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Review

The Crucial Role of Vitamin D in Regulating Gut Microbiota in Inflammatory Bowel Disease

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Abstract

In recent years, there has been an alarming increase in the incidence of inflammatory bowel disease (IBD), which includes both Crohn's disease (CD) and ulcerative colitis (UC), particularly in Western countries. This chronic condition is intricately linked to the composition and health of the gut microbiota (GM) — a complex community of microorganisms residing in the gastrointestinal (GI) tract. Despite extensive research, the underlying pathogenesis of IBD remains poorly understood, making it a wide area of investigation. This review aims to provide a comprehensive exploration of the complex relationship between GM and the onset and progression of IBD. A key focus is the nucleotide-binding oligomerization domain-containing protein 2 (NOD2) pathway, which plays a crucial role in the immune response to gut bacteria and may influence susceptibility to IBD. Through a review of the current literature, an attempt was made to understand how a gut microbiome (GM) imbalance – dysbiosis – can trigger the inflammatory processes associated with IBD. Moreover, this review highlights the crucial role of vitamin D (VitD), a fat-soluble vitamin that is often deficient in individuals affected by IBD.

Research suggests that VitD deficiency may impair the immune system and disrupt GM health, contributing to disease severity. Additionally, a growing body of evidence indicates that VitD metabolism is involved in NOD2 regulation. VitD supplementation could potentially act as a therapeutic strategy for managing IBD, alleviating symptoms and enhancing the overall gut health. This study aims to improve our understanding of the connection between gut bacteria, the immune system, and nutrition, ultimately paving the way for more effective prevention and treatment strategies for IBD.

Keywords
Inflammatory bowel disease (IBD); gut microbiota (GM); vitamin D (VitD)

1. Introduction

Inflammatory bowel disease (IBD) refers to a group of chronic disorders characterized by significant inflammation in the gastrointestinal (GI) tract, particularly impacting the large and small intestines. The prevalence of IBD has been rising alarmingly worldwide, with particularly notable increases observed in both developing countries and Western nations [1, 2].

The Western diet, which is high in saturated fats and ultra-processed foods, promotes inflammation due to both structural and behavioral changes in the resident microbiome [3].

This rising trend has stimulated extensive research into various dietary factors and environmental influences that may exacerbate these conditions.

From 1990 to 2019, the IBD burden remained high in countries with high and high-middle Socio-Demographic Index (SDI). However, the increasing incidence of IBD also involves some developing countries with low, low-middle, and middle SDI, like Korea, Northeast Brazil, and China [4]. Due to population growth and aging, the burden of IBD may continue to rise until 2050 [5].

The human gut microbiome is a complex ecosystem composed of about 100 trillion microorganisms, including bacteria, viruses, and fungi, that inhabit the GI tract in symbiosis with the human host [6]. These microbes play essential roles in various body host functions, such as digestion, fermentation, immune regulation, and pathogen defense. The delicate balance of these microorganisms is crucial for maintaining overall health; any disruption can lead to dysbiosis, which is an imbalance in the gut microbiota (GM) and is often a contributing factor in the development of several diseases, such as IBD [1, 2]. Dysbiosis is considered to contribute to increased intestinal permeability, commonly referred to as "leaky gut," allowing pathogens to pass through the gut barrier and triggering inflammatory responses that aggravate IBD symptoms [1, 2].

The pathophysiology of IBD is intricate and involves multiple mechanisms, including immune dysregulation, genetic susceptibility, and interactions between the host and GM.

Furthermore, research has established a significant link between IBD and vitamin D (VitD) deficiency.

While VitD is well-known for its critical role in regulating calcium and phosphate metabolism necessary for bone health, insufficient VitD levels can also lead to alterations in the composition and diversity of the GM, potentially compromising the integrity of the intestinal epithelial barrier. VitD possesses immunomodulatory properties as well. Studies have shown it can reduce

inflammation and promote a healthy immune response, underscoring its potential protective effects against IBD [7].

In addition, higher serum levels of VitD have been correlated with increased beneficial bacterial species, such as those from the *Lactobacillus* and *Bifidobacterium* genera, which are recognized for their positive contributions to gut health. Conversely, low VitD levels have been associated with a rise in harmful bacterial populations, which may further promote inflammation and the progression of IBD [7].

Moreover, VitD interacts with specific receptors in the immune system, particularly those involved in inflammation and maintaining gut homeostasis. Understanding the intricate interactions between VitD, the immune system, and GM is essential for elucidating the VitD protective role in the onset and exacerbation of IBD [7].

It is also essential to recognize the influence of genetic predispositions in IBD. Specific genetic mutations can increase an individual's risk of developing IBD, highlighting the need for a comprehensive approach that considers both genetic factors and lifestyle choices — including diet and nutrient intake — in the management and prevention of these debilitating conditions.

2. Vitamin D

VitD is a fat-soluble secosteroid that comes in two forms: VitD2 and D3. Upon exposure to UVB radiation from sunlight, the skin synthesizes VitD3 from 7-dehydrocholesterol, while plants and fungi convert ergosterol into VitD2. VitD3 is then transported to the liver, where it is converted into 25-hydroxyVitD3 [25(OH)D3] by cytochrome P450 family 2 subfamily R member 1 (CYP2R1). This form, 25(OH)D3, is the primary circulating form of VitD3. Finally, 25(OH)D3 is transformed into its active form, 1,25-dihydroxyVitD3 [1,25(OH)2D3], by renal cytochrome P450 family 27 subfamily B member 1 (CYP27B1) [8].

1,25(OH)2D, the active form of VitD, carries out most of its functions through the widely distributed nuclear VitD receptor (VDR) [9].

The extensive expression of the VDR gene suggests that VitD plays a role in regulating not only calcium levels but also many other functions [10]. The VDR element (VDRE) can be found in numerous genes that detail mechanisms associated with VitD, such as autophagy, cell proliferation, intestinal barrier function, modulation of GM, and immune functions, along with the well-known mechanism of calcium homeostasis and bone health [11].

A systematic review by Bellerba et al. [12] found that VitD has a substantial impact on GM, particularly on the phyla *Firmicutes*, *Actinobacteria*, and *Bacteroidetes*. Increased VitD intake seems to alter the bacterial composition and enhance species richness. Notably, the families *Veillonellaceae* and *Oscillospiraceae* within the *Firmicutes* phylum often decrease with higher levels of 25(OH)D and VitD supplementation.

Various diseases, including cancer, infections, and chronic inflammation, are linked to a deficiency in VDR [13].

3. IBD and Molecular Basis

IBD is a complex chronic inflammatory disorder of the intestinal tract, which includes Crohn's disease (CD) and ulcerative colitis (UC).

It is believed that IBD arises from an abnormal and ongoing immune response to gut microbes, influenced by the genetic predispositions of individuals. UC is a chronic inflammatory disease of unknown origin that continuously affects the colonic mucosa, starting from the rectum and extending to the colon. In contrast, CD is a progressive inflammatory disease that impacts the layers of the GI tract and can occur anywhere along it, with complications such as stenosis, fistulae, and abscesses happening more frequently than in UC [14, 15].

Although the exact cause of IBD is still largely unknown, it probably results from a complex interaction among environmental factors, the immune system, susceptibility genes, and alterations in the host's microbiome, all leading to disturbances in the intestinal mucosa [16, 17].

In recent years, the cytosolic nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) have emerged as critical players in the regulation of intestinal inflammation. These receptors are part of the innate immune system and help detect microbial components, thus initiating inflammatory responses. Among the NLR family, NOD2 (nucleotide-binding oligomerization domain-containing 2) has garnered significant attention as it was the first gene identified to be associated with an increased susceptibility to CD. The discovery of NOD2's role in this context has significantly enhanced our understanding of the underlying mechanisms driving IBD pathogenesis. NOD2 functions by recognizing specific bacterial motifs and triggering a cascade of immune responses, thereby influencing the balance between tolerance and inflammation in the gut. This advancement in research underscores the importance of NLRs in maintaining intestinal homeostasis and their potential involvement in various GI disorders [18].

The NOD2 gene is a vital component of the Nod1/Apaf-1 family of proteins, encoding an essential intracellular sensor crucial to the immune response. This gene produces a protein characterized by the presence of two caspase recruitment domains (CARDs) and six leucine-rich repeats (LRRs). These structural features are crucial for their function in immune signaling. Predominantly expressed in peripheral blood leukocytes, the NOD2 protein plays a vital role in recognizing and responding to intracellular bacterial threats, particularly those containing lipopolysaccharides (LPS) [18].

One of the primary functions of NOD2 is to detect muramyl dipeptide (MDP), a component derived from bacterial peptidoglycan. When MDP binds with NOD2, it triggers several essential cellular processes, including the activation of autophagy. This process plays a critical role in maintaining gut homeostasis and supporting intestinal barrier function in response to inflammation by regulating tight junctions [19]. Autophagy is a cellular mechanism that not only helps manage bacterial replication within cells but also enhances antigen presentation, influencing both innate and adaptive immune responses. The activation of NOD2 triggers a cascade of intracellular signaling events that involve the activation of key transcription factors, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), as well as pathways like the mitogen-activated protein kinase (MAPK). These pathways are essential for mediating inflammatory responses and orchestrating the immune system's reaction to pathogens [20].

Additionally, NF-κB and MAPK pathways are primarily triggered by Toll-like receptors (TLRs), which are well-known receptors that sense pathogen-associated molecular patterns (PAMPs) either present on the cell surface or within the endosomal compartment of immune cells. A dysregulation in the expression and functional activity of TLRs has been implicated in the pathogenesis of various inflammatory diseases, including IBD [21]. Research by Udden et al. [22] revealed that while NOD2 typically activates the NF-kB and MAPK pathways, it assumes an inhibitory role within the TLR pathway through IRF4 during colitis and colorectal tumorigenesis, leading to activation of NF-kB and

MAPK. This finding highlights the complexity of intracellular signaling networks and the interactions between various immune receptors to maintain immune homeostasis. This understanding emphasizes the critical role of NOD2 and related pathways in the immune response and their potential implications in conditions such as IBD [16, 22, 23].

NOD2 is also found in the epithelial cells of the small intestine, with a notable presence in Paneth cells, which are specialized cells that ensure the health and stability of the intestinal environment. NOD2 contributes to maintaining the dynamic equilibrium between intestinal microbiota and the immune system's regulatory factors [16, 24].

Recent research has highlighted the implications of NOD2 mutations in various inflammatory disorders, including IBD. The mutation occurs at a specific gene location in the pericentromeric region of chromosome 16 known as IBD1, and it is caused by the insertion of a cytosine. These mutations can disrupt the normal functioning of the NOD2 gene, which typically activates NF-kB in response to bacterial lipopolysaccharides (LPS). However, in the case of mutant NOD2, this activation is deficient, leading to an impaired immune response [24]. This weakening plays a significant role in the development of conditions such as CD and UC. Studies suggest that the link between these genetic variations and inflammation underscores the importance of NOD2 in both gut health and disease susceptibility [16, 22].

4. IBD and Gut Microbiota

IBD is a complex condition characterized by chronic inflammation of the GI tract. This inflammation derives from a combination of immune system dysfunctions, which are influenced by a multitude of factors, including genetic susceptibility and environmental contributors [25]. Recent research has highlighted the significant relationship between GM and autoimmune processes, particularly in individuals affected by IBD. Studies have demonstrated that GM in patients with IBD exhibits distinct characteristics compared to healthy individuals, suggesting a potential link between microbial composition and immune regulation. The relationship between GM and the host's immune system is intricate and crucial for maintaining immune balance. A healthy gut microbiome is vital for modulating immune functions and preventing inappropriate immune responses that could lead to conditions such as IBD. Environmental factors, including poor dietary habits, high stress levels, and lifestyle choices, can significantly affect GM diversity and stability, leading to alterations in intestinal homeostasis. Alterations in gut microbiome composition can trigger inflammation and disrupt immune regulation, highlighting the importance of microbiome composition for intestinal health. Understanding the interactions between the gut microbiome, environmental factors, and the immune system is crucial for preventing and developing treatments for IBD and related inflammatory disorders [26, 27].

In addition, the gut microbiome plays a crucial role in preserving mucosal integrity, which is essential for preventing the colonization of harmful pathogens through a mechanism known as colonization resistance. Furthermore, the microbiome enhances the production of immunoglobulin A (IgA), an essential antibody that helps in immune defense by neutralizing pathogens and toxins in the gut. Additionally, it contributes to the regulation of T-lymphocyte cells, which are pivotal for adaptive immune responses, as well as the production of anti-inflammatory cytokines. This regulation helps balance immune responses, thereby preventing excessive inflammation and maintaining overall gut health [1, 2, 28].

Recent studies regarding the genetic underpinnings of IBD have unveiled numerous interlinked functional host pathways essential for the onset of these diseases. These pathways encompass autophagy, the detection of intracellular bacteria, and the unfolded protein response, each playing a specific role in the interaction between the host and the complex microbial communities in the intestines. These pathways emphasize the functional relationship between the intestinal epithelium and the distinctive microbial and immune landscapes present on both its luminal and abluminal surfaces [29].

Investigations utilizing in *vitro* and in *vivo* models, alongside human clinical trials, have shown that autophagy plays a crucial role in upholding intestinal homeostasis, governing gut ecology, ensuring suitable immune responses in the intestines, and offering protection against pathogens [30].

The GM diversity and composition significantly influence the emergence of IBD and can lead to decreased protection and increased aggressive species [31, 32]. In general, a decrease in members of the dominant phyla, such as *Bacteroidetes* and/or *Firmicutes*, and an increase in members of the *Proteobacteria* have been observed [33].

Compared to healthy controls, levels of beneficial bacteria, such as *Bifidobacterium longum*, are markedly reduced in individuals suffering from UC. Similarly, key bacterial species, including *Eubacterium rectale*, *Faecalibacterium prausnitzii*, and *Roseburia intestinalis*, along with *Phascolarctobacterium* and other advantageous microorganisms, are also found in lower concentrations in the guts of CD and UC patients [31].

On the other hand, there is an alarming increase in the presence and activity of pathogenic bacteria such as *Bacteroides fragilis* and various species of *Clostridium* in these patient populations [31]. This shift in microbial balance can exacerbate inflammation and contribute to the symptoms of these diseases. Notably, beneficial bacteria like *Roseburia* play a crucial role in gut health by being associated with the production of anti-inflammatory regulatory T cells within the intestinal environment. This mechanism underscores the importance of maintaining a healthy composition of GI tract microbiota to support immune regulation. Meanwhile, *Faecalibacterium prausnitzii* is linked to the synthesis of butyrate, which is a short-chain fatty acid (SCFA) essential for promoting gut eubiosis — a state of microbial balance that supports overall digestive health and reduces inflammation [34]. *Faecalibacterium prausnitzii*, also *Eubacterium rectale*, and *Roseburia intestinalis* are the main butyrate-producing bacteria. Butyrate is an anti-inflammatory metabolite produced through fiber fermentation, and it inhibits the pathways responsible for generating pro-inflammatory cytokines [35].

The presence of these beneficial microorganisms is critical for maintaining intestinal homeostasis and preventing dysbiosis for several physiological effects, including enhancement of intestinal barrier function and mucosal immunity [36].

Analysis of GM has indicated that dysbiosis, characterized by fluctuations in specific bacterial species within the intestines of individuals affected by IBD, occurs globally. This dysbiosis, coupled with an imbalance of cytokines and the deterioration of the mucosal barrier, plays a role in triggering mucosal inflammation and the progression of IBD [37].

These insights imply that interventions like probiotic supplementation, fecal microbiota transplantation (FMT), and specific metabolites could help alleviate symptoms of IBD by reducing inflammation in the gut [38].

5. IBD, VitD, and Nutritional Status

One of the main risk factors for developing IBD is the nutritional status of the patients, which is often altered. Malnutrition, which could be triggered by reduced nutrient (deficit of macronutrients and micronutrients) intake, poor digestion, and intestinal malabsorption, is a potential pathogenetic condition in IBD patients, especially in CD condition that mainly affects the small bowel [39-41].

Regarding micronutrients, deficiencies in iron, VitD, vitamin B12, and calcium are detected in many patients with IBD [42]. According to Stallhofer et al. [43], low VitD levels in IBD are also linked to iron deficiency. They may be improved by downregulating hepcidin and upregulating ceruloplasmin, which enhances intestinal iron absorption.

In particular, VitD has recently gained attention for its role in maintaining intestinal homeostasis. VitD can enhance the balance between the gut microbiome and the intestinal immune system through its nuclear receptor [33].

VitD deficiency has been recognized as a significant predictor of adverse outcomes in individuals with IBD. This condition may be caused by an atypical immune response to gut bacteria in genetically predisposed individuals and is associated with changes in gut barrier function and GM [11, 44, 45].

The mechanisms connecting VitD, GM, and the immune system remain unclear, but interest among scientists in this field is increasing. Multiple *in vivo* research studies [46-49] were conducted to explain better the complex interactions among these three characters (Table 1).

Table 1 The proposed mechanisms linking VitD, GM, and immune modulation.

Model	Mechanisms	References
Zebrafish	VitD promotes the growth of acetate-releasing *Cetobacterium,* leading to the production of IL-22, which is involved in the generation of neutrophils, which are crucial for intestinal antimicrobial peptide (AMP) production and host defense.	[46]
Hens	Adequate VitD reversed the adverse effects of *Salmonella* and VitD deficiency on egg production by enhancing VitD metabolism. It improved gut health by reducing injury and inflammation, increasing the expression of tight junction proteins, and lowering pro-apoptotic markers in the jejunum. VitD also enriched beneficial probiotics, such as *Lactobacillus* and *Bacillus*, thereby restoring gut microflora balance.	[47]
Female non-obese diabetic (NOD) mice	800 IU/day VitD delayed and reduced the incidence of type 1 diabetes (T1D) and increased the frequency of regulatory T cells (Treg cells) expressing CD73 and altered GM.	[48]
Mice	Intestinal VDR protects mice from dysbiosis by regulating the JAK/STAT signaling pathway.	[49]

6. IBD, VitD, and Molecular Pathways

VitD level may relate both to the nutritional status and levels of inflammation in CD patients and disease progression [50].

Consequently, the potential role of VitD in the development of IBD and the immunological effects of VitD-related therapies are suggested.

VDRs have been identified in nearly all immune cells, including both activated and naive CD4+ and CD8+ T cells, B cells, neutrophils, and antigen-presenting cells (APCs), such as dendritic cells and macrophages. Notably, VitD3 enhances the chemotactic and phagocytic responses of macrophages, boosts the production of antimicrobial proteins like cathelicidin, inhibits the expression of major histocompatibility complex (MHC) II and costimulatory molecules on APC surfaces, and reduces the production of several pro-inflammatory cytokines, including interleukin (IL) 1, IL-6, IL-8, and TNF-α. The NOD2 gene may help clarify the molecular and genetic connection between CD and the VitD/immune system [51].

VitD significantly stimulates the expression of the NOD2/CARD15/IBD1 gene and protein in primary human monocytic and epithelial cells. A significant downstream signaling effect of NOD2 activation by the agonist muramyl dipeptide is the stimulation of the NF-kB transcription factor function, which promotes the expression of genes encoding the antimicrobial peptide defensin β2 (DEFB2/HBD2) (Figure 1) [52].

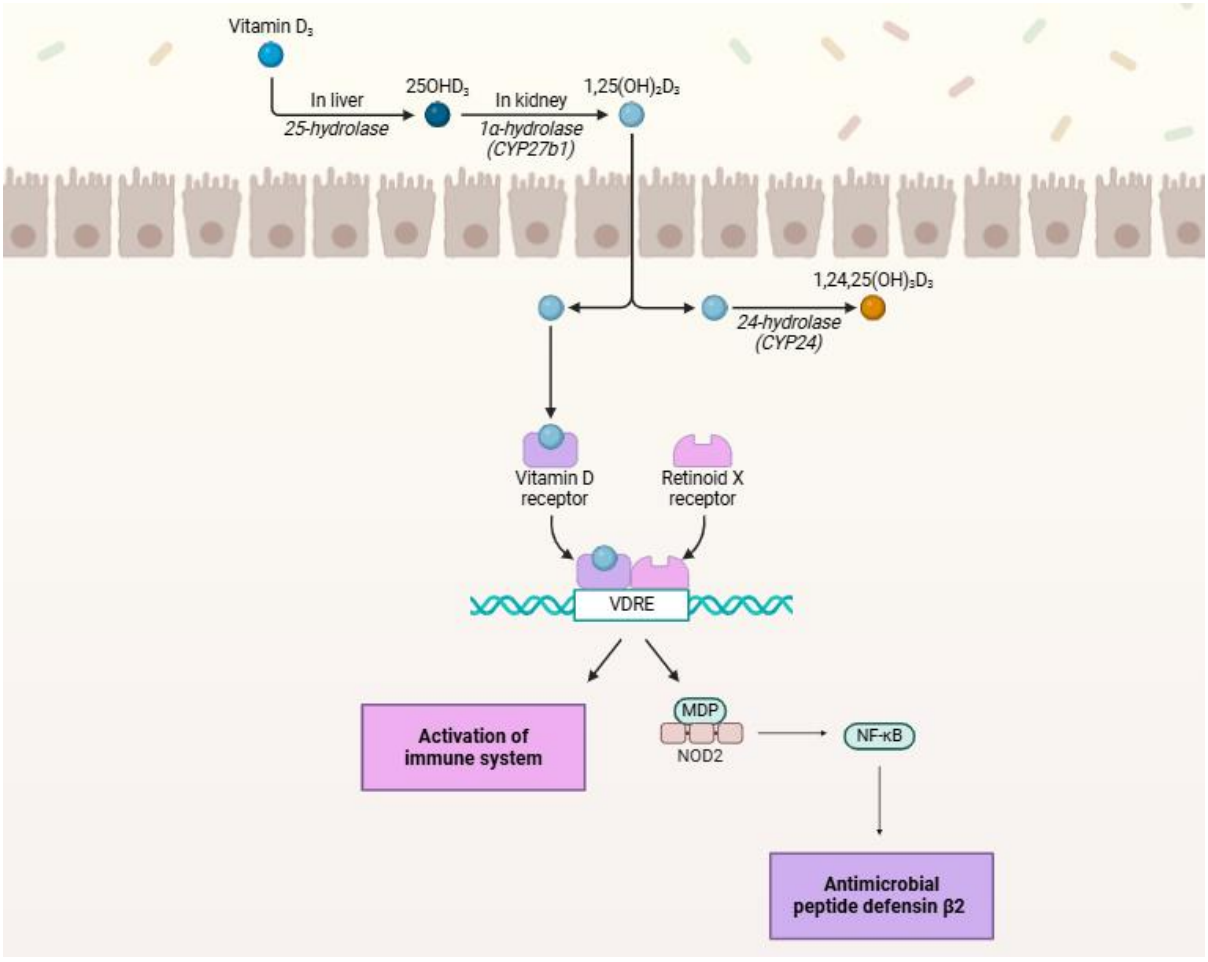

Figure 1 VitD's impact on the immune system and inflammatory markers.

Importantly, research by Wang T. et al. [52] indicated that mutations in the NOD2 gene are implicated in CD pathogenesis, and VitD supplementation is ineffective in patients with these mutations.

Aside from those with NOD2 mutations, VitD supplementation may contribute to improving the health of individuals with IBD.

The potential use of VitD as a treatment for IBD is promising. Although interpretations may differ, several studies show a correlation between VitD levels and IBD severity. A clinical trial found that patients with CD who received 1,200 IU of VitD experienced fewer relapses compared to those on a placebo. Additionally, animal studies suggest that VitD supplementation may prevent or reduce IBD development in genetically predisposed mice [53].

A review by Owczarek et al. [54] discussed three distinct studies [55-57] where VitD supplementation alleviated inflammatory processes associated with IBS/IBD. Additionally, a study involving Gulf War veterans demonstrated that VitD treatment reduced the frequency of bowel movements per day without leading to hypercalcemia [58].

Studies, including the one by Ayari et al., have shown that there are no significant differences in VitD levels between patients with CD and healthy individuals. Therefore, it is essential to clarify the relationship between VitD levels and the onset of IBD [59].

7. Conclusion

Research indicates that although the specific molecular pathways involved in the pathogenesis of IBD remain primarily undefined, there is a notable correlation between low serum VitD levels and the onset of this condition. This connection may be explicable by the role of the NOD2 gene, which is activated by the VDR.

The activation of this receptor is crucial for various cellular functions, particularly in immune regulation and maintaining intestinal health. Moreover, individuals with mutations in the NOD2 gene often exhibit changes in their GM composition, including a significant reduction in the abundance of *Roseburia* spp., which is known to produce butyrate. This SCFA is vital for colonic health, serving as an energy source for colonocytes and possessing anti-inflammatory properties. Impaired autophagy, a cellular process responsible for the degradation and recycling of cellular components, combined with these microbiota alterations, may further contribute to the progression of IBD by exacerbating inflammation and compromising the integrity of the epithelial barrier.

Given these insights, current research efforts are focused on developing targeted treatments for IBD that aim to modulate autophagy and alleviate inflammation [30].

These therapeutic strategies underscore the potential of VitD as a treatment option for individuals with IBD due to its multiple biological roles and targets related to immune function and gut barrier maintenance.

Additionally, the objectives of monitoring, treatment, and therapy for IBD diseases are typically consistent across various forms, including CD and UC [60].

Severe 25(OH)D deficiency may be a marker of a more aggressive clinical course of IBD [61]. IBD patients with lower VitD levels are often more prone to hospitalization and need more intensive medical interventions; this evidence suggests that beginning disease-modifying drugs earlier in the disease process can lead to slower progression of IBD and may help minimize long-term effects and complications following surgical procedures [44, 45, 60].

Indeed, higher pretreatment VitD levels predicted significant endoscopic improvement in patients with UC, and VitD can play a role in clinical and endoscopic outcomes and should be routinely assessed and optimized in patients with IBD [62, 63].

In conclusion, it is essential to establish effective strategies for the early treatment of IBD. This includes exploring less invasive treatment options, such as VitD supplementation. Comprehensive prospective studies in humans are essential to determine whether VitD supplementation can lower the risk of developing IBD in individuals with a genetic predisposition to this condition. Further clinical trials are necessary to evaluate the effectiveness of VitD in the treatment of IBD [53].

Addressing VitD deficiency can improve patient outcomes by supporting overall health and well-being, promoting intestinal balance, and helping manage IBD's severity.

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Competing Interests

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