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Review Article

Opportunities and Challenges of Vitamin D as A Dietary Supplement in Improving Ulcerative Colitis

Ziying Hu, Hongliang Gao*

The Second Department of Gastroenterology, The First Affiliated Hospital of Xinjiang Medical University, China

***Corresponding author:** Hongliang Gao, The Second Department of Gastroenterology, the First Affiliated Hospital of Xinjiang, Medical University, Urumqi 830000, Xinjiang, China

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Abstract

Ulcerative colitis (UC) is a long-term autoimmune condition that causes repeated episodes of inflammation in the colon and rectum. Traditional treatments, including hormones and aminosalicylates, have limited efficacy and significant side effects, forcing many patients to undergo colectomy. Therefore, clinical practice critically needs novel therapeutic strategies to strengthen intestinal immunity. Numerous studies show that vitamin D, a food-derived bioactive molecule, can effectively alleviate UC symptoms, reduce inflammation, and improve patients' quality of life. Its mechanisms include maintaining intestinal barrier integrity, regulating immune cells and inflammatory mediators, modulating gut microbiota, and controlling gene expression. This review systematically explores vitamin D's potential as a dietary supplement for UC treatment. It examines how vitamin D works with other drugs to address health problems, highlighting the importance of nanoparticles and lipid transport systems in enhancing bioavailability. Additionally, the review discusses vitamin D's therapeutic dosage, disease assessment, and clinical benefits and limitations.

Keywords: Ulcerative colitis; Vitamin D; Vitamin D receptor; Immune inflammatory response; Therapy

Introduction

Ulcerative colitis (UC) is a persistent, non-specific inflammatory bowel illness of uncertain cause, marked by a propensity for recurrence [1]. The prevalence rate of ulcerative colitis has been increasing in recent years, presenting a significant threat to public health [2]. A significant concern among UC patients is the elevated prevalence of vitamin D insufficiency, [3] heightening the likelihood of disease onset [4]. Additionally, there is an inverse relationship between disease activity and vitamin D levels [5]. Vitamin D regulates calcium, phosphorus, and other essential nutrients. In addition to these functions, it has significant anti-inflammatory, antioxidant, and immune regulatory effects, particularly beneficial for autoimmune diseases such as UC [6]. Recent domestic and international investigations have validated the advantageous effect of the vitamin D-vitamin D receptor (VDR) signalling pathway in the treatment of ulcerative colitis (UC). This article intends to elucidate the pertinent mechanisms of vitamin D in treating ulcerative colitis (UC), describe its therapeutic effects, recommend appropriate supplementation doses, and emphasize its significance in UC's assessment and clinical application.

Overview of Vitamin D

Vitamin D is a steroid that is fat-soluble and is necessary for the development and growth of an organism. Two basic forms of vitamin D are available: vitamin D2 (ergocalciferol), which is obtained from foods produced by plants, and vitamin D3 (cholecalciferol), which is obtained from meals originating from animals. Among these, vitamin D3 has higher biological activity and is predominantly found in foods such as fish liver oil, milk, egg yolks, and animal liver.

Once ingested, vitamin D3 will reach the circulatory system, which will attach to the vitamin D-binding protein (VDP) in the plasma and then be delivered to the liver. It is subjected to the hydroxylation process by 25-hydroxylase (CYP2R1), resulting in 25-hydroxyvitamin D3 [25(OH)D3] in the liver. This metabolite is the principal blood circulation type of vitamin D ood and acts as an essential biomarker for evaluating vitamin D levels.

Finally, the kidney plays a role in the transformation of 25(OH) D3 into the more active form, 1,25-dihydroxyvitamin D3 [1,25(OH)$_2$D3], This conversion is carried out by kidney cytochrome P450 enzymes and 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1).1,25(OH)$_2$D3 subsequently binds to the intracellular vitamin D receptor (VDR) [7]. VDR resides in practically every cell of the immune system, particularly dendritic cells, macrophages, B cells, neutrophils, and activated T cells with CD4 and CD8 receptors [8], enabling vitamin D to broadly regulate immune function.

Upon the specific activation of VDR by 1,25(OH)$_2$D3, it forms a heterodimer with the retinoid X receptor (RXR). This complex then migrates to the nucleus. It modulates the transcription of target genes by interacting with vitamin D response elements (VDREs) in their promoter regions [9].

Mechanisms of Vitamin D Treatment in UC

Maintaining the intestinal barrier

An effective intestinal barrier serves as the primary defence against external infections and toxic chemicals, and its impairment is a significant contributor to the onset of UC. In order to prevent and cure UC, it is vital to ensure that the integrity of the intestinal barrier is preserved, and that mucosal healing is encouraged. Damage to the 1,25(OH)$_2$D3/VDR signalling pathway can impair the intestinal barrier, thereby triggering UC, which highlights the critical role of this pathway in maintaining intestinal barrier function [10]. Research has shown that the level of histone H3 acetylation in the colonic epithelium of individuals with UC is much lower, and this decrease has a negative correlation with the severity of the illness. In various colitis models, the histone deacetylase inhibitor MS-275 has been found to activate VDR by inhibiting the deacetylation of its promoter, thereby protecting the intestinal epithelial barrier. Additionally, VDR has the ability to lower the production of NF-κB-related inflammatory factors and decrease cell apoptosis by directly interacting with p65, offering a promising new approach for the treatment of colitis [11].

Other studies have identified that Na/H exchanger isoform 8 (NHE8) in the colonic epithelium is crucial in regulating cell proliferation, intracellular pH, and mucus secretion. The notable downregulation of NHE8 expression in UC patients suggests its possible role in safeguarding the intestinal mucosal barrier [12]. Recent research in colitis mice has shown that paricalcitol promotes colonic mucosal repair by upregulating NHE8 expression. In contrast, in VDR-deficient colitis mice, a decrease in NHE8 expression is seen, and the function of the intestinal barrier is compromised. Moreover, another research has shown that VDR enhances NHE8 expression by suppressing the activation of the NF-κB p65 signalling pathway, therefore serving a protective function in the intestinal barrier [13].

Claudin proteins, as significant components of the intestinal epithelial tight junctions, are intricately associated with endothelial cell permeability [14] with Claudin-2 and Claudin-15 playing pivotal roles in intestinal barrier function through paracellular transport. Claudin-2 expression has been shown to have a positive correlation with inflammatory activity in individuals with UC, whereas Claudin-15 expression is negatively correlated. Studies have indicated that 1,25(OH)$_2$D$_3$ can lower Claudin-2 expression by inhibiting IL-13-mediated Stat-6 phosphorylation, which helps protect the intestinal barrier [15]. Furthermore, the combination of vitamin C (VC) and vitamin D3 (VD3) is more efficient for preserving the intestinal barrier than vitamin D3 by itself. The expression of Claudin-2 is inhibited, and mucosal barrier damage is mitigated as a result of VC's ability to promote VD3 activation and modify the Notch-1 signalling pathway [16].

At the same time, the mRNA level of Claudin-15 is much lower among individuals with UC, and the expression of this protein has a positive correlation with VDR. The fact that Claudin-15 is the targeted gene of VDR has been confirmed by the findings of molecular investigations, which have directly identified VDRE binding sites in the promoter of Claudin-15. Similarly, intestinal epithelial VDR overexpression enhances Claudin-15 synthesis, which preserves the intestinal barrier [17].

In summary, VDR is crucial in protecting the intestinal barrier and facilitating epithelial repair by regulating multiple signalling pathways, providing novel strategies and approaches for preventing and treating UC.

Regulation of immune cells and inflammatory factors

It has been shown in previous research that vitamin D3 upregulated protein 1 (VDUP1) is diminished in the colonic tissues of individuals with UC and that the loss of VDUP1 significantly worsens the symptoms of colitis induced by dextran sulfate sodium (DSS). The disease activity index (DAI) and histological scores of VDUP1 knockout mice were determined to be greater than those of wild-type (WT) mice after the administration of 2% DSS-induced colitis, characterized by goblet cell loss, increased apoptotic cells, and significantly reduced MUC2 mRNA expression. Furthermore, it was observed that mice lacking VDUP1 exhibited an increase in the expression of phosphorylated p65 in colon tissue. This led to an increase in the expression of downstream pro-inflammatory mediators in NF-κB signalling pathways, including IL-1β, IL-6, and TNF-α. This, in turn, facilitated the migration of macrophages to inflammatory sites, significantly exacerbating colitis. Based on these data, it seems that VDUP1 may play a significant part in the regulation of inflammatory responses and may represent a possible target for both the protection and the therapy of UC [18].

Theoretically, UC is caused by Th2 cell immune dysfunction [19], but Th1 cells and Th17 cells also play important roles [20]. In the lack of vitamin D, naïve CD4+ T cells have a preference for differentiating into Th1 and Th17 effector T cells, resulting in the release of significant quantities of pro-inflammatory cytokines, including IL-17 and IFN-α. Research has shown that vitamin D has the ability to decrease the amount of CD4+ T cells in colitis models and prevent the differentiation of Th1 and Th17 cells. Supplementation with vitamin D has been shown to lower inflammatory markers, including TNF-α, IL-12, and IFN-γ, in individuals with mild to severe UC. This beneficial impact is a reflection of vitamin D's ability to suppress the Th1 immune response [21].

Recent research has found that lncRNA OIP5-AS1 exacerbates inflammation by promoting Th17 differentiation. Interestingly, vitamin D levels in UC patients are negatively correlated with lncRNA OIP5-AS1. Vitamin D inhibits OIP5-AS1, leading to upregulation of miR-26a-5p, which targets IL-6 to suppress Th17 differentiation, thereby reducing inflammation. Intervention with lncRNA OIP5-AS1 or miR-26a-5p can reverse the benefits of vitamin D, indicating that the OIP5-AS1/miR-26a-5p/IL-6 axis plays an important role in the anti-inflammatory effects of vitamin D [22].

Additionally, the development and progression of UC are closely linked to oxidative stress. In UC models, ACSL4 expression is significantly elevated, while iron content increases and antioxidant systems (e.g., GSH, GPX4) are reduced, indicating that ferroptosis may contribute to the pathological process of UC. Research has demonstrated that vitamin D may reduce oxidative stress and inflammation by inhibiting the activity of ACSL4 and increasing the activity of GPX4. Nevertheless, the curative properties of vitamin D may be dramatically diminished when ACSL4 is overexpressed [23].

Vitamin D suppresses the activation of NOD-like receptor proteins (NLRP) inflammasomes by binding to VDR, thus decreasing the synthesis and secretion of inflammatory mediators, which helps alleviate inflammation. Research has shown that vitamin D enhances the ubiquitination of NLRP3 after binding with VDR, suppressing NLRP3 inflammasome activation and reducing IL-1 maturation, caspase-1 release, and ROS production, thus improving UC [24]. Similarly, NLRP6 is regulated by the VD3-VDR signalling pathway. VDR transcriptionally inhibits NLRP6 expression, suppressing NLRP6 inflammasome activation and thereby delaying UC progression [25].

Moreover, vitamin D stimulates the synthesis of an antimicrobial peptide in human colonic epithelial cells, known as the vitamin D-regulated human antimicrobial peptide. This peptide has anti-inflammatory, antibacterial, antifibrotic, and anti-tumor properties and can prevent and treat colitis without disrupting the balance of gut microbiota [26].

In conclusion, vitamin D alleviates UC pathology through several mechanisms, including inhibition of macrophage migration, Th1 and Th17 differentiation, NLRP inflammasome activation, and ferroptosis. It also exerts anti-inflammatory and antibacterial effects via antimicrobial peptide secretion, making it a potential target for the treatment of UC.

Regulation of Gut Microbiota

Recent studies have shown that an imbalance in the microbiota of the gut plays an essential part in the development of ulcerative colitis (UC). This imbalance is characterized by a drop in the number of helpful bacteria, an increase in the number of pathogenic bacteria, a decrease in the variety of microorganisms, and a reduction in species richness [27]. These changes in microbiota composition lead to alterations in metabolic profiles, particularly impacting bile acids (BAs) metabolism. Clinical studies have demonstrated that UC patients exhibit BAs metabolic disturbances, such as increased levels of primary bile acids BAs (e.g., CA, GCDCA, TCA, TCDCA), which correlate positively with pro-inflammatory cytokines and pathogenic bacteria such as Enterococcus and Klebsiella. In contrast, secondary BAs (e.g., LCA, DCA, GDCA, GLCA, TLCA) are significantly reduced and positively correlated with beneficial bacteria, such as Butyricicoccus and Clostridium IV [28].

Bile acids influence gut immune function through nuclear receptors (e.g., VDR) and membrane receptors (e.g., TGR5), which are integral in controlling inflammatory responses, cell growth, and programmed cell death [29]. In UC patients, the expression of TGR5 is elevated, while VDR expression is decreased in colonic tissue. This suggests microbiota dysbiosis and BA metabolism abnormalities may mediate inflammatory responses through TGR5 and VDR signaling [30]. Moreover, a recent study found that a newly discovered metabolite derived from the microbiota, 12-keto lithocholic acid (12-KLCA), by increasing the expression of VDR and decreasing the amount of IL-17A that is secreted by colonic group 3 innate lymphoid cells (ILC3), has the ability to exert powerful anti-inflammatory effects in DSS-induced colitis [31].

Additionally, when it comes to the antibacterial action of Paneth cells, VDR is a very important factor. Defects in antimicrobial peptide secretion and a decreased population of beneficial bacteria, such as Lactobacillus, elevate the likelihood of colitis and Salmonella infection in VDR-deficient Paneth cells. Based on these results, it seems that VDR supports host defense and prevents intestinal damage by regulating Paneth cells [32].

Probiotics, particularly Saccharomyces boulardii, have significant potential for regulating gut microbiota and managing UC. Studies show that Saccharomyces boulardii improves VDR signaling and regulates miRNA expression associated with UC (e.g., upregulating miRNA-155 and miRNA-223, downregulating miRNA-143 and miRNA-375), thereby alleviating inflammation and restoring mucosal microbiota balance. This offers new avenues for preventing and treating UC [33].

In summary, VDR is crucial for preserving the balance of gut microbiota and modulating the metabolome, and its related mechanisms provide promising directions for UC therapy.

Gene Expression Regulation

The exact mechanisms underlying UC remain unclear, but genetic factors will likely significantly influence its development and severity. VDR expression is associated with UC susceptibility. It is widely distributed throughout the body, and its function is determined through the interaction of vitamin D with its receptor, which regulates the expression of approximately 3,000 related genes. Several studies have explored the relationship between VDR gene polymorphisms (e.g., rs10735810, rs11568820, rs731236, rs7975232, rs1544410, often called FokI, Cdx2, TaqI, ApaI, Bsm) along with factors like vitamin D levels, UC disease activity, and intestinal lesions. These studies have demonstrated significant associations between disease activity in UC patients and the rs10735810 (FokI) polymorphism, as well as between the endoscopic lesion category and the rs11568820 (Cdx2) polymorphism [34].

In addition, vitamin D binding protein (DBP) is essential for regulating vitamin D levels in the body by binding and transporting vitamin D and its metabolites. Genetic variations in the DBP gene may alter the features of the protein it encodes, which in turn can influence the body's vitamin D function. Two key loci, rs7041 and rs4588, have been identified as important for gene expression; however, polymorphisms at these loci do not seem to influence the likelihood of UC development in Han Chinese patients. On the other hand, UC patients carrying the DBP gene haplotype CG tend to produce more malondialdehyde (MDA), which induces the secretion of arachidonic acid as well as pro-inflammatory molecules like TNF-α, leading to programmed cell death within the cells of the intestinal epithelium [35].

Vitamin D treatment has also been demonstrated to greatly boost the expression of the CTLA-4 gene in people with mild to moderate UC, according to research, and this expression is negatively correlated with erythrocyte sedimentation rate (ESR) levels. Considering the significant impact of vitamin D supplementation on CTLA-4 expression of genes in persons with sufficient baseline levels of vitamin D, it is advisable to elevate vitamin D levels above commonly recognized standards [36]. A further randomized, double-blind, placebo-controlled study found that CD40L expression levels in UC patients exhibited a favourable correlation with inflammatory markers, including TNF-α, ESR, and hs-CRP. Furthermore, a reduction in CD40L gene expression was seen in individuals with mild to severe UC who took vitamin D supplements, suggesting that vitamin D has the potential to act as a new treatment target for UC by inhibiting the CD40L/CD40 inflammatory pathway [37].

These studies highlight the close relationship between VDR and DBP gene polymorphisms, vitamin D function, and the pathological processes of UC. Further investigation into how genetic variations influence inflammatory pathways is needed, and there is a possibility that immunological responses may provide fresh perspectives on the accurate diagnosis and management of UC.

Vitamin D therapy for UC

UC patients often experience significant loss of vitamin D-binding proteins in the digestive tract due to dietary restrictions, impaired intestinal absorption, as well as poor solubility of vitamin D, which raises the probability of individuals suffering from a lack of vitamin D. Vitamin D supplementation can effectively raise serum levels and improve disease activity scores [38]. However, due to individual differences in absorption capacity, the vitamin D requirements of UC patients can vary, and there is no universally accepted standard for the ideal level of serum 25(OH)D3. The Endocrine Society recommends that blood serum 25(OH) vitamin D levels below 50 nmol/L (20 ng/mL) indicate a deficiency. In comparison, levels that fall between 50-75 nmol/L (20-30 ng/mL) are indicative of insufficiency. Furthermore, levels that exceed 200 nmol/L might raise the likelihood of hypercalcemia or kidney calcification. Based on these guidelines, the target range for vitamin D supplementation is generally between 75-125 nmol/L [39].

Daily supplementation of 2000 international units of vitamin D for a period of twelve weeks resulted in a substantial rise in blood 25(OH)D levels, an improvement in standard of living, and a reduction in illness severity in patients with mild to moderate UC, according to the findings of a randomized, double-blind testing study. In contrast, 1000 IU daily only improved the quality of life [40]. A weekly dosage of 50,000 international units was shown to be helpful in raising blood 25(OH)D levels over 40 ng/mL and lowering the likelihood of recurrence, as reported in another study [41]. Experts generally recommend that patients in remission receive ≥2000 IU daily, while those in the active disease phase should take 5000-10,000 IU daily to optimize UC management.

[42] However, the intervention effects are highly heterogeneous due to inconsistent baseline serum vitamin D levels among patients. Results of a study have shown that using high-dose vitamin D supplements for a brief period of time (≥300,000 IU/day) significantly increases serum levels and effectively improves patients' ESR, CRP, and Ca^{2+} markers [43]. However, the optimal dosing regimen has yet to be determined due to variations in the route of administration, dosage, and duration of treatment across studies.

Recent research has demonstrated that vitamin D formulations in nano-solution form have superior bioavailability compared to traditional small-bag formulations. They directly enter the gastrointestinal tract, offering stable and long-lasting efficacy, and may become a research focus in the future [44]. Additionally, efficient lipid transport systems, such as structured triacylglycerol (STG), exhibit higher vitamin D utilization than traditional triacylglycerol (PM). At the same dose, STG significantly improves colonic tissue damage, intestinal barrier protein levels, and inflammation markers [45].

In summary, vitamin D is crucial in managing the disease in UC patients, and its optimal supplementation dose and form should be optimized based on individual characteristics. Future in-depth research on nano-formulations and lipid transport systems may provide more efficient vitamin D intervention strategies for UC patients.

The Assessment of vitamin D in UC and its Clinical Significance

Deficiency in vitamin D is a frequent problem in individuals with UC, particularly after total proctocolectomy with ileal pouch-anal anastomosis (IPAA). It does not show a strong association with age, sex, ethnicity, or preoperative drug use [46]. Insufficient vitamin D levels are correlated with an elevated risk of bowel resection in UC patients, functioning as an effective predictor and screening marker for surgical outcomes [47]. Research shows a negative correlation between serum 25-(OH)D3 levels and inflammatory markers, disease activity scores, and fecal calprotectin (FCP), positioning it as an auxiliary biomarker for UC activity [48]. Based on blood biomarkers, a predictive model for endoscopic activity in UC patients demonstrates that vitamin D is the most accurate predictor of severe endoscopic activity, effectively distinguishing various degrees of endoscopic involvement [49]. Moreover, pre-treatment vitamin D elevation is tied to significant advancements in endoscopic activity [50]. Insufficient serum vitamin D levels serve as a standalone predictor of poor quality of life in UC patients. There is a strong connection between them and the elevated likelihood of disease relapse and unfavourable clinical outcomes [51,52]. Consequently, vitamin D holds a key role in both the clinical and endoscopic evaluation of UC, necessitating regular assessment and optimization of its levels.

According to the findings of a number of studies, the combination of vitamin D with other medications may result in improved therapeutic results. In UC patients, there is a positive relationship between blood vitamin D3 levels and Treg levels, and the combination of vitamin D3 and infliximab (IFX) treatment results in a considerable increase in IL-10 production and Treg differentiation when compared to the treatment delivered by IFX alone, resulting in a cooperative suppression of colitis. Furthermore, VitD3 alone or in combination can significantly increase Foxp3 and IL-10 levels in colon tissue. For patients who cannot tolerate standard doses of IFX or the combination of IFX and AZA, this therapy offers an alternative option [53]. Vitamin D deficiency before anti-TNF treatment diminishes induction therapy's effectiveness [54]. Moreover, there is a significant correlation between the trough concentrations of IFX and the levels of vitamin D, which suggests that vitamin D supplementation is essential for individuals who have low levels of vitamin D [55]. In individuals with UC who are getting therapy with mesalazine and have mild to moderate disease activity, vitamin D supplementation improves the effectiveness of the medication, [56] improves Mayo scores and intestinal barrier function, reduces inflammatory cytokine production, and demonstrates no significant safety concerns [57].

As the prevalence of UC continues to rise, the use of traditional Chinese medicine and its active components is becoming more widespread. One example of this is the combination of vitamin D and curcumin, which, due to its antioxidant and anti-inflammatory properties, safeguards the colon from the damaging effects of acetic acid [58]. With a single dosage of Gardenia or vitamin D, symptoms of UC are greatly alleviated, and colonic damage is reduced. This is achieved by reducing levels of IL-6 and TNF-α while simultaneously boosting levels of IL-10. However, the combined treatment results in minimal symptom improvement, likely due to the inhibition of p38 MAPK activation, which limits vitamin D receptor signaling [59].

Therefore, developing effective vitamin D combination therapies may represent a promising direction for future research.

Summary and Prospect

In summary, vitamin D has demonstrated certain potential and positive effects in treating ulcerative colitis; however, several aspects still require further investigation. Future research should prioritize large-scale, multicenter, and rigorously designed clinical studies that can comprehensively assess the effectiveness and safety of vitamin D in managing UC. Additionally, when it comes to refining treatment regimens, such as identifying the appropriate dosage and time of administration, research should have the goal of elucidating the exact molecular pathways via which vitamin D exerts its therapeutic benefits. Furthermore, exploring vitamin D's synergistic and antagonistic effects when combined with other existing treatments is crucial to developing more effective and rational integrated therapeutic strategies. The application of innovative technologies, including genetic testing, could further aid in identifying mechanisms underlying individual differences in response to vitamin D therapy, thus enabling personalized medicine. With continuous research advancements, vitamin D holds promise for breakthroughs in ulcerative colitis treatment, offering hope for patients.

Author Contributions

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Data Availability Statement

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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