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Review Article

The Role of the Gastrointestinal Microbiome and Vitamin D Intake in Inflammatory Bowel Disease

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Abstract
Chronic gastrointestinal inflammation, known as inflammatory bowel disease (IBD), is associated with severe morbidity and mortality. According to recent research, microbiota composition, vitamin D level, and the immune system are the three most important elements that should have been taken into account in determining susceptibility to IBD disease. There is broad agreement that alterations in the composition and metabolism of the gut microbiota are related to IBD susceptibility (dysbiosis). In IBD disease, the composition of the gastrointestinal microbiome is changed and the beneficial ones are replaced by the pathogenic microbiome. Furthermore, a drop in serum vitamin D levels is noted in IBD patients. Vitamin D prevents the onset of IBD by reducing inflammatory cytokines and cells as well as limiting the expansion of pathogenic microbiota by inducing the release of antimicrobial peptides (AMPs). However, more research is needed to completely comprehend the intricate relationships between the microbiota and vitamin D, it is suggested that modifying these factors could be an alternative treatment for IBD disorders. To restore dysbiosis, using FMT, probiotics, and vitamin D supplementation have been proposed as alternative treatments. The purpose of this article is to review the involvement of these key parameters and their interactions in the susceptibility and pathogenesis of IBD.

Keywords: Gastrointestinal Microbiome, Immune System, Inflammatory Bowel Diseases, Vitamin D
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Introduction

Inflammatory bowel diseases (IBDs) are a family of chronic systemic diseases characterized by gastrointestinal tract inflammation. IBDs are represented by ulcerative colitis (UC), which affects only the large intestine; Crohn's disease (CD), which can affect the entire gastrointestinal tract; and indeterminate colitis, which is characterized by large-intestine inflammation.[1]

According to different studies, the ratio of prevalence to incidence of IBD is from 6.6 to 23 years.[2] Within a defined geographic area, incidence occurs differently.[3] Epidemiological studies showed the highest rate in North America, northern Europe, and the United Kingdom.[2,4] However, this disease is more common in developed and western countries, increasing incidence of IBD in developing countries was also reported.[5,6] Populations in urban areas have a higher incidence rate than those in rural areas, and urban populations experienced an increase in incidence before rural populations.[7] CD occurs at a peak age of 20-30 years, whereas the peak age for UC is 30-40 years. The second peak is around 60-70 years old, but this observation was not confirmed.[8,9] However, the susceptibility of men and women to IBD is similar, race and ethnicity influence this distribution.[3] Men are somewhat more likely than women to get UC (60%), but women are 20-30% more likely to develop CD, especially in the high-incidence area.[10,11] On the other side, in some low-incidence places, Men were shown to be more susceptible than women to having CD.[12] In pediatric patients, CD is more prominent in boys and UC in girls.[9] Race can impress the incidence of IBD disease in the way that the incidence rate in white and non-white were 21.6 and 13 cases per 100,000 persons, respectively.[13] The prevalence of this inflammatory disease was high in Jewish people and remained higher in people who live outside Israel compared to non-Jewish people. Another study showed a lower incidence of IBD in Jewish people who were born in other countries compared to Jewish lived in Israel.[14]

Slightly greater mortality was seen in patients with CD compared with the healthy population. In this connection,

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the standardized mortality ratio of these patients was 1.52 in the meta-analysis study.[15] Over the last 30 years, mortality has reduced marginally, albeit not statistically significantly.[15] In a study of Danish CD patients, women diagnosed before the age of 50 had the highest mortality rate.[16]

The cause of IBD diseases is poorly understood. Several factors contribute to susceptibility to this disease, including dysfunction in the mucosal barrier, lifestyle, environmental factors, immune response dysregulation, microbiota disturbance, and genetic predisposition.[17,18] Genome-wide association studies have introduced more than 100 genes for IBD susceptibility, but genetics cannot explain more than 7.5% of the incidence and prevalence.[19] The relationship between IBD and several loci that are involved in epithelial hemostasis (e.g., CLDN2, COL7A1, GUCY2C), autophagy (e.g., ATG16L1, IRGM), mucosal immunity (MUC, TNFSF15, Foxp3, IL23R, IL12R), innate immunity (NOD2, CARD9), and IBD signaling are reported.[20-22] An association between the genetic locus of NOD2 (nucleotide-binding oligomerization domain 2) with IBD was first identified in a linkage study.[20]

Epidemiological studies showed an association between susceptibility to IBD disease and multiple risk factors including smoking, appendectomy, microbiomes, vitamin D (Vit D), physical activity, diet, smoking, hygiene, and medications (Figure 1). Smoking is mentioned as an important factor in IBD pathogenesis by various studies. Interestingly, smoking is harmful in CD patients but beneficial in UC patients.[1] A meta-analysis reported that smoking has been associated with a twofold increase in CD risk. While former smoking and UC had the same magnitude of association, current smoking showed a strong inverse relationship.[23] Appendectomy shows divergent effects on CD and UC, similar to smoking. A protective role of appendectomy was reported in a meta-analysis study on UC patients by Gilaad et al. On the other side, an appendectomy increased the risk of CD by 1-4 years after surgery.[24] Furthermore, Crohn's disease can be prevented by physical activity.[25]

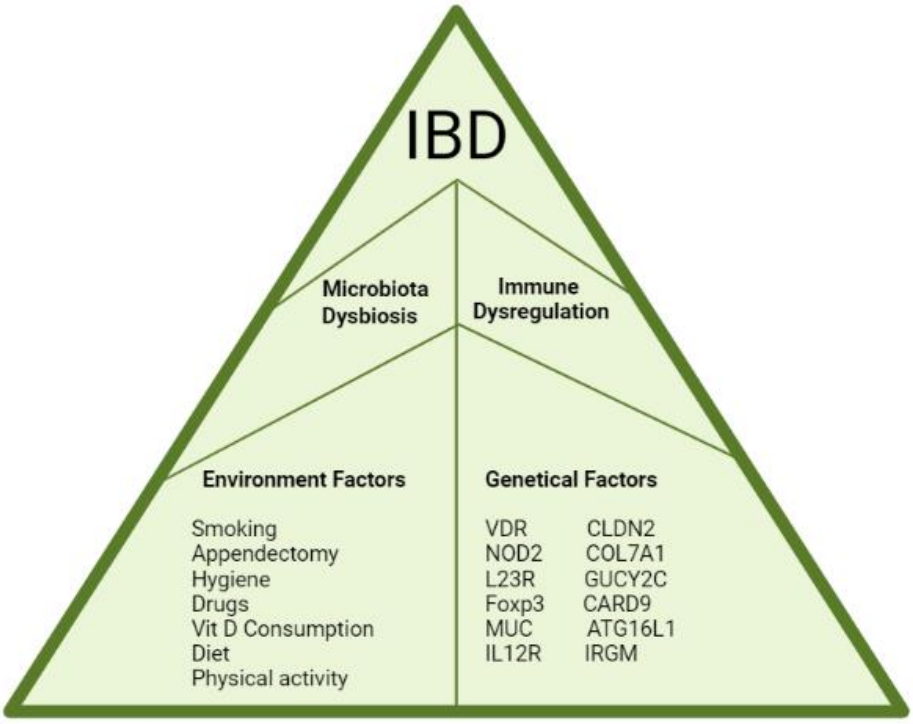

Figure 1. Risk Factors Involved in IBD Susceptibility. IBD disease can be caused by immune system dysregulation or microbial dysbiosis. Both of the aforementioned disorders are impacted by environmental and genetic factors.

Numerous studies have offered evidence supporting the hygiene hypothesis within the context of IBD. There is a negative correlation between CD or UC susceptibility and family size, the number of siblings, living on a farm, drinking unpasteurized milk, and exposure to pets.[26,27] Although IBD and breastfeeding have a strong inverse relationship in the development of early-onset IBD, this is not consistent across all cohorts.[28] The consumption of fiber in the diet reduces susceptibility to IBD.[3] An inverse association with fiber consumption could be explained by several mechanisms.[3] Short-chain fatty acids derived from fiber (fruits and vegetables) inhibit the transcription of proinflammatory molecules by intestinal bacteria.[29] Further, fiber maintains epithelial integrity and inhibits the spread of *E. coli* through Peyer's patches.[30] In an animal model, the aryl hydrocarbon receptor was activated by indole-3-carbinol present in fruits and vegetables and subsequently attenuated colitis.[31]

Microbiota in IBD

Bacteria, protozoa, fungi, and viruses make up diverse, enormous, and dynamic microbiota in the various parts of humans. In addition to the skin, mouth cavity, respiratory, and urogenital tracts, the microbiota is mostly found in the entire gastrointestinal system. At least 10^{14} microbial cells are living in the human gut, almost more than all eukaryotic cells put together.[32] The density and variety of microbiota considerably vary in different sections of the gastrointestinal tract. The microbiota in the upper small gastrointestinal tract is sparse, while microbial density increases from the duodenum to the distal colon.[33] The colonization of microbial organisms in any part of the body has a significant effect on the regulation and instruction of the immune system. Abnormal interaction between the mucosal immune system and gut microbial communities has been characterized as an important defect that leads to intestinal inflammation.[34] Therefore, expanding our knowledge about human gut microbiota is important to understand the pathogenesis of IBD.

Normal Gut Microbiota

It is vital to determine a "healthy and proper" gut microbiota in order to understand the biological significance of different microbial colonization patterns associated with a specific disease. Indeed, the microbiota in healthy guts is still poorly understood in terms of composition and function.[32] From an ecological perspective, it is possible to consider the stability of a community (bacterial or otherwise) as a functional characteristic describing its state of health. The ability of a community to resist change under ecological stress (resistance) or to return to equilibrium following a stress-related distribution (resilience) is referred to as stability. Resistance and resilience as fundamental aspects of a healthy microbiome are compatible with recognized microbial ecology theories.[35]

Active interaction between the human host and the commensal microbiota probably has important implications for health.[36] The host gives the gut microbiota a place to live and a nutrient-rich environment, and the microbiota in turn benefits the host by creating vital vitamins and short-chain fatty acids. Symbiosis is the name for this cooperative association between the host and the gut microbiota.[37] In healthy individuals, the gut microbiota also controls a number of additional biological processes, such as improvement of the immune system, food processing, energy homeostasis maintenance, and defense against pathogen invasion.[38]

According to phylum, classes, orders, families, genera, and species, bacteria are categorized taxonomically. In healthy individuals, only two divisions of the *Bacteroidetes* and *Firmicutes* account for more than 90% of all phylotypes. *Proteobacteria*, *Actinobacteria*, and *Fusobacteria* are the additional subgroups identified in samples from the human gut. *Prevotella* and *Bacteroides* are two of the most common genera in the family *Bacteroidetes*. There are more than 200 different genera in the *Firmicutes phylum*, including *Lactobacillus, Bacillus, Clostridium, Ruminicoccus, and Enterococcus*. Throughout the *Firmicutes phylum*, 95% of the genera are *Clostridium*. The majority of the members of the phylum *Actinobacteria*, which is relatively less common, are found in the genus *Bifidobacterium*.[39,40]

According to research findings, the fecal microbiota's composition changes over time in a permanent way. Although the fecal microbiota prefers to gain its normal pattern of composition again (resilience).[41] Following exposure to various foods, drugs, or physical situations, temporal fluctuations may appear. The way the fetus was delivered, the host's genotype, stress, age, antibiotic consumption, and place of origin are additional factors that could affect the gut microbiota.[35] Determining which species of bacterial flora cause the initial intestinal inflammation is challenging due to the microbial community's diversity.[36] Therefore, to define the gut microbiome's function in pathogenesis, a thorough characterization of the gut microbiota in health and disease is a requirement.

Gut Microbiota Dysbiosis in IBD

Recent developments in sequencing technologies have allowed for culture-independent investigation of the gut microbiota. These technologies demonstrate that the pathophysiology of numerous diseases is influenced by changes in the balance of the gut microbiota's contents rather than specific pathogens. The term "dysbiosis" refers to this change in the balance of the gut microbiota (Figure 2).[42] Due to molecular mimicry, which postulates that foreign microbial peptides may have structural and functional similarities to self-antigens and hence be capable of triggering immune cell auto-reactivity, the microbiome is of special interest in autoimmune diseases such as IBD.[78]

Bacteria

Multiple studies have documented differences in the profile of the gut microbiota between healthy individuals and patients with IBD, particularly concerning microbial diversity and the relative abundance of specific bacterial taxa.[43,44] A drop in the diversity of *Firmicutes* is mostly to blame for the decreased variety of the gut microbiota seen in IBD patients.[45] Numerous studies have found that the *Clostridium leptum* groups of *Firmicutes*, particularly *Faecalibacterium prausnitzii*, have declined in IBD.[46,47] F. prausnitzii stimulated peripheral blood mononuclear cells to reduce IL-12 and IFN-γ production and increase IL-10 secretion. Due in part to released metabolites that can prevent NF-κB activation and IL-8 generation, *F. prausnitzii* demonstrates anti-inflammatory properties in cellular and mouse

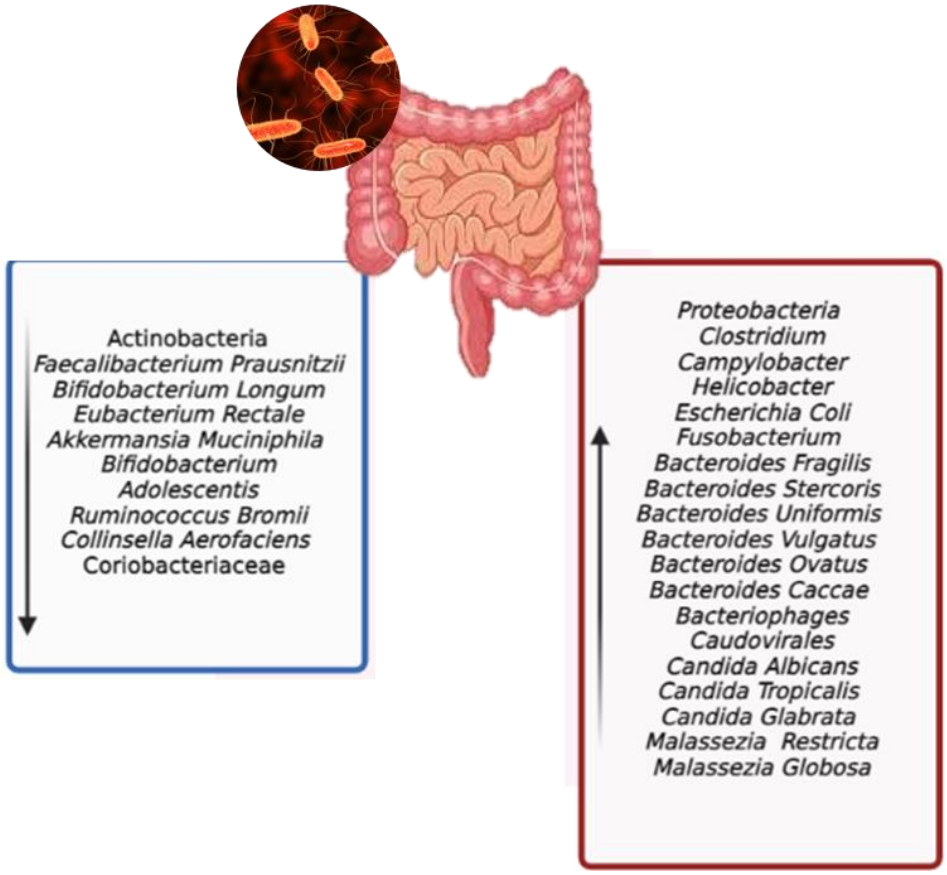

Figure 2. Change in the Balance of the Gut Microbiota's Composition in IBD Patients. At least 10^{14} microbial cells are living in the human gut and the density and variety of microbiota considerably vary in different sections of the gastrointestinal tract. The colonization of microbial organisms in any part of the body has a significant effect on the regulation and instruction of the immune system. Abnormal interaction between the mucosal immune system and gut microbial communities has been characterized as an important defect that leads to intestinal inflammation. The beneficial microbiomes in IBD that are replaced by the pathogenic microbiome are listed.

colitis models.[47] There has also been a reported decrease in the Bacteroidetes phylum's numbers[48] and an increase in the *Proteobacteria phylum*.[49] The majority of known pathogenic bacteria are from the *Proteobacteria phylum*.[49] In UC, there is an increase in the abundance of certain bacteria, including Escherichia coli, *Fusobacterium*, *Campylobacter*, and *Helicobacter*, which are linked to intestinal inflammation and increased membrane permeability of epithelial cells.[50] According to another study, the number of beneficial bacteria, including *Bifidobacterium longum* in UC, *Eubacterium rectale*, *F. prausnitzii*, and *Roseburia intestinalis* in CD and UC were significantly lower when compared to healthy controls. On the other hand, harmful bacteria such as *Bacteroides fragilis* and *Escherichia coli* grow more quickly and become more prevalent.[51] However, the level of *Akkermansia muciniphila* falls in UC patients, *Eubacterium rectum* and *E.coli* are enriched and inconsistent results about *Enterobacteriaceae, Bacteroides, Bifidobacteria species, and Lactobacillus species* were reported.[52] In a metagenomic investigation in China, the differential bacteria of the healthy group were predominantly the phyla *Firmicutes*, and *Actinobacteria*, whereas in IBD group they were the *phylum Bacteroidetes*. *Eubacterium rectale, Bifidobacterium adolescentis, Faecalibacterium prausnitzii, Bifidobacterium longum, Ruminococcus bromii* and *Collinsella aerofaciens* were found in higher frequencies in healthy individuals. The IBD patients were characterized by a higher number of *Bacteroides stercoris, Bacteroides fragilis, Bacteroides uniformis, Roseburia intestinalis, Bacteroides vulgatus, Bacteroides ovatus,* and *Bacteroides caccae*.[53] A considerable drop in the Coriobacteriaceae (phylum Actinobacteria) family was found in CD and UC patients' stool samples compared to healthy controls.[54] Another study found a significant reduction in *Eubacterium rectale* (*phylum Firmicutes*) in UC patients that is not confirmed in CD patients. Consistent with other studies, *E. coli* population assessment in UC and CD patients versus controls revealed a rise in the number of these bacteria in the patient group.[52]

Viruses

Another type of microbiota found in the gastrointestinal tract is viruses. Although intestinal viruses have members that attack eukaryotic cells directly, the majority of them are made up of bacteriophages.[55] Bacteriophages are 10 times

more numerous than bacteria and are probably the most prevalent foreign microorganism on mammalian bodies.[56] Bacteriophages can exist in the gut in two forms: free phage virions embedded in the mucus layer and prophages within their bacterial host. By controlling invading bacterial populations, they are thought to contribute to the maintenance of the intestinal barrier.[57] When compared to healthy controls, the bacteriophages' composition in people with IBD is different as well.[58] For those with IBD, the most noticeable change is an increase in the order of bacteriophages, *Caudovirales*.[58] Although they do not directly infect cell hosts, they do contain a number of chemicals that have the ability to modulate the immune system.[59] *Bacteriophage* and phage DNA trigger the immune system activation via binding to Toll-Like Receptor 9 (TLR9). A positive association between bacteriophages with IFN-γ levels was reported by Gogokhia et al. and colitis was made worse by a rise in *bacteriophage* levels.[60]

Fungi

According to metagenomic sequencing, fungal genes comprise fewer than 0.1% of the microbial genomes in the gut. Thus, the fungal effect on IBD susceptibility is negligible. Fungal agents may exert their influence through ecological interactions with bacteria.[61] More than 99% of the fungal population belongs to two dominant phyla, Ascomycota and Basidiomycota with no significant difference between patients and healthy groups.[62] There are controversial results about fungal diversity in IBD patients compared with healthy people. Several studies report reduction,[62] increase[63] or no change[64] in the diversity of fungal species in flamed mucosa. With a higher *Basidiomycota/Ascomycota* ratio and a higher proportion of *Candida albicans* and lower proportion of *Saccharomyces cerevisiae*, Sokol et al. found that the fungal microbiome in IBD is out of balance and skewed.[65] There is a broad consensus about a significant increase or trend of Candida in the feces of patients with IBD. In addition to *C. albicans*, other types of candida such as *C. tropicalis* and C. *glabrata* have also been shown. Furthermore, a positive association between *Malassezia spp. (M. restricta and M. globosa)* and susceptibility to IBD was reported in some investigations.[61,66]

Fecal Microbiota Transplantation (FMT)

Based on these studies, changes in the microbiome composition in gastrointestinal tracts are associated with susceptibility to IBD. As a potential treatment, fecal microbiota transplantation (FMT) has been proposed to restore dysbiosis. In this strategy, stool from a healthy individual is transferred to the patients with IBD. FMT is effective in treating up to 90% of those with *Clostridium difficile (C. difficile)*-related recurrent diarrhea.[67] Following FMT in two children affected by mild and moderate UC, improvements in clinical conditions were noted, and ecological analysis showed that the diversity and phylogenetic distance of the microbiota increased. This increase was mostly caused by the inherited strains of *Collinsella aerofaciens* and *Eubacterium biforme* from the respective donors. Additionally, the patient's condition improved when *Proteus* and *Blautia producta* levels dropped and *Parabacteroides, Mogibacteriaceae, Bacteroides eggerthi, Bacteroides plebeius, Ruminococcus bromii*, and *Bacteroides ovatus* levels rose.[68] Within animal models that contain human microbiota, FMT intervention can improve body weight, colon weight, and colon length while decreasing the expression of certain cytokines and the colon's oxidative condition. Additionally, gut microbiota were restored by reducing the relative quantity of *Bacteroidetes* and *Proteobacteria* and raising the abundance of *Firmicutes*. A decrease in *Helicobacter*, *Bacteroides* and *Clostridium* and an increase in *Lactobacillus*, *Butyricicoccus, Lachnoclostridium, Olsenella*, and *Odoribacter* were also reported.[69] Additional consideration must be given to secondary infection when administering FMT to individuals with IBD. There are still significant issues to be resolved regarding ideal stool preparation, administration methods, frequency, and donor and recipient characteristics.[70]

The Role of Vit D in IBD

According to epidemiological studies, known genetic variations only account for a portion of the variation in disease occurrence, suggesting that environmental factors like Vit D have a substantial impact.[71] In addition to Vit D, Zinc, iron, and B12 Vit are the most common micronutrient deficiencies seen in IBD patients that contribute to disease severity.[72]

Vit D

Vit D, which is a fat-soluble vitamin, has two chemical forms: cholecalciferol (Vit D3) and ergocalciferol (Vit D2). There are two main ways to obtain Vit D by consuming foods (fatty fish, mushrooms, dairy products, and supplements) or by exposing the skin to ultraviolet B (UVB) rays, which convert 7-dehydrocholesterol in the skin to cholecalciferol. Following the transport of Vit D in the liver and transforming to 25(OH)D (25-hydroxyvitamin D) and hydroxylation in the kidneys, an active form of Vit D (calcitriol) is obtained. The Vit D performs its functions through the nuclear Vit D receptor (VDR), which is expressed in numerous tissues including colon, small intestines, skin, parathyroid gland, and adipocyte.[73]

The appropriate level of Vit D in the blood is a matter of debate. The Institute of Medicine (IOM) states that a minimum Vit D blood level of 20 ng/ml (50 nmol/L) is sufficient. When the 25(OH)D blood level is less than 12 ng/ml (30 nmol/L), the risk of Vit D deficiency is considered.[74,75] Despite the long-standing role of Vit D as a key regulator of calcium and phosphorus metabolism and

bone health, it is also known to have other physiological functions, including regulation of the immune system, especially innate immunity.[71,76] Deficiency of Vit D was reported in several diseases such as cancer, autoimmune diseases, cardiovascular diseases and hypertension, infectious diseases, type 2 diabetes and metabolic syndrome.[73] Among autoimmune illnesses, a recent assessment has shown an inverse relationship between Vit D level and susceptibility to CD, UC, Systemic lupus erythematosus (SLE), psoriasis, Multiple sclerosis (MS) and Rheumatoid arthritis (RA).[77]

Table 1. Relationship Between Vit D and Gut Microbiota

Authors	Study Design	Conclusion	Reference
Wang et al	Genome-wide association study (GWAS) of the gut microbiota using two cohorts from northern Germany totaling 1,812 individuals	Vit D status and its receptor alter the gut microbiome's composition.	87
Singh et al	Measuring serum Vit D levels and gut microbiota composition using ELISA and 16S rRNA gene sequencing	Vit D consumption was associated with an increase in the Bacteroidetes to Firmicutes ratio and enrichment of probiotic taxa Akkermansia and Bifidobacterium	88
Jin et al.	Pyro sequencing of 454 fecal and cecal stool samples from Vdr knockout (Vdr(-/-)) and wild-type mice	In absence of Vit D, Lactobacillus was decreased, whereas *Clostridium* and *Bacteroides* were increased in the fecal stool of Vdr(-/-) mice	89
Schäffler et al	Evaluation of intestinal bacterial composition using 16S ribosomal RNA gene amplicon sequencing	Vit D3 treatment changed the composition of the gut microbiota only in CD patients who were in remission and not in healthy individuals	90
Garg et al	Evaluation of intestinal bacterial composition using 16S ribosomal RNA gene sequencing	Following treatment with Vit D, *Enterobacteriaceae* became prevalent in persons with UC, while *E. coli* and *Fusobacterium nucleatum* did not alter significantly.	91
Soltys et al	Evaluation of relationship between then seasonal serum Vit D level to the microbial composition of IBD patients using HPLC and 16S rRNA sequencing	In UC and CD patients, a decrease in serum Vit D levels during the winter/spring season was reported that led to a reduction of microbiota composition	92
Jones et al	Assessment of serum LDL and Vit D over the 9-week intervention by biochemistry analyzer and RIA	Oral administration of the bile salt hydrolase (BSH)-active *Lactobacillus reuteri* elevated serum Vit D by increasing either the synthesis of 7-dehydrocholesterol (7-DHC) or intraluminal lactic acid	93

Vit D in IBD

A review of the literature indicated that Vit D plays an important role in the pathogenesis and treatment of inflammatory bowel disease.[78] Unmeasured variables could be confounder factors (genetic background, smoking, alcohol consumption and physical activity) that play a role in the relationship between Vit D levels and IBD activity. Between 16 and 95% of IBD patients have inadequate levels of Vit D.[79] Moreover, epidemiological research showed that IBD was more common in areas with lower sunlight exposure and levels of natural Vit D production than in areas with higher levels of these factors.[71] An analysis of a multicenter IBD cohort found that low level of serum 25(OH) D3 (<50 nmol/L) was associated with an increased risk of hospitalization and surgery.[80] Several characteristics of IBD, including its initiation, activity, requirement for hospitalization, and risk of malignant transformation, have been linked to Vit D insufficiency.[71,76] The association between low Vit D levels and the chances of clinically active disease, mucosal inflammation, clinical relapse, and negative quality of life scores among 8316 IBD patients was assessed in the meta-analysis by Gubatan et al.[81] When VDR was also knocked out, IBD developed rapidly and severely.[82] Similar to humans, Vit D-deficient mice frequently exhibit diarrhea, wasting disease, and eventual death, whereas Vit D-sufficient ones might not show any indications of IBD. In IBD mouse models, reduction of TNF-α and colitis suppression was seen with exogenous Vit D treatment or a VDR agonist administration.[83] Thus, Vit D supplementation has been recommended as a complementary therapy for IBD.[80,84] It could be a valuable supplementary therapy that decreases markers of inflammation including high-sensitivity C-reactive protein (hs-CRP) and erythrocyte sedimentation rate (ESR), the Th1 immune response, and the clinical disease activity index.[84,85] In routine therapy for individuals with IBD, the status of VDR should be considered. Vit D supplementation could not act as intended in patients with IBD who have genetic VDR mutations or VDR malfunction in their biological roles.[74] Various methodologies, limited patient cohorts, various sunlight exposures or daytime hours, uneven inclusion of suitable control groups, and varied definitions of deficiency may all contribute to differences in reported rates of Vit D advantage.[86]

Vit D and Gut Microbiota

Numerous in vivo investigations have demonstrated a clear link between gut microbiota colonization and Vit D administration. It has been demonstrated that Vit D status and its receptor alter the gut microbiome's composition.[87] Studies on rodents show that Vit D deficiency caused by dietary restriction, the absence of CYP27B1 (an enzyme that produces an active form of Vit D3), or the absence of VDR, encourage the growth of the Bacteriodetes and Proteobacteria phyla.[42,71] Vit D consumption was associated with an increase in the *Bacteroidetes* to *Firmicutes* ratio and enrichment of probiotic taxa *Akkermansia* and *Bifidobacterium* (known as health-promoters).[88] A drop in Lactobacillus and an increase in *Clostridium* and *Bacteroides* were seen in individuals who

had VDR downregulation or who were unable to synthesize the active form of Vit D.[74,89] According to Schaffler et al. study, Vit D3 treatment changed the composition of the gut microbiota only in CD patients who were in remission and not in healthy individuals.[90] In another study, after increasing Vit D supplement, there were no differences in alpha diversity between groups before and after Vit D supplementation and just *Ruminococcus gnavus* showed a little decrease. Additionally, following treatment with Vit D, *Enterobacteriaceae* became prevalent in persons with UC, while *E. coli* and *Fusobacterium nucleatum* did not alter significantly.[91] The potential relationship between the seasonal variations in the microbiota and serum Vit D levels was examined in another study. In UC and CD patients, a decrease in serum Vit D levels during the winter/spring season was reported that led to a reduction of microbiota composition.[92] The role of Vit D3 in regulating gut microbiota in IBD in humans is still not fully understood.

The use of probiotic microorganisms to increase Vit D levels is one advised method to lessen the severity of IBD. Probiotic treatment increases the expression and activity of VDR in the host and then attenuates intestinal inflammation. In this connection, oral administration of the bile salt hydrolase (BSH)-active *Lactobacillus reuteri* elevated serum Vit D by increasing either the synthesis of 7-dehydrocholesterol (7-DHC) or intraluminal lactic acid.[93] An increase in VDR expression of human epithelial colonic cells was also reported, following treatment with probiotics *Lactobacillus rhamnosus* strain GG and *Lactobacillus plantarum* administration.[94]

Vit D and Immune System

Through two different mechanisms, Vit D inhibits the development of IBD (Figure 3). First, Vit D modulates the immune system and suppresses inflammatory cytokines and cells. The second function of Vit D is to restrict the growth of pathogenic microbiota and alleviate chronic infections by triggering the release of antimicrobial peptides (AMPs).

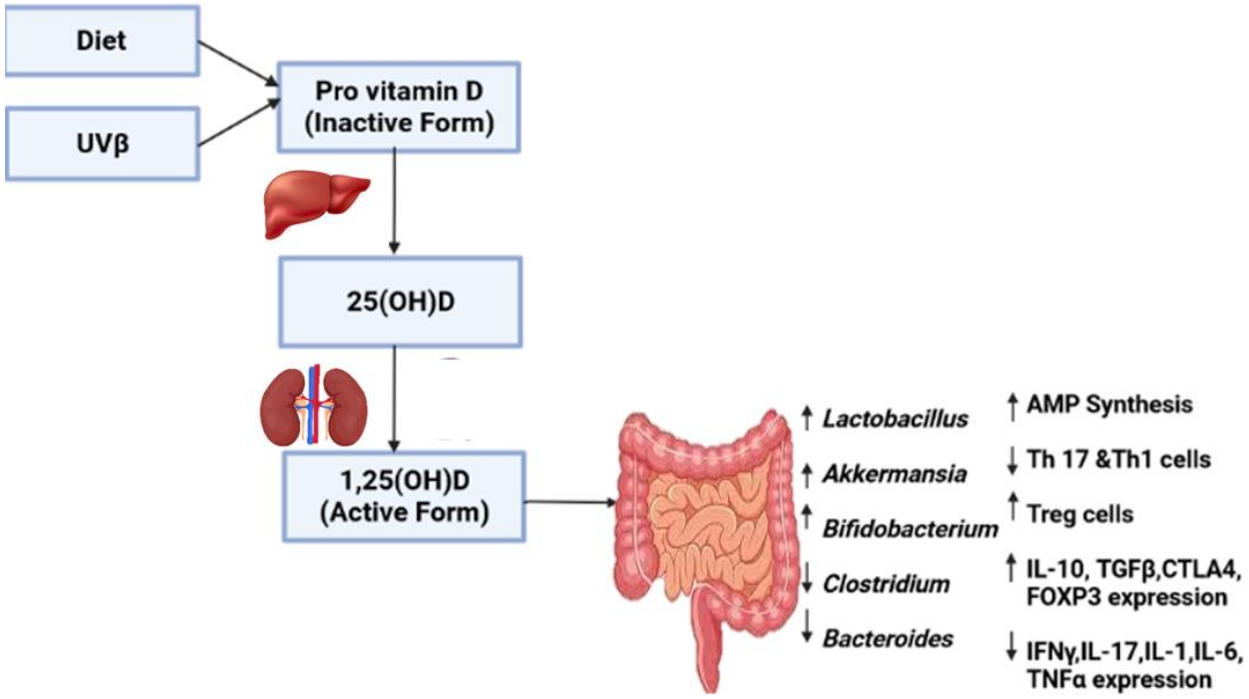

Figure 3. The Modulatory Role of Vit D on the Gastrointestinal System. Vit D is regarded as a supplementary treatment for reducing inflammation (by reducing inflammatory mediators and immune cells while increasing suppressive immune cells and regulatory cytokines). Furthermore, VitD improves the host-microbiome interaction by enhancing beneficial microbiota and decreasing pathogenic microbiota.

Nearly all immune cells, including neutrophils, active or naive $CD4^+$ and $CD8^+$ T cells, B cells, and APCs (DCs and macrophages) have been found to contain VDRs. Vit D induces Treg cell proliferation, reduces B cell development and function, and decreases monocyte activation.[95] Vit D3 down regulates the production of many proinflammatory cytokines including IL-1, IL-6, IL-8, and TNF-α, as well as macrophage chemotactic. It also inhibits the surface expression of the MHC-II-complex antigen and costimulatory molecules.[96,97] In a VDR-dependent mechanism, 1,25(OH)(2)D3 induces monocytes to less effectively react to bacterial components by lowering levels of TLR2 and TLR4.[98] The gut epithelial cells of mice with a VDR deletion developed severe clinical colitis, which was characterized by heightened Th1 and Th17 responses and an increase in IFN-γ^+, IL-17^+, and IFN-γ^+/$IL17^+$ T cells in the mucosa.[99] The ratio of Treg cells to Th17 cells is out of balance in patients with IBD, and this ratio is decreased in individuals with CD who are Vit D

deficient.[100,101] Vit D inhibits the differentiation of naïve T cells into Th1 and Th17 cells (known as inflammatory cells) while inducing Treg cell differentiation.[102] Remarkably, Treg cells have been reported to decline in UC and non-smoking CD patients who are Vit D deficient as well as in the colon mucosa of patients with IBD.[100,103] Vit D can improve Treg function by boosting the synthesis of IL-10, TGF-β, FOXP3, and cytotoxic T-lymphocyte associated protein 4 (CTLA4), which reduces inflammation.[104] In addition, restoring Vit D levels in UC patients can enhance CTLA4 expression and reduce T cell activation.[105] A Vit D-treated group in rat CD models had significantly reduced disease activity than the control group and this was followed by reduced levels of IL-17, IL17R, and Th17 cells in the colonic mucosa, suggesting that Vit D may lessen CD-induced inflammation and the disease severity.[106]

The innate immune system is another area where Vit D and gut immunity interact. In addition to bone tissue, skin epithelium, and parathyroid glands, cells in the mucosal lining of the lung and colon also synthesize Vit D. 1,25(OH)2D3 is produced when the 1 hydroxylase is activated, and then Vit D interacts with VDR to cause the synthesis of AMPs. Immunological and epithelial cells produce AMPs which are capable of eliminating a variety of infections.[107] As a result, particular groups of pathogenic bacteria may be inhibited in order to shape the healthy commensal gut microbiota.[108,109] In cattle and humans, Vit D can activate several β-defensin genes as well as the cathelicidin (LL-37) antimicrobial peptide gene.[110] Nucleotide-binding oligomerization domain 2 (NOD2) is one of the most crucial factors involved in the interaction between Vit D, immunological regulation and microbiota in IBD.[35] NOD2 is an intracellular receptor that binds to peptidoglycan from bacterial cell walls.[111] When Vit D and VDR interactions stimulate NOD2 transcription in paneth epithelial cells, defensin-2 and cathelicidin are expressed.[42] Due to the crucial relationship between NOD2 and VDR, the loss of VDR activities alters the microbiota recognition by NOD2 and subsequently decreases host defense by lowering the synthesis of lysozyme, cathelicidin, and the autophagy-related protein, ATG16L1.[76,112] These results imply that genetic variety, appropriate Vit D intake, interaction with NOD2 (which interacts with gut microbiota), and diversity of gut microbiome affect VDR expression.[113] In addition, VDR regulates the immune response to non-gastrointestinal infections such chlamydiosis and lowers the chance of a protracted infection with Chlamydia muridarum.[113]

The Effect of IBD on Vit D Level

On the one hand, a variety of animal models, in vitro studies, and epidemiologic evidence point to the possibility that Vit D influences the development and manifestation of IBD. On the other hand, having IBD might cause a Vit D shortage.[83] The severity of IBD symptoms was exacerbated by low Vit D levels, or did IBD cause Vit D to drop? Whatever the case, additional study is required to define the connections between Vit D and IBD. Individuals with IBD may experience Vit D deficiency due to decreased nutritional intake, physical activity, and sun exposure. Furthermore, Vit D intake is decreased as a result of abdominal pain and malabsorption, as well as disruption of the enterohepatic circulation of bile acids, which leads to the malabsorption of fat-soluble vitamins.[77,80] Due to problems with nutritional absorption, it can be difficult for IBD patients to take Vit D supplements, and additional dosages are frequently required to reach the optimal circulating level (above 20 ng/ml).

Conclusion

IBD is influenced by three key factors, including the microbiome, vitamin D, and the immune system. The diverse, massive, and heterogeneous microbiota found in many human organs is composed of bacteria, protozoa, fungi, and viruses. Active interaction between the human host and the commensal microbiota probably has important implications for health. The host gives the gut microbiota a place to live and a nutrient-rich environment, and the microbiota in turn benefits the host by creating vital vitamins and short-chain fatty acids. This dual interaction is called Symbiosis. In IBD disease, the composition of the microbial gastrointestinal is changed and the beneficial microbiome is replaced by the pathogenic microbiome. To restore dysbiosis, using FMT and probiotics have been proposed as alternative treatments. Additionally, Vit D is considered a complementary treatment for lowering inflammation and restoring symbiosis between the host and microbiome. However, modulating these parameters is thought to be an alternative therapy for IBD disorders, more research is required to fully understand the complex interactions between the microbiota, Vit D, and immune cells in IBD disorders.

Authors' Contributions

All authors contributed equally to write manuscript, critical review, and final approval of the manuscript. All authors read and approved the manuscript and all data were generated in-house.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

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References

1. Ramos GP, Papadakis KA. Mechanisms of Disease:

Inflammatory Bowel Diseases. Mayo Clin. Proc. 2019; 94(1):155-65. doi:10.1016/j.mayocp.2018.09.013
2. Cosnes J, Gower–Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 2011;140(6):1785-94. doi:10.1053/j.gastro.2011.01.055
3. Ananthakrishnan AN. Epidemiology and risk factors for IBD. Nat Rev Gastroenterol Hepatol. 2015;12(4):205-17. doi:10.1038/nrgastro.2015.34
4. Hovde Ш, Moum BA. Epidemiology and clinical course of Crohn's disease: results from observational studies. World J Gastroenterol. 2012;18(15):1723-31. doi:10.3748/wjg.v18.i15.1723
5. Loftus Jr EV. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology. 2004;126(6):1504-17. doi:10.1053/j.gastro.2004.01.063
6. Molodecky NA, Soon S, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46-54. doi:10.1053/j.gastro.2011.10.001
7. Loftus EV, Silverstein MD, Sandborn WJ, Tremaine WJ, Harmsen WS, Zinsmeister AR. Ulcerative colitis in Olmsted County, Minnesota, 1940–1993: incidence, prevalence, and survival. Gut. 2000;46(3):336-43. doi:10.1136/gut.46.3.336
8. Kelsen J, Baldassano RN. Inflammatory bowel disease: the difference between children and adults. Inflamm Bowel Dis. 2008;14(suppl_2):S9-11. doi:10.1002/ibd.20560
9. Auvin S, Molinié F, Gower-Rousseau C, Brazier F, Merle V, Grandbastien B, et al. Incidence, clinical presentation and location at diagnosis of pediatric inflammatory bowel disease: a prospective population-based study in northern France (1988-1999). J Pediatr Gastroenterol Nutr. 2005; 41(1):49-55.
10. Bernstein CN, Wajda A, Svenson LW, MacKenzie A, Koehoorn M, Jackson M, et al. The epidemiology of inflammatory bowel disease in Canada: a population-based study. Am J Gastroenterol. 2006;101(7):1559-68.
11. Gearry RB, Richardson A, Frampton CM, Collett JA, Burt MJ, Chapman BA, et al. High incidence of Crohn's disease in Canterbury, New Zealand: results of an epidemiologic study. Inflamm. Bowel Dis. 2006;12(10): 936-43. doi:10.1097/01.mib.0000231572.88806.b9
12. Devlin HB, Datta D, Dellipiani AW. The incidence and prevalence of inflammatory bowel disease in North Tees Health District. World J Surg. 1980;4:183-92. doi:10.1007/BF02393573
13. Aniwan S, Harmsen WS, Tremaine WJ, Loftus Jr EV. Incidence of inflammatory bowel disease by race and ethnicity in a population-based inception cohort from 1970 through 2010. Therap Adv Gastroenterol. 2019;12: 1-8. doi:10.1177/1756284819827692
14. Fireman Z, Grossman A, Lilos P, Eshchar Y, Theodor E, Gilat T. Epidemiology of Crohn's disease in the Jewish population of central Israel, 1970-1980. Am J Gastroenterol. 1989;84(3):255-8.
15. Canavan C, Abrams KR, Mayberry JF. Meta-analysis: mortality in Crohn's disease. Aliment Pharmacol Ther. 2007;25(8):861-70. doi:10.1111/j.1365-2036.2007.03276.x
16. Jess T, Winther KV, Munkholm P, Langholz E, Binder V. Mortality and causes of death in Crohn's disease: follow-up of a population-based cohort in Copenhagen County, Denmark. Gastroenterology. 2002;122(7):1808-14. doi:10.1053/gast.2002.33632
17. Cai Z, Wang S, Li J. Treatment of inflammatory bowel disease: a comprehensive review. Front Med. 2021;8: 765474. doi:10.3389/fmed.2021.765474
18. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. Lancet. 2017;389 (10080):1756-70.
19. Barrett JC, Lee JC, Lees CW, Prescott NJ, Anderson CA, Phillips A, et al. Genome-wide association study of ulcerative colitis identifies three new susceptibility loci, including the HNF4A region. Nat Genet. 2009;41(12): 1330-4. doi:10.1038/ng.483
20. Hugot JP, Laurent-Puig P, Gower-Rousseau C, Olson JM, Lee JC, Beaugerie L, et al. Mapping of a susceptibility locus for Crohn's disease on chromosome 16. Nature. 1996;379(6568):821-3. doi:10.1038/379821a0
21. Kuballa P, Huett A, Rioux JD, Daly MJ, Xavier RJ. Impaired autophagy of an intracellular pathogen induced by a Crohn's disease associated ATG16L1 variant. PloS One. 2008;3(10):e3391. doi:10.1371/journal.pone.0003391
22. Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science. 2006;314(5804):1461-3. doi:10.1126/science.1135245
23. Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc. 2006;81(11):1462-71. doi:10.4065/81.11.1462
24. Kaplan GG, Jackson T, Sands BE, Frisch M, Andersson RE, Korzenik J. The risk of developing Crohn's disease after an appendectomy: a meta-analysis. Am J Gastroenterol. 2008;103(11):2925-31. doi:10.1111/j.1572-0241.2008.02118.x
25. Wang Q, Xu KQ, Qin XR, Wang XY. Association between physical activity and inflammatory bowel disease risk: a meta-analysis. Dig Liver Dis. 2016; 48(12):1425-31. doi:10.1016/j.dld.2016.08.129
26. Timm S, Svanes C, Janson C, Sigsgaard T, Johannessen A, Gislason T, et al. Place of upbringing in early childhood as related to inflammatory bowel diseases in adulthood: a population-based cohort study in Northern Europe. Eur J Epidemiol. 2014;29:429-37. doi:10.1007/s10654-014-9922-3
27. Radon K, Windstetter D, Poluda AL, Mueller B, Mutius EV, Koletzko S, et al. Contact with farm animals in early life and juvenile inflammatory bowel disease: a case-control study. Pediatrics. 2007;120(2):354-61. doi:10.1542/peds.2006-3624
28. Barclay AR, Russell RK, Wilson ML, Gilmour WH, Satsangi J, Wilson DC. Systematic review: the role of breastfeeding in the development of pediatric inflammatory bowel disease. J Pediatr. 2009;155(3):421-6. doi:10.1016/j.jpeds.2009.03.017
29. Pituch-Zdanowska A, Banaszkiewicz A, Albrecht P. The role of dietary fibre in inflammatory bowel disease. Gastroenterol Rev. 2015;10(3):135-41. doi:10.5114/pg.2015.52753
30. Roberts CL, Keita EV, Duncan SH, O'Kennedy N, Suderholm JD, Rhodes JM, et al. Translocation of Crohn's disease Escherichia coli across M-cells: contrasting effects of soluble plant fibres and emulsifiers. Gut. 2010;59 (10):1331-9. doi:10.1136/gut.2009.195370
31. Ananthakrishnan AN, Khalili H, Konijeti GG, Higuchi LM, De Silva P, Korzenik JR, et al. A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis. Gastroenterology. 2013; 145(5):970-7. doi:10.1053/j.gastro.2013.07.050
32. Osman MA, Neoh HM, Ab Mutalib NS, Chin SF, Jamal R. 16S rRNA gene sequencing for deciphering the colorectal cancer gut microbiome: current protocols and workflows.

Front Microbiol. 2018;9:767. doi:10.3389/fmicb.2018.00767
33. Kohl KD, Dearing MD, Bordenstein SR. Microbial communities exhibit host species distinguishability and phylosymbiosis along the length of the gastrointestinal tract. Mol Ecol. 2018;27(8):1874-83. doi:10.1111/mec.14460
34. Gensollen T, Iyer SS, Kasper DL, Blumberg RS. How colonization by microbiota in early life shapes the immune system. Science. 2016;352(6285):539-44. doi:10.1126/science.aad9378
35. Bäckhed F, Fraser CM, Ringel Y, Sanders ME, Sartor RB, Sherman PM, et al. Defining a healthy human gut microbiome: current concepts, future directions, and clinical applications. Cell Host Microbe. 2012;12(5):611-22. doi:10.1016/j.chom.2012.10.012
36. Manichanh C, Borruel N, Casellas F, Guarner F. The gut microbiota in IBD. Nat Rev Gastroenterol Hepatol. 2012;9(10):599-608.
37. Wu GD, Bushmanc FD, Lewis JD. Diet, the human gut microbiota, and IBD. Anaerobe. 2013;24:117-20. doi:10.1016/j.anaerobe.2013.03.011
38. Lopetuso LR, Scaldaferri F, Franceschi F, Gasbarrini A. The gastrointestinal microbiome–functional interference between stomach and intestine. Best Pract Res Clin Gastroenterol. 2014;28(6):995-1002. doi:10.1016/j.bpg.2014.10.004
39. Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, et al. Enterotypes of the human gut microbiome. Nature. 2011;473(7346):174-80. doi:10.1038/nature09944
40. Rinninella E, Raoul P, Cintoni M, Franceschi F, Miggiano GA, Gasbarrini A, et al. What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases. Microorganisms. 2019;7(1):14. doi:10.3390/microorganisms7010014
41. Caporaso JG, Lauber CL, Costello EK, Berg-Lyons D, Gonzalez A, Stombaugh J, et al. Moving pictures of the human microbiome. Genome Biol. 2011;12:R50. doi:10.1186/gb-2011-12-5-r50
42. Matsuoka K, Kanai T. The gut microbiota and inflammatory bowel disease. Seminars in immunopathology. Springer Berlin Heidelberg. 2015;37:47-55. doi:10.1007/s00281-014-0454-4
43. Caporaso JG, Lauber CL, Costello EK, Berg-Lyons D, Gonzalez A, Stombaugh J, et al. Moving pictures of the human microbiome. Genome Biol. 2011;12:R50. doi:10.1186/gb-2011-12-5-r50
44. Guo X, Huang C, Xu J, Xu H, Liu L, Zhao H, et al. Gut microbiota is a potential biomarker in inflammatory bowel disease. Front Nutr. 2022;8:818902. doi:10.3389/fnut.2021.818902
45. Lucas López R, Grande Burgos MJ, Gálvez A, Pérez Pulido R. The human gastrointestinal tract and oral microbiota in inflammatory bowel disease: a state of the science review. Apmis. 2017;125(1):3-10. doi:10.1111/apm.12609
46. Sokol H, Seksik P, Furet JP, Firmesse O, Nion-Larmurier I, Beaugerie L, et al. Low counts of *Faecalibacterium prausnitzii* in colitis microbiota. Inflamm. Bowel Dis. 2009;15(8):1183-9. doi:10.1002/ibd.20903
47. Sokol H, Pigneur B, Watterlot L, Lakhdari O, Bermúdez-Humarán LG, Gratadoux JJ, et al. *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci U S A. 2008;105(43):16731-6. doi:10.1073/pnas.0804812105
48. Mahalhal A, Williams JM, Johnson S, Ellaby N, Duckworth CA, Burkitt MD, et al. Oral iron exacerbates colitis and influences the intestinal microbiome. PloS One. 2018;13(10):e0202460. doi:10.1371/journal.pone.0202460
49. Munyaka PM, Sepehri S, Ghia JE, Khafipour E. Carrageenan gum and adherent invasive *Escherichia coli* in a piglet model of inflammatory bowel disease: impact on intestinal mucosa-associated microbiota. Front Microbiol. 2016;7:462. doi:10.3389/fmicb.2016.00462
50. Zou J, Liu C, Jiang S, Qian D, Duan J. Cross talk between gut microbiota and intestinal mucosal immunity in the development of ulcerative colitis. Infect Immun. 2021;89(9):e0001421. doi:10.1128/iai.00014-21
51. Vich Vila A, Imhann F, Collij V, Jankipersadsing SA, Gurry T, Mujagic Z, et al. Gut microbiota composition and functional changes in inflammatory bowel disease and irritable bowel syndrome. Sci Transl Med. 2018;10(472):eaap8914. doi:10.1126/scitranslmed.aap8914
52. Pittayanon R, Lau JT, Leontiadis GI, Tse F, Yuan Y, Surette M, et al. Differences in gut microbiota in patients with vs without inflammatory bowel diseases: a systematic review. Gastroenterology. 2020;158(4):930-46. doi:10.1053/j.gastro.2019.11.294
53. Ma Y, Zhang Y, Jiang H, Xiang S, Zhao Y, Xiao M, et al. Metagenome analysis of intestinal bacteria in healthy people, patients with inflammatory bowel disease and colorectal cancer. Front Cell Infect Microbiol. 2021;11:599734. doi:10.3389/fcimb.2021.599734
54. Zhong W, Lu X, Shi H, Zhao G, Song Y, Wang Y, et al. Distinct microbial populations exist in the mucosa-associated microbiota of diarrhea predominant irritable bowel syndrome and ulcerative colitis. J Clin Gastroenterol. 2019;53(9):660-72. doi:10.1097/MCG.0000000000000961
55. Virgin HW. The virome in mammalian physiology and disease. Cell. 2014;157(1):142-50. doi:10.1016/j.cell.2014.02.032
56. Suttle CA. Viruses in the sea. Nature. 2005;437(7057):356-61. doi:10.1038/nature04160
57. Barr JJ, Auro R, Furlan M, Whiteson KL, Erb ML, Pogliano J, et al. Bacteriophage adhering to mucus provide a non–host-derived immunity. Proc Natl Acad Sci U S A. 2013;110(26):10771-6. doi:10.1073/pnas.1305923110
58. Norman JM, Handley SA, Baldridge MT, Droit L, Liu CY, Keller BC, et al. Disease-specific alterations in the enteric virome in inflammatory bowel disease. Cell. 2015;160(3):447-60. doi:10.1016/j.cell.2015.01.002
59. Roach DR, Leung CY, Henry M, Morello E, Singh D, Di Santo JP, et al. Synergy between the host immune system and bacteriophage is essential for successful phage therapy against an acute respiratory pathogen. Cell Host Microbe. 2017;22(1):38-47. doi:10.1016/j.chom.2017.06.018
60. Gogokhia L, Buhrke K, Bell R, Hoffman B, Brown DG, Hanke-Gogokhia C, et al. Expansion of bacteriophages is linked to aggravated intestinal inflammation and colitis. Cell Host Microbe. 2019;25(2):285-99. doi:10.1016/j.chom.2019.01.008
61. Underhill DM, Braun J. Fungal microbiome in inflammatory bowel disease: a critical assessment. J Clin Invest. 2022;132(5).e155786. doi:10.1172/JCI155786
62. Qiu X, Ma J, Jiao C, Mao X, Zhao X, Lu M, et al. Alterations in the mucosa-associated fungal microbiota in patients with ulcerative colitis. Oncotarget. 2017;8(64):107577-88. doi:10.18632/oncotarget.22534
63. Nelson A, Stewart CJ, Kennedy NA, Lodge JK, Tremelling M, UK IBD Genetics Consortium, et al. The impact of NOD2 genetic variants on the gut mycobiota in Crohn's disease patients in remission and in individuals without gastrointestinal inflammation. J Crohns Colitis.

2021;15(5):800-12. doi:10.1093/ecco-jcc/jjaa220
64. Imai T, Inoue R, Kawada Y, Morita Y, Inatomi O, Nishida A, et al. Characterization of fungal dysbiosis in Japanese patients with inflammatory bowel disease. J Gastroenterol. 2019;54:149-59. doi:10.1007/s00535-018-1530-7
65. Sokol H, Leducq V, Aschard H, Pham HP, Jegou S, Landman C, et al. Fungal microbiota dysbiosis in IBD. Gut. 2017;66(6):1039-48. doi:10.1136/gutjnl-2015-310746
66. Limon JJ, Tang J, Li D, Wolf AJ, Michelsen KS, Funari V, et al. Malassezia is associated with Crohn's disease and exacerbates colitis in mouse models. Cell Host Microbe. 2019;25(3):377-88. doi:10.1016/j.chom.2019.01.007
67. Blanchaert C, Strubbe B, Peeters H. Fecal microbiota transplantation in ulcerative colitis. Acta Gastro-Enterol Belg. 2019;82(4):519-28.
68. Quagliariello A, Del Chierico F, Reddel S, Russo A, Onetti Muda A, D'Argenio P, et al. Fecal microbiota transplant in two ulcerative colitis pediatric cases: gut microbiota and clinical course correlations. Microorganisms. 2020;8(10):1486. doi:10.3390/microorganisms8101486
69. Zhang W, Zou G, Li B, Du X, Sun Z, Sun Y, et al. Fecal microbiota transplantation (FMT) alleviates experimental colitis in mice by gut microbiota regulation. J Microbiol Biotechnol. 2020;30(8):1132-41. doi:10.4014/jmb.2002.02044
70. Cheng YW, Fischer M. Fecal microbiota transplantation for ulcerative colitis. Are we ready for primetime?. Gastroenterol Clin. 2020;49(4):739-52. doi:10.1016/j.gtc.2020.08.006
71. Mouli VP, Ananthakrishnan AN. vitamin D and inflammatory bowel diseases. Aliment Pharmacol Ther. 2014;39(2):125-36. doi:10.1111/apt.12553
72. Rocha R, Sousa UH, Reis TL, Santana GO. Nutritional status as a predictor of hospitalization in inflammatory bowel disease: A review. World J Gastrointest Pharmacol Ther. 2019;10(2):50-6. doi:10.4292/wjgpt.v10.i2.50
73. Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord. 2017;18:153-65. doi:10.1007/s11154-017-9424-1
74. Battistini C, Ballan R, Herkenhoff ME, Saad SM, Sun J. Vitamin D modulates intestinal microbiota in inflammatory bowel diseases. Int J Mol Sci. 2020;22(1):362. doi:10.3390/ijms22010362
75. Del Valle HB, Yaktine AL, Taylor CL, Ross AC, editors. Dietary reference intakes for calcium and vitamin D; 2011.
76. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: modulator of the immune system. Curr Opin Pharmacol. 2010;10(4):482-96. doi:10.1016/j.coph.2010.04.001
77. Szodoray P, Nakken B, Gaal J, Jonsson R, Szegedi A, Zold E, et al. The complex role of vitamin D in autoimmune diseases. Scand J Immunol. 2008;68(3):261-9. doi:10.1111/j.1365-3083.2008.02127.x
78. Fletcher J, Cooper SC, Ghosh S, Hewison M. The role of vitamin D in inflammatory bowel disease: mechanism to management. Nutrients. 2019;11(5):1019. doi:10.3390/nu11051019
79. Mouli VP, Ananthakrishnan AN. vitamin D and inflammatory bowel diseases. Aliment Pharmacol Ther. 2014;39(2):125-36. doi:10.1111/apt.12553
80. Ananthakrishnan AN, Cagan A, Gainer VS, Cai T, Cheng SC, Savova G, et al. Normalization of plasma 25-hydroxy vitamin D is associated with reduced risk of surgery in Crohn's disease. Inflamm. Bowel Dis. 2013;19(9):1921-7. doi:10.1097/MIB.0b013e3182902ad9
81. Gubatan J, Chou ND, Nielsen OH, Moss AC. Systematic review with meta-analysis: association of vitamin D status with clinical outcomes in adult patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2019;50(11-12):1146-58. doi:10.1111/apt.15506
82. Limketkai BN, Mullin GE, Limsui D, Parian AM. Role of vitamin D in inflammatory bowel disease. Nutr Clin Pract. 2017;32(3):337-45. doi:10.1177/0884533616674492
83. Fletcher J, Cooper SC, Ghosh S, Hewison M. The role of vitamin D in inflammatory bowel disease: mechanism to management. Nutrients. 2019;11(5):1019. doi:10.3390/nu11051019
84. Guzman-Prado Y, Samson O, Segal JP, Limdi JK, Hayee BH. Vitamin D therapy in adults with inflammatory bowel disease: a systematic review and meta-analysis. Inflamm. Bowel Dis. 2020;26(12):1819-30. doi:10.1093/ibd/izaa087
85. 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. 2019;127(10):681-7. doi:10.1111/apm.12982
86. Ghaly S, Lawrance I. The role of vitamin D in gastrointestinal inflammation. Expert Rev Gastroenterol Hepatol. 2014;8(8):909-23. doi:10.1586/17474124.2014.925796
87. Wang J, Thingholm LB, Skiecevičienė J, Rausch P, Kummen M, Hov JR, et al. Genome-wide association analysis identifies variation in vitamin D receptor and other host factors influencing the gut microbiota. Nat Genet. 2016;48(11):1396-406. doi:10.1038/ng.3695
88. Singh P, Rawat A, Alwakeel M, Sharif E, Al Khodor S. The potential role of vitamin D supplementation as a gut microbiota modifier in healthy individuals. Sci Rep. 2020;10(1):21641. doi:10.1038/s41598-020-77806-4
89. Jin D, Wu S, Zhang YG, Lu R, Xia Y, Dong H, et al. Lack of vitamin D receptor causes dysbiosis and changes the functions of the murine intestinal microbiome. Clin Ther. 2015;37(5):996-1009. doi:10.1016/j.clinthera.2015.04.004
90. Schäffler H, Herlemann DP, Klinitzke P, Berlin P, Kreikemeyer B, Jaster R, et al. Vitamin D administration leads to a shift of the intestinal bacterial composition in Crohn's disease patients, but not in healthy controls. J Dig Dis. 2018;19(4):225-34. doi:10.1111/1751-2980.12591
91. 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. doi:10.1093/ecco-jcc/jjy052
92. Soltys K, Stuchlikova M, Hlavaty T, Gaalova B, Budis J, Gazdarica J, et al. Seasonal changes of circulating 25-hydroxyvitamin D correlate with the lower gut microbiome composition in inflammatory bowel disease patients. Sci Rep. 2020;10(1):6024. doi:10.1038/s41598-020-62811-4
93. Jones ML, Martoni CJ, Prakash S. Oral supplementation with probiotic *L. reuteri* NCIMB 30242 increases mean circulating 25-hydroxyvitamin D: a post hoc analysis of a randomized controlled trial. J Clin Endocrinol Metab. 2013;98(7):2944-51. doi:10.1210/jc.2012-4262
94. Yoon SS, Sun J. Probiotics, nuclear receptor signaling, and anti-inflammatory pathways. Gastroent Res Pract. 2011;2011(1):971938. doi:10.1155/2011/971938
95. Wu Z, Liu D, Deng F. The role of vitamin D in immune system and inflammatory bowel disease. J Inflamm Res. 2022:3167-85.
96. Sun J. Vitamin D and mucosal immune function. Curr

Opin Gastroen. 2010;26(6):591-5. doi:10.1097/MOG.0b013e32833d4b9f
97. Ardesia M, Ferlazzo G, Fries W. Vitamin D and inflammatory bowel disease. BioMed Res Int. 2015; 2015(1):470805. doi:10.1155/2015/470805
98. Sadeghi K, Wessner B, Laggner U, Ploder M, Tamandl D, Friedl J, et al. Vitamin D3 down-regulates monocyte TLR expression and triggers hyporesponsiveness to pathogen-associated molecular patterns. Eur J Immunol. 2006;36(2):361-70. doi:10.1002/eji.200425995
99. He L, Liu T, Shi Y, Tian F, Hu H, Deb DK, et al. Gut epithelial vitamin D receptor regulates microbiota-dependent mucosal inflammation by suppressing intestinal epithelial cell apoptosis. Endocrinology. 2018; 159(2):967-79. doi:10.1210/en.2017-00748
100. Schardey J, Globig AM, Janssen C, Hofmann M, Manegold P, Thimme R, et al. Vitamin D inhibits pro-inflammatory T cell function in patients with inflammatory bowel disease. J Crohns Colitis. 2019;13 (12):1546-57. doi:10.1093/ecco-jcc/jjz090
101. Yang Y, Cui X, Li J, Wang H, Li Y, Chen Y, et al. Clinical evaluation of vitamin D status and its relationship with disease activity and changes of intestinal immune function in patients with Crohn's disease in the Chinese population. Scand J Gastroenterol. 2021;56(1):20-9. doi:10.1080/00365521.2020.1844793
102. Zhou Q, Qin S, Zhang J, Zhon L, Pen Z, Xing T. 1, 25 (OH) 2D3 induces regulatory T cell differentiation by influencing the VDR/PLC-γ1/TGF-β1/pathway. Mol Immunol. 2017;91:156-64. doi:10.1016/j.molimm.2017.09.006
103. Liu Z, Feng BS, Yang SB, Chen X, Su J, Yang PC. Interleukin (IL)-23 suppresses IL-10 in inflammatory bowel disease. J Biol Chem. 2012;287(5):3591-7. doi:10.1074/jbc.M111.304949
104. Littman DR, Rudensky AY. Th17 and regulatory T cells in mediating and restraining inflammation. Cell. 2010;140 (6):845-58. doi:10.1016/j.cell.2010.02.021
105. Sharifi A, Vahedi H, Honarvar MR, Alipoor B, Nikniaz Z, Rafiei H, et al. Vitamin D increases CTLA-4 gene expression in patients with mild to moderate ulcerative colitis. Middle East J Dig Dis. 2019;11(4):199-204. doi:10.15171/mejdd.2019.149
106. Xia Y, Chen H, Xiao H, Yang J, Li Z, Wang Y, et al. Immune regulation mechanism of vitamin D level and IL-17/IL-17R pathway in Crohn's disease. Exp Ther Med. 2019;17(5):3423-8. doi:10.3892/etm.2019.7389
107. Lehrer RI, Ganz T. Cathelicidins: a family of endogenous antimicrobial peptides. Curr Opin Hematol. 2002;9(1):18-22.
108. Ramos GP, Papadakis KA. Mechanisms of disease: inflammatory bowel diseases. Mayo Clin Proc. 2019; 94(1):155-65. doi:10.1016/j.mayocp.2018.09.013
109. Hewison M. Antibacterial effects of vitamin D. Nat Rev Endocrinol. 2011;7(6):337-45. doi:10.1038/nrendo.2010.226
110. Guo C, Sinnott B, Niu B, Lowry MB, Fantacone ML, Gombart AF. Synergistic induction of human cathelicidin antimicrobial peptide gene expression by vitamin D and stilbenoids. Mol Nutr Food Res. 2014;58(3):528-36. doi:10.1002/mnfr.201300266
111. Strober W, Watanabe T. NOD2, an intracellular innate immune sensor involved in host defense and Crohn's disease. Mucosal Immunol. 2011;4(5):484-95. doi:10.1038/mi.2011.29
112. Wang Q, Wang K, Wu W, Giannoulatou E, Ho JW, Li L. Host and microbiome multi-omics integration: applications and methodologies. Biophys Rev. 2019;11 (1):55-65. doi:10.1007/s12551-018-0491-7
113. He Q, Ananaba GA, Patrickson J, Pitts S, Yi Y, Yan F, et al. Chlamydial infection in vitamin D receptor knockout mice is more intense and prolonged than in wild-type mice. J Steroid Biochem Mol Biol. 2013;135:7-14. doi:10.1016/j.jsbmb.2012.11.002