UCDAI and SSCAI scores, and improved the quality of life of patients who reached VD levels above those considered normal.

Oral daily doses of 1,000 IU for 12 weeks could elevate the levels above 20 ng/mL in UC or CD subjects with active disease. Doses of 50,000 IU per week were sufficient to raise the levels above 40 ng/mL, and doses of 60,000 IU daily for seven weeks could reduce UCDAI, CRP, and calprotectin. These results show that higher doses should not be necessary. However, it is still a challenge to predict the best dose of VD to be administered, whether it should be used alone or in association with calcium, and which are the best routes of administration.

Our review's limitations include several factors related to the use of VD in IBD patients: the form and time of administration and the concentrations used differ widely between studies, which precludes effective comparisons of how much VD helps in maintenance or induction remission. Another important point is that the stage of the disease is also different in many studies, thus compromising an accurate and definitive assessment of the necessary doses of VD, time of intervention, and form of administration for successful results.

Conclusions

Since inflammation is the primary harmful mechanism involved in the pathophysiologic architecture of IBD, VD contributes to the prevention and treatment of this condition by decreasing the pro-inflammatory secretory pattern. These properties strengthen the therapeutic use of VD supplementation not only to prevent but also, to induce remission in IBD patients.

However, the studies that investigated the use of VD in IBD patients were performed using different doses, different associations, administration routes, and intervention time, which may be difficult to identify the best way of VD

clinical use. Therefore, more clinical trials are needed to elucidate optimal dosages, long-term effects, and routes of administration of VD.

References

1. Seyedian SS, Nokhostin F, Malamir MD. A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease. J Med Life. 2019;12(2):113–22.
2. Kaplan GG, Windsor JW. The four epidemiological stages in the global evolution of inflammatory bowel disease. Nature Rev Gastr Hepatol. 2021;18(1):56–66.
3. Kim S, Kang Y, Park S, Koh H, Kim S. Association of vitamin D with inflammatory bowel disease activity in pediatric patients. J Korean Med Sci. 2019;34(32):e204.
4. Wang L, Gao M, Kang G, Huang H. The potential role of phytonutrients flavonoids influencing gut microbiota in the prophylaxis and treatment of inflammatory bowel disease. Front Nutr. 2021;8:798038.
5. Li J, Chen N, Wang D, Zhang J, Gong X. Efficacy of vitamin D in treatment of inflammatory bowel disease: A meta-analysis. Medicine (Baltimore). 2018;97(46):e12662.
6. Motta J-P, Rolland C, Edir A, Florence A-C, Sagnat D, Bonnart C, et al. Epithelial production of elastase is increased in inflammatory bowel disease and causes mucosal inflammation. Mucosal Immunol. 2021;14(3):667–78.
7. Barbalho SM, Goulart RA, Gasparini RG. Associations between inflammatory bowel diseases and vitamin D. Crit Rev Food Sci Nutr. 2019;59(8):1347–56.
8. Neri B, Mossa M, Scucchi L, Sena G, Palmieri G, Biancone L. Histological scores in inflammatory bowel disease. J Digest Diseases. 2021;22(1):9–22.
9. Kővári B, Báthori Á, Friedman MS, Lauwers GY. Histologic diagnosis of inflammatory bowel diseases. Adv Anat Pathol. 2022;29(1):48–61.
10. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68(Suppl 3):s1–s106.
11. Fucilini LMP, Genaro LM, Sousa DCE, Coy CSR, Leal RF, Ayrizono MLS. Epidemiological profile and clinical characteristics of inflammatory bowel diseases in a Brazilian referral center. Arq Gastroenterol. 2021;58(4):483–90.
12. Mechie NC, Mavropoulou E, Ellenrieder V, Petzold G, Kunsch S, Neesse A, et al. Serum vitamin D but not zinc levels are associated with different disease activity status in patients with inflammatory bowel disease. Medicine (Baltimore). 2019;98(15):e15172.
13. Kim K-U, Kim J, Kim W-H, Min H, Choi CH. Treatments of inflammatory bowel disease toward personalized medicine. Arch Pharmacal Research. 2021;44(3):293–309.
14. Eichele DD, Young R. Medical management of inflammatory bowel disease. Surg Clin North Am. 2019;99(6):1223–35.
15. Roberti R, Iannone LF, Palleria C, De Sarro C, Spagnuolo R, Barbieri MA, et al. Safety profiles of biologic agents for inflammatory bowel diseases: a prospective pharmacovigilance study in Southern Italy. Cur Medl Res Opinion. 2020; 36(9):1457–63.
16. Tran V, Limketkai BN, Sauk JS. IBD in the elderly: management challenges and therapeutic considerations. Cur Gastroent Reports. 2019;21(11):60.
17. Stone M, Morrison M, Forster E. P076 The role of dual biologic therapy in inflammatory bowel disease. Am J Gastroenterol. 2021;116(Suppl 1):S20.
18. Iria I, Soares RRG, Brás EJS, Chu V, Gonçalves J, Conde JP. Accurate and rapid microfluidic ELISA to monitor Infliximab titers in patients with inflammatory bowel diseases. Analyst. 2022.
19. Papamichael K, Cheifetz AS. Optimizing therapeutic drug monitoring in inflammatory bowel disease: a focus on therapeutic monoclonal antibodies. Expert Opin Drug Metab Toxicol. 2022;1–9.
20. Le Berre C, Ananthakrishnan AN, Danese S, Singh S, Peyrin-Biroulet L. Ulcerative colitis and Crohn's disease have similar burden and goals for treatment. Clin Gastroenterol Hepatol. 2020;18(1):14–23.
21. Borg-Bartolo SP, Boyapati RK, Satsangi J, Kalla R. Precision medicine in inflammatory bowel disease: concept, progress and challenges. F1000Res. 2020;9.
22. Gubatan J, Moss AC. Vitamin D in inflammatory bowel disease: more than just a supplement. Curr Opin Gastroenterol. 2018;34(4):217–25.
23. Rosen CJ. From gut to blood: the travels and travails of vitamin D supplementation. Am J Clin Nutrition. 2021;114(3): 831–2.
24. Fletcher J, Cooper SC, Ghosh S, Hewison M. The role of vitamin D in inflammatory bowel disease: mechanism to management. Nutrients. 2019;11(5).
25. Linneman Z, Reis C, Balaji K, Moore J, Braude S. The vitamin D positive feedback hypothesis of inflammatory bowel diseases. Med Hypotheses. 2019;127:154–8.
26. Frigstad SO, Høivik ML, Jahnsen J, Cvancarova M, Grimstad T, Berset IP, et al. Pain severity and vitamin D deficiency in IBD patients. Nutrients. 2019;12(1).
27. Wellington VNA, Sundaram VL, Singh S, Sundaram U. Dietary supplementation with vitamin D, fish oil or resveratrol modulates the gut microbiome in inflammatory bowel disease. Int J Mol Sci. 2021;23(1).
28. Pagnini C, Di Paolo MC, Graziani MG, Delle Fave G. Probiotics and vitamin D/vitamin D receptor pathway interaction: potential therapeutic implications in inflammatory bowel disease. Front Pharmacol. 2021;12:747856.
29. Dattola A, Silvestri M, Bennardo L, Passante M, Scali E, Patruno C, et al. Role of vitamins in skin health: a systematic review. Cur Nutr Reports. 2020;9(3):226–35.
30. Min J, Jo H, Chung YJ, Song JY, Kim MJ, Kim MR. Vitamin D and the immune system in menopause: a review. J Menopausal Med. 2021;27(3):109–14.
31. Bae JH, Choe HJ, Holick MF, Lim S. Association of vitamin D status with COVID-19 and its severity: Vitamin D and COVID-19: a narrative review. Rev Endocr Metab Disord. 2022;1–21.
32. Stöcklin E, Eggersdorfer M. Vitamin D: an essential nutrient with versatile functions in nearly all organs. Int J Vitam Nutr Res. 2013;83(2):92–100.
33. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Inter Medicine. 2009;151(4): 264–9, w64.
34. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical research ed). 2021;372:n71.
35. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons. 2019.
36. Sharifi A, Vahedi H, Nedjat S, Rafiei H, Hosseinzadeh-Attar MJ. Effect of single-dose injection of vitamin D on immune cytokines in ulcerative colitis patients: a randomized placebo-controlled trial. APMIS: acta pathologica, microbiologica, et immunologica. Scandinavica. 2019;127(10):681–7.

37. Garg M, Hendy P, Ding JN, Shaw S, Hold G, Hart A. The effect of vitamin D on intestinal inflammation and faecal microbiota in patients with ulcerative colitis. J Crohns Colitis. 2018;12(8): 963–72.
38. 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. Nutrit Journal. 2019; 18(1):16.
39. Garg M, Rosella O, Rosella G, Wu Y, Lubel JS, Gibson PR. Evaluation of a 12-week targeted vitamin D supplementation regimen in patients with active inflammatory bowel disease. Clin Nutrition (Edinburgh, Scotland). 2018;37(4): 1375–82.
40. de Bruyn JR, Bossuyt P, Ferrante M, West RL, Dijkstra G, Witteman BJ, et al. High-dose vitamin D does not prevent postoperative recurrence of Crohn's disease in a randomized placebo-controlled trial. Clin Gastroenterol Hepatol. 2021; 19(8): 1573–82.e5.
41. Ahamed ZR, Dutta U, Sharma V, Prasad KK, Popli P, Kalsi D, et al. Oral nano vitamin D supplementation reduces disease activity in ulcerative colitis: a double-blind randomized parallel group placebo-controlled trial. J Clin Gastroenterol. 2019;53(10):e409–e15.
42. Bafutto M, Oliveira E, Costa M, Silva K, Costa J, Bafutto E, et al. P-112 Evaluation of vitamin D supplementation in moderate to severe Crohn's disease patients using anti-TNF: replacement or immunomodulation? Inflam Bowel Diseases 2017;23(suppl_11):S40–S.
43. Mathur J, Naing S, Mills P, Limsui D. A randomized clinical trial of vitamin D(3) (cholecalciferol) in ulcerative colitis patients with hypovitaminosis D(3). PeerJ. 2017;5:e3654.
44. Sharifi A, Vahedi H, Nedjat S, Mohamadkhani A, Hosseinzadeh Attar MJ. Vitamin D decreases beck depression inventory score in patients with mild to moderate ulcerative colitis: a double-blind randomized placebo-controlled trial. J Diet Suppl. 2019;16(5):541–9.
45. Emami MR, Sharifi A, Yaseri M, Derakhshanian H, Hosseinzadeh-Attar MJ. Vitamin D suppresses proangiogenic factors in patients with ulcerative colitis: A randomized double blind placebo controlled clinical trial. Compl Ther Clin Practice. 2020;39:101086.
46. Wingate KE, Jacobson K, Issenman R, Carroll M, Barker C, Israel D, et al. 25-Hydroxyvitamin D concentrations in children with Crohn's disease supplemented with either 2000 or 400 IU daily for 6 months: a randomized controlled study. J Pediatr. 2014;164(4):860–5.
47. Raftery T, Martineau AR, Greiller CL, Ghosh S, McNamara D, Bennett K, et al. Effects of vitamin D supplementation on intestinal permeability, cathelicidin and disease markers in Crohn's disease: Results from a randomised double-blind placebo-controlled study. Uni Europ Gastroenterol Journal. 2015;3(3):294–302.
48. Boothe D, Lakehomer H, Jacob V, Scherl E, Bosworth B. High dose vitamin D3 improves clinical activity in Crohn's disease: 1215. Off J Amer College Gastroenterol ACG. 2011;106.
49. Narula N, Cooray M, Anglin R, Muqtadir Z, Narula A, Marshall JK. Impact of high-dose vitamin D3 supplementation in patients with Crohn's disease in remission: a pilot randomized double-blind controlled study. Dig Dis Sci. 2017;62(2): 448–55.
50. Simek RZ, Prince J, Syed S, Sauer CG, Martineau B, Hofmekler T, et al. Pilot study evaluating efficacy of 2 regimens for hypovitaminosis d repletion in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2016; 62(2):252–8.
51. 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. 2016;22(4):316–23.
52. Yang L, Weaver V, Smith JP, Bingaman S, Hartman TJ, Cantorna MT. Therapeutic effect of vitamin d supplementation in a pilot study of Crohn's patients. Clin Trans Gastroenterol. 2013;4(4):e33.
53. Pappa HM, Mitchell PD, Jiang H, Kassiff S, Filip-Dhima R, DiFabio D, et al. Treatment of vitamin D insufficiency in children and adolescents with inflammatory bowel disease: a randomized clinical trial comparing three regimens. J Clin Endocrinol Metab. 2012;97(6):2134–42.
54. Bendix M, Dige A, Jørgensen SP, Dahlerup JF, Bibby BM, Deleuran B, et al. Decrease in mucosal IL17A, IFNγ and IL10 expressions in active Crohn's disease patients treated with high-dose vitamin alone or combined with infliximab. Nutrients. 2020;12(12).
55. Bendix M, Dige A, Jørgensen SP, Dahlerup JF, Bibby BM, Deleuran B, et al. Seven weeks of high-dose vitamin D treatment reduces the need for infliximab dose-escalation and decreases inflammatory markers in Crohn's disease during one-year follow-up. Nutrients. 2021;13(4):1083.
56. Bendix M, Dige A, Deleuran B, Dahlerup JF, Jørgensen SP, Bartels LE, et al. Flow cytometry detection of vitamin D receptor changes during vitamin D treatment in Crohn's disease. Clin Exp Immunol. 2015;181(1):19–28.
57. Pappa HM, Mitchell PD, Jiang H, Kassiff S, Filip-Dhima R, DiFabio D, et al. Maintenance of optimal vitamin D status in children and adolescents with inflammatory bowel disease: a randomized clinical trial comparing two regimens. J Clin Endocrinol Metab. 2014;99(9):3408–17.
58. Bartels LE, Bendix M, Hvas CL, Jørgensen SP, Agnholt J, Agger R, et al. Oral vitamin D3 supplementation reduces monocyte-derived dendritic cell maturation and cytokine production in Crohn's disease patients. Inflammopharmacol. 2014;22(2):95–103.
59. Tan B, Li P, Lv H, Yang H, Li Y, Li J, et al. Treatment of vitamin D deficiency in Chinese inflammatory bowel disease patients: A prospective, randomized, open-label, pilot study. J Dig Dis. 2018;19(4):215–24.
60. Aksan A, Tugal D, Hein N, Boettger K, Caicedo-Zea Y, Diehl I, et al. Measuring vitamin D status in chronic inflammatory disorders: how does chronic inflammation affect the reliability of vitamin D metabolites in patients with IBD? J Clin Med 2020;9(2).
61. Szilagyi A, Xue X. Comparison of geographic distributions of irritable bowel syndrome with inflammatory bowel disease fail to support common evolutionary roots: irritable bowel syndrome and inflammatory bowel diseases are not related by evolution. Med Hypotheses. 2018;110:31–7.
62. van der Sloot KWJ, Amini M, Peters V, Dijkstra G, Alizadeh BZ. Inflammatory bowel diseases: review of known environmental protective and risk factors involved. Inflamm Bowel Dis. 2017;23(9):1499–509.
63. Perri MR, Romano C, Marrelli M, Zicarelli L, Toma CC, Basta D, et al. Beneficial role of fruits, their juices, and freeze-dried powders on inflammatory bowel disease and related dysbiosis. Plants (Basel). 2021;11(1).
64. Verstockt B, Bressler B, Martinez-Lozano H, McGovern D, Silverberg MS. Time to revisit disease classification in IBD: is the current classification of IBD good enough for optimal clinical management? Gastroenterol 2021.
65. Kuhnen A. Genetic and environmental considerations for inflammatory bowel disease. Surg Clin North Am. 2019;99(6): 1197–207.

66. Andreou NP, Legaki E, Gazouli M. Inflammatory bowel disease pathobiology: the role of the interferon signature. Ann Gastroenterol. 2020;33(2):125–33.
67. Jacenik D, Fichna J, Małecka-Wojciesko E, Mokrowiecka A. Protease-activated receptors – key regulators of inflammatory bowel diseases progression. J Inflamm Res. 2021;14: 7487–97.
68. Zhao J, Lu Q, Liu Y, Shi Z, Hu L, Zeng Z, et al. Th17 Cells in inflammatory bowel disease: cytokines, plasticity, and therapies. J Immunol Res. 2021;2021:8816041.
69. Luo W, Tian L, Tan B, Shen Z, Xiao M, Wu S, et al. Update: innate lymphoid cells in inflammatory bowel disease. Dig Dis Sci. 2022;67(1):56–66.
70. Mehta M, Ahmed S, Dryden G. Immunopathophysiology of inflammatory bowel disease: how genetics link barrier dysfunction and innate immunity to inflammation. Innate Immun. 2017;23(6):497–505.
71. Alshehri D, Saadah O, Mosli M, Edris S, Alhindi R, Bahieldin A. Dysbiosis of gut microbiota in inflammatory bowel disease: Current therapies and potential for microbiota-modulating therapeutic approaches. Bosn J Basic Med Sci. 2021;21(3): 270–83.
72. Heinken A, Hertel J, Thiele I. Metabolic modelling reveals broad changes in gut microbial metabolism in inflammatory bowel disease patients with dysbiosis. NPJ Sys Biol Appl. 2021;7(1):19.
73. Ruemmele FM. Role of diet in inflammatory bowel disease. Ann Nutr Metab. 2016;68 Suppl 1:33–41.
74. Kamp KJ, Pennings B, Javelli D, Wyatt G, Given B. Dietary patterns, beliefs and behaviours among individuals with inflammatory bowel disease: a cross-sectional study. J Hum Nut Diet. 2021;34(2):257–64.
75. Wark G, Samocha-Bonet D, Ghaly S, Danta M. The role of diet in the pathogenesis and management of inflammatory bowel disease: a review. Nutrients. 2021;13(1):135.
76. Bevivino G, Monteleone G. Advances in understanding the role of cytokines in inflammatory bowel disease. Expert Rev Gastroenterol Hepatol. 2018;12(9):907–15.
77. Zou J, Liu C, Jiang S, Qian D, Duan J, Richardson AR. Cross talk between gut microbiota and intestinal mucosal immunity in the development of ulcerative colitis. Infec Immun. 2021;89(9):e00014–21.
78. Dharmasiri S, Garrido-Martin EM, Harris RJ, Bateman AC, Collins JE, Cummings JRF, et al. Human intestinal macrophages are involved in the pathology of both ulcerative colitis and Crohn disease. Inflam Bowel Dis. 2021;27(10): 1641–52.
79. He T, Wang K, Zhao P, Zhu G, Yin X, Zhang Y, et al. Integrative computational approach identifies immune-relevant biomarkers in ulcerative colitis. FEBS Open Bio. 2021.
80. Chen E, Chuang LS, Giri M, Villaverde N, Hsu NY, Sabic K, et al. Inflamed ulcerative colitis regions associated with MRGPRX2-mediated mast cell degranulation and cell activation modules. Defining a New Therapeutic Target. Gastroenterology. 2021;160(5):1709–24.
81. Feuerstein JD, Cheifetz AS. Crohn disease: epidemiology, diagnosis, and management. Mayo Clin Proc. 2017;92(7): 1088–103.
82. Caparrós E, Wiest R, Scharl M, Rogler G, Gutiérrez Casbas A, Yilmaz B, et al. Dysbiotic microbiota interactions in Crohn's disease. Gut Microbes. 2021;13(1):1949096.
83. Sudhakar P, Verstockt B, Cremer J, Verstockt S, Sabino J, Ferrante M, et al. Understanding the molecular drivers of disease heterogeneity in Crohn's disease using multi-omic data integration and network analysis. Inflam Bowel Dis. 2020;27(6):870–86.
84. Reich KM, Fedorak RN, Madsen K, Kroeker KI. Vitamin D improves inflammatory bowel disease outcomes: basic science and clinical review. World J Gastroenterol. 2014; 20(17):4934–47.
85. Peroni DG, Trambusti I, Di Cicco ME, Nuzzi G. Vitamin D in pediatric health and disease. Pediatr Allergy Immunol. 2020;31(Suppl 24):54–7.
86. Alia E, Kerr PE. Vitamin D: skin, sunshine, and beyond. Clin Dermatol. 2021;39(5):840–6.
87. Dimar JR, Lane JM, Lehman RA, Anderson PA. The basics of bone physiology, healing, and osteoporosis. Instr Course Lect. 2021;70:527–36.
88. Wimalawansa SJ. Vitamin D deficiency: effects on oxidative stress, epigenetics, gene regulation, and aging. Biology (Basel). 2019;8(2).
89. Pludowski P, Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB, et al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. Autoimmun Rev. 2013;12(10):976–89.
90. Kumar R, Rathi H, Haq A, Wimalawansa SJ, Sharma A. Putative roles of vitamin D in modulating immune response and immunopathology associated with COVID-19. Virus Res. 2021;292:198235.
91. Bishop EL, Ismailova A, Dimeloe S, Hewison M, White JH. Vitamin D and immune regulation: antibacterial, antiviral, anti-inflammatory. JBMR Plus. 2021;5(1):e10405.
92. Benedik E. Sources of vitamin D for humans. Int J Vitam Nutr Res. 2021.
93. Francis I, AlAbdali N, Kapila K, John B, Al-Temaimi RA. Vitamin D pathway related polymorphisms and vitamin D receptor expression in breast cancer. Int J Vitam Nutr Res. 2021;91(1–2):124–32.
94. Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Kostenberger M, Tmava Berisha A, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. Eur J Clin Nutr. 2020.
95. Fu L, Fei J, Tan Z-X, Chen Y-H, Hu B, Xiang H-X, et al. Low vitamin D status is associated with inflammation in patients with chronic obstructive pulmonary disease. J Immunol. 2021;206(3):515.
96. Ben-Shoshan M. Vitamin D deficiency/insufficiency and challenges in developing global vitamin D fortification and supplementation policy in adults. Int J Vitam Nutr Res. 2012;82(4):237–59.
97. Tohari AM, Alhasani RH, Biswas L, Patnaik SR, Reilly J, Zeng Z, et al. Vitamin D attenuates oxidative damage and inflammation in retinal pigment epithelial cells. Antioxidants (Basel). 2019;8(9).
98. Gunasegaran P, Tahmina S, Daniel M, Nanda SK. Role of vitamin D-calcium supplementation on metabolic profile and oxidative stress in gestational diabetes mellitus: A randomized controlled trial. J Obst Gynaecol Res. 2021;47(3):1016–22.
99. Zhao JF, Li BX, Zhang Q. Vitamin D improves levels of hormonal, oxidative stress and inflammatory parameters in polycystic ovary syndrome: a meta-analysis study. Ann Palliat Med. 2021;10(1):169–83.
100. Mansouri F, Ghanbari H, Marefati N, Arab Z, Salmani H, Beheshti F, et al. Protective effects of vitamin D on learning and memory deficit induced by scopolamine in male rats: the roles of brain-derived neurotrophic factor and oxidative stress. Naunyn-Schmiedeberg's Arch Pharmacol. 2021; 394(7):1451–66.
101. Bhat JR, Geelani SA, Khan AA, Roshan R, Rathod SG. Vitamin D toxicity due to self-prescription: A case report. J Family Med Prim Care. 2022;11(4):1561–3.

102. Torres J, Ellul P, Langhorst J, Mikocka-Walus A, Barreiro-de Acosta M, Basnayake C, et al. European Crohn's and Colitis Organisation topical review on complementary medicine and psychotherapy in inflammatory bowel disease. J Crohns Colitis. 2019;13(6):673–85e.
103. Jun JC, Yoon H, Choi YJ, Shin CM, Park YS, Kim N, et al. The effect of vitamin D administration on inflammatory markers in patients with inflammatory bowel disease. Intest Res. 2019;17(2):210–7.
104. Zhou YQ, Xu RY, Wan YP. The role of dietary factors in inflammatory bowel diseases: New perspectives. J Dig Dis. 2019;20(1):11–7.
105. Sahu P, Kedia S, Ahuja V, Tandon RK. Diet and nutrition in the management of inflammatory bowel disease. Indian J Gastroenterol. 2021;40(3):253–64.
106. Szymczak-Tomczak A, Kaczmarek-Ryś M, Hryhorowicz S, Michalak M, Eder P, Skrzypczak-Zielińska M, et al. Vitamin D, vitamin D receptor (VDR) gene polymorphisms (ApaI and FokI), and bone mineral density in patients with inflammatory bowel disease. J Clin Dens. 2021;24(2):233–42.
107. Kelly P, Suibhne TN, O'Morain C, O'Sullivan M. Vitamin D status and cytokine levels in patients with Crohn's disease. Int J Vitam Nutr Res. 2011;81(4):205–10.
108. Gubatan J, Mehigan GA, Villegas F, Mitsuhashi S, Longhi MS, Malvar G, et al. Cathelicidin mediates a protective role of vitamin D in ulcerative colitis and human colonic epithelial cells. Inflamm Bowel Dis. 2020.
109. Cantorna MT. IBD: Vitamin D and IBD: moving towards clinical trials. Nat Rev Gastroenterol Hepatol. 2016;13(6): 322–3.
110. Chun RF, Liu PT, Modlin RL, Adams JS, Hewison M. Impact of vitamin D on immune function: lessons learned from genome-wide analysis. Front Physiol. 2014;5:151.
111. Battistini C, Ballan R, Herkenhoff ME, Saad SMI, Sun J. Vitamin D modulates intestinal microbiota in inflammatory bowel diseases. Int J Mol Sci. 2021;22(1):362.
112. Kellermann L, Jensen KB, Bergenheim F, Gubatan J, Chou ND, Moss A, et al. Mucosal vitamin D signaling in inflammatory bowel disease. Autoimmun Rev. 2020;19(11):102672.
113. Javad Hosseinzadeh-Attar M, Sharifi A, Nedjat S, Mohamadkhani A, Vahedi H. The effect of vitamin D on serum asymmetric dimethylarginine in patients with mild to moderate ulcerative colitis. Int J Vitam Nutr Res. 2020;90(1–2): 17–22.
114. Barbalho SM, Goulart RA, Araujo AC, Guiguer EL, Bechara MD. Irritable bowel syndrome: a review of the general aspects and the potential role of vitamin D. Expert Rev Gastroenterol Hepatol. 2019;13(4):345–59.
115. Kuhne H, Schutkowski A, Weinholz S, Cordes C, Schierhorn A, Schulz K, et al. Vitamin D receptor regulates intestinal proteins involved in cell proliferation, migration and stress response. Lipids Health Dis. 2014;13:51.
116. Charoenngam N, Shirvani A, Kalajian TA, Song A, Holick MF. The effect of various doses of oral vitamin D3 supplementation on gut microbiota in healthy adults: a randomized, double-blinded. Dose-response study. Anticancer Res. 2020;40(1):551–6.
117. Meeker SM, Seamons A, Treuting PM, Paik J, Brabb T, Hsu CC, et al. Effect of chronic vitamin D deficiency on the development and severity of DSS-induced colon cancer in Smad3(-/-) mice. Comp Med. 2020;70(2):120–30.
118. Cantorna MT, Rogers CJ, Arora J. Aligning the paradoxical role of vitamin D in gastrointestinal immunity. Trends Endocrinol Metab. 2019;30(7):459–66.
119. Yamamoto EA, Jorgensen TN. Relationships between vitamin D, gut microbiome, and systemic autoimmunity. Front Immunol. 2019;10:3141.
120. Ham NS, Hwang SW, Oh EH, Kim J, Lee H-S, Park SH, et al. Influence of severe vitamin d deficiency on the clinical course of inflammatory bowel disease. Dig Dis Sci. 2021; 66(2):587–96.
121. Guzman-Prado Y, Samson O, Segal JP, Limdi JK, Hayee B. Vitamin D therapy in adults with inflammatory bowel disease: a systematic review and meta-analysis. Inflam Bowel Dis. 2020;26(12):1819–30.
122. Goulart RA, Barbalho SM. Can vitamin D induce remission in patients with inflammatory bowel disease? Ann Gastroenterol 2022;35(2):140–9.

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Conflict of interest
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