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**Protective links between vitamin D, inflammatory bowel disease, and colon cancer**

Meeker S *et al*. Vitamin D, IBD, and colon cancer

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**Abstract**

Vitamin D deficiency has been associated with a wide range of diseases and multiple forms of cancer including breast, colon, and prostate cancers. Relatively recent work has demonstrated vitamin D to be critical in immune function and therefore important in inflammatory diseases such as inflammatory bowel disease (IBD). Because vitamin D deficiency or insufficiency is increasingly prevalent around the world, with an estimated 30%-50% of children and adults at risk for vitamin D deficiency worldwide, it could have a significant impact on IBD. Epidemiologic studies suggest that low serum vitamin D levels are a risk factor for IBD and colon cancer, and vitamin D supplementation is associated with decreased colitis disease activity and/or alleviated symptoms. Patients diagnosed with IBD have a higher incidence of colorectal cancer than the general population, which supports the notion that inflammation plays a key role in cancer development and underscores the importance of understanding how vitamin D influences inflammation and its cancer-promoting effects. In addition to human epidemiological data, studies utilizing mouse models of colitis have shown that vitamin D is beneficial in preventing or ameliorating inflammation and clinical disease. The precise role of vitamin D on colitis is unknown; however, vitamin D regulates immune cell trafficking and differentiation, gut barrier function and antimicrobial peptide synthesis, all of which may be protective from IBD and colon cancer. Here we focus on effects of vitamin D on inflammation and inflammation-associated colon cancer and discuss the potential use of vitamin D for protection and treatment of IBD and colon cancer.

**Key words:** Vitamin D; Inflammatory bowel disease; Colitis; Colon Cancer; Inflammation-associated colon cancer; Mouse models

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**Core tip:** Vitamin D is inversely related to inflammation-associated diseases such as inflammatory bowel disease (IBD) and colon cancer. As vitamin D deficiency and insufficiency are prevalent worldwide, it can significantly impact risk and progression of these diseases. Here we provide an overview of human epidemiologic and animal studies linking vitamin D, IBD and colon cancer. We also review potential mechanisms of vitamin D action that were elucidated by using animal models. Finally, we address current knowledge gaps in this field of research to help determine the potential benefits and risks of using vitamin D to prevent and/or treat IBD and cancer.

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**Introduction**

Vitamin D is primarily known for its role in regulation of bone metabolism by controlling intestinal calcium absorption[1-3] and bone remodeling[4], the importance of which is demonstrated by prolonged vitamin D deficiency resulting in delayed growth and rickets in children[1] as well as osteoporosis and osteopenia in adults[5]. In addition to its role in bone metabolism, it has become increasingly apparent that vitamin D participates in a variety of other physiological functions, including immune responses. Consequently, vitamin D deficiency is also associated with a wide range of diseases including: asthma[6], multiple sclerosis[7], rheumatoid arthritis[8], type 1 diabetes[9,10], heart disease[11,12], depression[13,14], and tuberculosis[15]. For our interests, epidemiologic studies link low serum vitamin D levels with an increased risk of developing inflammatory bowel disease (IBD) and colon cancer[16-22]. As vitamin D deficiency or insufficiency is increasingly prevalent around the world, with estimates of 30-50% of children and adults at risk of vitamin D deficiency worldwide[3], it could significantly influence incidence and progression of IBD and colon cancer. In this paper, we will review current evidence linking vitamin D, IBD, and colitis-associated colon cancer (CAC) and summarize the potential benefits and risks of using vitamin D to prevent or treat these diseases. Several reviews have been published recently concerning vitamin D and the immune system[18,23-26] and cancer[19,27,28].

**OVERVIEW OF IBD, CAC, AND VITAMIN D**

IBD is a group of diseases characterized as chronic remittent or progressive inflammation of the gastrointestinal tract. The two primary conditions in humans are Crohn’s Disease (CD) and ulcerative colitis (UC), and the prevalence of both conditions have been increasing in western countries over the past 50 years with CD affecting 50-200/100000 people and UC affecting 120-200/100000 people per year[29]. Though the precise etiology underlying IBD remains unclear, dysregulation of the mucosal immune system in response to enteric antigens is believed to be one of the initiators of the chronic inflammation[30]. Patients diagnosed with IBD are at increased risk for developing CAC compared to the general population, especially if the colitis is not well controlled[30-32]. Inflammation is believed to play a role in the development of CAC through promotion of angiogenesis, tumor-promoting cytokine production, tumor cell invasive behavior, cellular proliferation and alterations in immune responses[33]. Treatments to limit inflammation may be beneficial in reducing the incidence of CAC in these high-risk populations[34]. Because vitamin D has been shown to alter many of the pathways involved in inflammation as well as tumorigenesis, the potential to use vitamin D supplementation as an adjunct therapy in IBD patients is being explored[35-38].

We have recently shown that dietary vitamin D supplementation provides protection against IBD and subsequent inflammation-induced colon cancer in the *Smad3-/-* mouse model of CAC[39]. Our data suggest that the chemoprotective effect of vitamin D is likely due to decreased colitis prior to tumor development. Our findings are consistent with other studies demonstrating association between vitamin D supplementation and decreased colitis, disease activity and/or alleviated symptoms of IBD in both mice[39-42] and humans[21,36,37]. Additionally, both our work and others have demonstrated that vitamin D decreases the incidence of dysplasia, a precursor to cancer, in models of IBD-associated colon cancer[39,42,43]. These data support the notion that vitamin D may be a beneficial adjunct therapy for IBD and CAC. Because there is currently no cure for IBD, patients typically require long-term immunomodulatory drug therapy to manage their symptoms with substantial economic costs over their lifetime[44]. The use of vitamin D as a treatment in patients with IBD would be simple and inexpensive to implement. However, the specific mechanisms through which vitamin D ameliorates colitis remain unknown though vitamin D has been shown to regulate immune cell trafficking and differentiation, gut barrier function, and antimicrobial peptide synthesis, all of which may play a role in mediating protection from disease[45-47]. Thus, additional studies are needed to determine the patient populations that might benefit from vitamin D therapy.

**VITAMIN D METABOLISM AND SIGNALING**

To explain mechanisms by which vitamin D might influence IBD and colon cancer, we will briefly review the metabolism and actions of vitamin D. More thorough reviews on this topic can be found in recent publications[3,48].

Humans obtain the majority of their vitamin D from exposure to sunlight as UVB radiation is able to convert 7-dehydrocholesterol to vitamin D3 (cholecalciferol) in the skin (Figure 1). Diet, however, becomes an important means of obtaining vitamin D in individuals with limited exposure to sunlight, such as might occur due to insufficient exposure to natural sunlight because of residing at higher latitudes or limited amounts of time spent outdoors, or increased protection against sun exposure through clothing and/or sunscreen. Therefore, inadequate intake of foods rich in vitamin D such as oily fish, beef liver, and fortified milk products can significantly impact vitamin D status in some individuals[2,49].

Vitamin D, synthesized in the skin or taken up from the diet, undergoes two hydroxylation steps to become biologically active 1,25-dihydroxyvitamin D (1,25(OH)2D) (Figure 1). The first hydroxylation step occurs in the liver where a 25-hydroxylase (Cyp2R1 and possibly other enzymes) produces 25-hydroxyvitamin D (25(OH)D)[50,51]. This is the main circulating form of vitamin D and is most often used as an indicator of nutritional vitamin D status, both in humans and animals, as it is highly stable and has a long half-life[3]. The majority of 25-hydroxyvitamin D circulates in blood bound to either vitamin D binding protein (DBP; 85%-90% bound) or albumin (10%-15% bound) with < 1% unbound as free vitamin D[45]. The second hydroxylation-step occurs primarily in the kidney by 1α-hydroxylase (Cyp27b1) to produce active 1,25-dihydroxyvitamin D (1,25(OH)2D) (Figure 1). The active form of vitamin D can also be measured in the serum, although its concentrations do not reflect nutritional vitamin D status as the half-life is relatively short (4-20 h) and its production is highly regulated[3] by serum levels of calcium and phosphorus as well as activities of parathyroid hormone and fibroblast-like growth factor-23[3]. Both 25(OH)D and 1,25(OH)2D can also be inactivated through further hydroxylation by 24-hydroxylase (Cyp24a1), which is induced by vitamin D signaling in almost all target tissues of vitamin D[3]. More detailed information on the synthesis, uptake, and metabolism of vitamin D is reviewed in[3, 52]. Although the majority of vitamin D hydroxylation occurs in the liver (25-hydroxylation) and kidney (1α -hydroxylation), other tissues, including intestinal epithelial cells and immune cells (T and B cells, macrophages, dendritic cells), express vitamin D hydroxylase enzymes (Cyp27b1, Cyp24a1)[53,54], suggesting that these cells can regulate levels of the active hormone locally.

1,25(OH)2D elicits its effects through binding to the vitamin D receptor (VDR), a transcription factor for genes with promoters containing vitamin D response elements (VDREs)[55] (Figure 1). VDR bound by 1,25(OH)2D can recruit transcription machinery to activate a plethora of down-stream genes. Through chromatin precipitation parallel DNA sequencing studies (CHIP-seq) more than 2776 VDR binding sites have been identified throughout the human genome[56]. Interestingly, this study noted that VDR binding sites were significantly enriched near genes known to be associated with autoimmune disease and cancer, including *PTPN2,* a gene that has been implicated in CD and UC due to its important role in maintaining epithelial barrier function[56]. This suggests that expression of these genes may be decreased in people with inadequate levels of vitamin D due to reduced VDR ligand. More in-depth reviews on VDR and gene expression have been previously published[57-59].

Multiple VDR polymorphisms have been reported in humans and are associated with various diseases including IBD, cancer, asthma and obesity[60-62]. However, many of these polymorphisms occur in non-coding regions of the VDR gene and appear to have no direct consequence to the VDR protein itself, except for one polymorphism where the transcription start site is changed resulting in a shorter and more active VDR[60]. More frequently, VDR gene polymorphisms affect VDR transcription due to changes in the promoter region or 3’UTR, but the functional consequence(s) of these changes is not well defined[60]. Loss of function mutations in the VDR result in vitamin D deficiency symptoms including rickets[63]. When mutations affect VDR’s binding to its ligand, 1,25(OH)2D, symptoms are similar to vitamin D nutritional deficiency. However, when mutations affect VDR’s binding to DNA (*via* VDREs), alopecia can occur in addition to symptoms of vitamin D deficiency, suggesting that VDR has ligand-independent functions[63]. These types of mutations have been replicated in murine models[64,65], and studies using these animal models revealed that VDR can actively suppress down-stream genes when bound to VDREs without its ligand. Thus, mice with VDR mutations affecting ligand binding but maintaining DNA binding ability have more severe skeletal defects than mice with vitamin D deficiency or mice with VDR null mutations[64]. The mutated VDR, VDRgem, does not respond to endogenous VDR ligand 1,25(OH)2D but can be activated by synthetic analogs, gemini ligands. Hence, the VDRgem model may be useful in deciphering ligand-dependent and -independent roles of VDR[64]. For our interests, this mouse model could be used to determine if ligand-independent VDR function influences immune responses and thus the development of IBD/CAC and to develop drugs to target these specific functions[64].

**HUMAN EPIDEMIOLOGIC DATA ASSOCIATING SERUM VITAMIN D LEVELS, IBD, AND CAC**

It has been observed that the incidence of IBD is higher in people residing at northern latitudes compared to those at more southern latitudes both in the United States[66] and in Europe[67-69], suggesting that limited exposure to UVB and resultant decreased vitamin D levels may influence risk of IBD. In addition, lower UVB exposure and vitamin D deficiency has been associated with onset of IBD[16], increased clinical disease activity[70-73], greater rates of hospitalization, prolonged hospitalization and an increased need for bowel surgery in patients with IBD[74,75], and risk of malignant transformation[22]. Along similar lines, results from a questionnaire assessing the overall quality of life of IBD patients (141 CD and 79 UC), noted that increased serum vitamin D levels correlated with increased health-related quality of life in both CD and UC patients during winter/spring months[76]. Interestingly, VDR expression was significantly decreased in intestinal epithelial cells from IBD patients compared to healthy controls. In addition, intestinal VDR expression was lower in patients with active CD compared to those with quiescent disease despite one cohort of patients studied having “adequate” serum levels of vitamin D[77], suggesting that epithelial responses to vitamin D may be diminished during active IBD and this may not be altered by increasing serum vitamin D alone.

Similar to the findings in IBD patients, epidemiologic data demonstrate a significant north/south gradient associated with colon cancer with increasing incidence and mortality associated with reduced exposure to natural light[17,20,78]. Prospective cohort studies have demonstrated an inverse association between serum vitamin D levels [25(OH)D] and cancer development (colon, breast and prostate)[28,79,80]. Interestingly, Ananthakrishnan *et al*[22] demonstrated that within a cohort of 2809 IBD patients almost a third of the patients were vitamin D deficient. Over an eleven-year follow up period, 7% of those patients went on to develop cancer. Strikingly, the patients that went on to develop cancer had significantly lower vitamin D levels than those who did not develop cancer. It was estimated that for every 1 ng/ml increase in plasma 25(OH)D concentration, there was a 6% reduction in colorectal cancer risk[22].

Although there is a strong inverse association between serum levels of 25(OH)D and the risk for IBD/CAC, there is no consensus about what the adequate serum vitamin D should be to prevent these diseases. Historically, adequate levels of vitamin D were defined based on maintenance of calcium homeostasis without causing bone disease. However, as our knowledge of the impacts of vitamin D on human health and disease become broader, experts have sought to re-define the levels of vitamin D to provide the most protective health benefits. Unfortunately, this is much more difficult to determine as “health benefit” is hard to define. According to the Institute of Medicine, vitamin D sufficiency was determined to be ≥ 50 nmol/L serum 25(OH)D, while serum vitamin D levels of 25-50 nmol/L were classified as insufficient and < 25 nmol/L deficient[52]. In contrast, the Endocrine society defined vitamin D sufficiency as ≥ 75 nmol/L serum 25(OH)D and deficiency as < 50 nmol/L[81]. At this time, further research investigating how varied serum levels of vitamin D are related to health and disease are needed in order to better define “adequate” serum vitamin D levels.

Though the epidemiologic data suggest a link between circulating vitamin D levels and disease outcome, these studies cannot address the question as to whether vitamin D deficiency is a cause of or sequela of the disease. For these questions, animal models have been useful to address mechanisms through which vitamin D influences inflammation and cancer development.

**POTENTIAL MECHANISMS OF ACTION OF VITAMIN D IN IBD DEVELOPMENT AND PROGRESSION**

Animal models are an important and necessary tool for studying the effects of vitamin D deficiency and/or supplementation on IBD and cancer. Mouse models permit modulation of vitamin D levels while controlling for other environmental and genetic factors that may influence disease development. Tables 1 and 2 provide summaries of animal models of IBD (Table 1) and CAC (Table 2) in which the role of vitamin D with regard to disease has been addressed. Mouse models of IBD and CAC have been categorized into vitamin D supplementation, vitamin D deficiency, and animals with genetically altered VDR. Categories have been further broken down to highlight studies that show amelioration vs. exacerbation of disease. In the following section, we briefly discuss some of the important mechanisms through which vitamin D impacts IBD and CAC using the models outlined in Tables 1 and 2.

***Vitamin D – Impact on immune responses***

One mechanism through which vitamin D may impact IBD development and progression is through altering immune responses[18,26,82,83]. Multiple studies have demonstrated that T cells are both direct and indirect targets of vitamin D[84-87]. CD4+ effector T cells that lack VDR or CYP27B1 express higher concentrations of the inflammatory cytokines interleukin (IL)-17 and interferon gamma (IFNγ), proliferate more rapidly, and induce more severe colitis following adoptive transfer into naïve recipient mice, compared to WT cells. In addition, *Vdr-/-*mice fail to develop iNKT and CD8αα T cell populations, both of which are important regulatory T cell subsets necessary in the resolution of inflammation[88-90]. Treatment of T cells or mice with active vitamin D both *in vitro* and *in vivo* results in decreased proliferation of both CD4+ and CD8+ subsets as well as decreased secretion of IL-2 and IFNγ*,* resulting in decreased Th1 and Th17 responses and an overall dampening of inflammation[85,88]. In addition to affecting T cells directly, vitamin D alters inflammation by affecting antigen-presenting cells. Macrophages and dendritic cells treated with vitamin D have decreased secretion of proinflammatory cytokines following activation[91,92]. In addition, vitamin D treatment modulates dendritic cell differentiation and maturation: vitamin D-treated dendritic cells express fewer maturation markers including CD80, CD86, and MHCII and secrete less IL-12. This results in decreased dendritic cell-mediated activation and proliferation of T cells and an increase in T cells with regulatory phenotypes[92-94]. The effects of vitamin D on NK cell responses are understudied considering the role these cells have been shown to have in autoimmune disease[95] as well as their role in interacting with dendritic and T cells and modulating their responses[96]. While vitamin D has been shown to enhance cytotoxic function of human NK cell lines[97,98], vitamin D may also impair NK cell development and inflammatory cytokine expression in the presence of vitamin D[99].

***Vitamin D - Effects on intestinal barrier function***

Another mechanism through which vitamin D may protect against IBD is by improving intestinal epithelial barrier function. Patients with CD have increased intestinal barrier permeability which has been associated with inflammation and dysbiosis[100] as it results in increased exposure of the immune system to intestinal microbiota. *In vitro* studies demonstrate that vitamin D signaling is imperative for the maintenance of epithelial barrier integrity by increasing the expression of tight junction proteins including Occludin, Zo-1, Zo-2, Vinculin, and Claudin, and altering transepithelial resistance[101-104]. Interestingly, Kong *et al*[102]have demonstrated that mice lacking VDR have decreased transepithelial electric resistance and disruption of the epithelial cell tight junctions resulting in an increased susceptibility to dextran sodium sulfate (DSS)-induced colitis. Conversely, Liu *et al*[77] have demonstrated that overexpression of VDR within the colonic epithelial cells is protective in several different mouse models of colitis, including DSS and the adoptive transfer of T cells into naïve mice, by preserving epithelial tight junctions and attenuating epithelial cell apoptosis thus preserving the gut epithelial barrier function.

***Vitamin D deficiency***

In agreement with the epidemiologic human data, vitamin D deficiency exacerbates IBD in mouse models. Mice fed a vitamin D deficient diet are more susceptible to DSS-induced colitis compared to those fed a vitamin D sufficient diet[105]. Similarly, vitamin D deficient *Il10-/-* mice, which develop colitis in response to enteric flora, develop more severe disease compared to vitamin D sufficient animals[106]. In addition, mice lacking VDR or CYP27B1 develop more severe IBD following treatment with DSS compared to wild type controls[84,91,102], again supporting the epidemiologic evidence that vitamin D deficiency may play a role in IBD development and progression. Conversely, vitamin D supplementation ameliorates symptoms of colitis in vitamin D deficient animals[77, 107]. However, in mice, vitamin D deficiency does not always worsen IBD and CAC. While increased dietary vitamin D protected *Smad3-/-* mice from developing IBD and CAC induced by *Helicobacter*, a vitamin D-deficient diet did not increase colitis and CAC in these mice compared to a control group fed normal levels of dietary vitamin D[39]. Mice fed a vitamin D deficient diet had significantly lower levels of serum 25(OH)D compared to controls. Interestingly, while high vitamin D diet suppressed early inflammation, the vitamin D deficient diet did not cause more severe inflammation compared to controls, suggesting that high levels of vitamin D may inhibit inflammation but lack of vitamin D does not accelerate or exacerbate the process. Another possible explanation for this observation is that the severity of the deficiency may be important to disease susceptibility in this mouse model: in this study, although serum levels of vitamin D were significantly decreased at the time of disease initiation, mice were not completely vitamin D deficient as they had only been on diet for two weeks prior to infection with *Helicobacter*.

**EFFICACY OF VITAMIN D TREATMENT IN IBD**

Despite the majority of studies showing a strong inverse association between vitamin D levels and IBD, studies that use vitamin D to treat IBD have as of yet, yielded variable results (Table 1). Larmonier *et al*[108] used supplemental dietary vitamin D to ameliorate IBD in an adoptive T cell transfer model of colitis. In this study, animals were placed on increased dietary vitamin D supplementation after the onset of colitis but there was no difference in colitis or expression in proinflammatory cytokines in vitamin D supplemented animals[108]. In a study performed by Glenn *et al*[109]*, Il10-/*- mice were fed either 25 IU/kg or 5000 IU/kg vitamin D in the diet throughout life until 3 mo of age, when the animals were necropsied. While animals fed low levels of dietary vitamin D had decreased VDR expression in proximal colon, there were no differences in incidence or severity of IBD nor were there differences in gene expression by microarray between the groups[109]. Ryz *et al*[41] demonstrated that while daily treatment with active vitamin D was sufficient to protect against DSS-induced colitis, it exacerbated colitis induced by infection with *Citrobacter rodentium.* Our group showed protection with supplemental vitamin D using a bacterially-induced colitis model. In *Smad3-/-* mice, increased dietary vitamin D resulted in decreased inflammation, dysplasia, and colon cancer incidence[39]. We also demonstrated dietary supplementation of vitamin D was a convenient and effective way to improve vitamin D nutritional status as evidenced by a significant increase in serum vitamin D in mice fed increased vitamin D compared to those fed control diet. Importantly, we showed that dietary vitamin D levels that were 5–10 times that of control diet levels did not alter serum calcium levels. These studies as well as others are summarized in Table 1.

One of the conundrums of vitamin D therapy has been how to achieve effective concentrations of the active form of vitamin D within the target tissues without inducing hypercalcemia and vitamin D toxicity. Although effective as an anti-inflammatory or anti-tumor agent, administering metabolically active 1,25(OH)2D3 to animals and humans has resulted in hypercalcemia[40,110-113]. Interestingly, Li *et al*[114] attempted to avoid vitamin D toxicity by genetically engineering intestinal macrophages to upregulate expression of *Cyp27b1* (1α-hydroxylase) specifically in the intestinal tissue following an inflammatory trigger. Using this strategy, they were able to protect mice against DSS-induced colitis and decrease the expression of proinflammatory cytokines without altering serum calcium levels by localizing the active vitamin D to the colon[114]. Other investigators including Strauch *et al*[118] and Zhu *et al*[115,116] have administered 1,25(OH)2D analogs and shown protection against IBD in mouse models while avoiding hypercalcemic effects of active vitamin D.

**VITAMIN D AND INFLAMMATION-ASSOCIATED COLON CANCER**

Chronic inflammation is believed to play a key role in carcinogenesis[33]. Links between inflammation and cancer have been observed in colon cancer in human patients with IBD[30] as well as in liver, pancreatic, stomach, esophageal, and prostate cancers[33]. As discussed above, both human and animal studies suggest that vitamin D can be beneficial in preventing or ameliorating inflammation and clinical disease in IBD[40,41,117]; however, few of these studies further evaluate how these changes in inflammation impact subsequent tumor development. Our laboratory has demonstrated that increased dietary vitamin D significantly decreases the incidence and severity of IBD in *Smad3-/-* mice, which resulted in significant decreases in resultant tumor formation[39]. Consistent with these results, other investigators have demonstrated that increased concentrations of dietary vitamin D are protective against preneoplasic lesions in another model of inflammation-associated cancer, DSS/azoxymethane (AOM), in a dose-dependent manner[42,118]. Results of animal studies performed evaluating the effects of vitamin D on CAC are summarized in Table 2. Based on our data and that of others, we believe that vitamin D is protective against inflammation-associated cancer at least in part by altering key inflammatory pathways and dampening inflammation that *precedes cancer development*. However, we have not yet determined whether vitamin D is protective against CAC after the onset of inflammation in *Smad3*-/- mice, an important question to address, and one that can be addressed, using this animal model. While these studies suggest that vitamin D supplementation may be a useful therapy in a subset of patients with IBD and/or CAC, further research to understand the mechanisms through which vitamin D is working in order to better predict the timing of when patients should be treated with supplemental vitamin D and which populations would benefit the most. In addition, research of vitamin D analogs that do not cause hypercalcemia would be useful in the treatment of IBD/CAC without significant vitamin D toxicity. Lu *et al*[119,120]and Klampfer *et al*[119,120] provide additional comprehensive reviews of vitamin D signaling pathways and how they might be involved in carcinogenesis.

**GUT MICROBIOTA, IBD, AND VITAMIN D**

Aberrant immune responses to intestinal microbiota have been implicated in the etiology of IBD in humans[121]. Similarly, the role of gut bacteria in IBD development is well documented in animal models of IBD[122,123]. While no specific bacteria have been identified as a causative pathogen for IBD, general dysbiosis[119,124-126] as well as an overall decrease in microbial diversity[22,127] has been observed in IBD patients compared to healthy controls. In addition, UC patients had lower microbial diversity during active disease periods compared to periods of disease remission[47,127], demonstrating the fluidity of the microbial composition even within the same individual. Studies using twin pairs discordant for IBD also show that microbial diversity is reduced in twins with IBD compared to healthy counterparts[128]. Interestingly, the twin pairs discordant for UC had not only lower microbial diversity but also reduced host gene transcripts in colonic mucosa compared to healthy twin pairs, suggesting that cross-talk between host and microbiota might also be reduced in UC patients[128]. Antibiotics are part of the treatment armamentarium for IBD patients with active and/or fistulizing disease[36], indicating that manipulation of the microbiome can affect the disease process. In addition, studies are underway to examine the benefit of fecal transplantation for therapy and/or cure of IBD[23,27,37,48,129].

The gut microbiome is not only strongly linked to IBD, but also linked to the development of colon cancer in humans and mice[130]. The microbiota of colorectal cancer patients has been found to be enriched in bacteria that reflect an overall pro-inflammatory configuration[131]. Although the association between an altered gut microbiome and IBD appears to be strong, it is currently unknown whether this is a cause or a consequence of the disease. Recently, the bacterial driver-passenger model has been proposed by Tjalsma *et al*[132] as a hypothesis that could explain microbial changes observed during colon tumorigenesis. In this model, specific bacterial populations with pro-carcinogenic features (driver bacteria) contribute to tumor initiation through the induction of epithelial cell damage, DNA damage, and inciting of inflammation. Then as the tumor progresses, other bacterial populations (passenger bacteria) gain growth advantage with changes in the tumor microenvironment, slowly replacing the “driver” bacteria. *Candela et al*[131] delve further into the potential role of gut microbiota in colon cancer carcinogenesis in their recent review.

Recent studies indicate that diet plays a role in regulating the microbiome[128] and that the interaction between the gut microbiota and diet may significantly affect IBD development[133,134]. However, mechanistic studies evaluating the impact of individual dietary nutrients on disease and microbiota are not feasible to perform in human populations and therefore, animal models are crucial for answering these questions.

As vitamin D plays a significant role in host immune responses, it has the potential to influence the gut microbiome. Although the role of vitamin D in shaping the microbiome has not been explored, studies indicate several mechanisms through which vitamin D may influence microbiota. Vitamin D can affect both immune cells and colonic epithelial cells; via modulating immune cell differentiation and maturation, colon barrier function, and the secretion of antimicrobial peptides, mucins, and cytokines, all of which have the potential to modulate the gut bacteria[91,101,135]. Vitamin D deficient mice have decreased expression of Angiogenin-4 (an antimicrobial peptide) within the colon and consequently have an increased bacterial load with decreases in Lactobacillus species and increases in Clostridium and Bacteroides species within the colon, suggesting that vitamin D deficiency may impair microbial homeostasis[105, 136]. Similarly, mice lacking VDR in the colonic epithelial cells have increased bacterial loads within the colonic mucosa, an increased concentration of *Bacteroides fragilis,* a bacterial species that has been associated with IBD in humans, and an increased susceptibility to colitis[137]. In addition, mice lacking the ability to respond to vitamin D (due to lack of VDR or CYP27B1) have distinct differences in their gut microbiome compared to wild-type littermates with intact vitamin D signaling[91,137], demonstrating that host responses to vitamin D impact the microbiome. Conversely, Wu *et al*[138]have demonstrated that specific gut bacteria such as *Lactobacillus rhamnosus* and *Lactobacillus plantarum*, two bacteria commonly found in probiotics, are associated with increased VDR expression in colon epithelial cells and ameliorate colitis in a VDR-dependent manner. Interestingly, when the VDR mutant animals are co-housed with wild type animals, the wild type mice exhibit an increase in susceptibility to DSS colitis, indicating that the susceptibility-inducing microbiota is transferrable and directly influences clinical disease[137].

While these studies suggest that vitamin D signaling can influence the microbiome and vice versa, further studies are needed to better understand specifically how vitamin D is altering the composition of the microbiome and what role this could play in disease development. Recent technical advancements in germ-free animal research and microbiome research provide opportunities to address whether microbiota play a causative role on IBD/CAC as well as whether nutrients such as vitamin D can influence disease by modulating the microbiome.

**Conclusion**

Both human epidemiologic and animal studies suggest that vitamin D plays a role in the development of inflammatory bowel disease as well as colon cancer[16-22]. While vitamin D has been shown to regulate immune cell trafficking and differentiation, cellular proliferation, gut barrier function and antimicrobial peptide synthesis[45-47], the specific mechanisms through which vitamin D ameliorates colitis remain unknown. The majority of evidence demonstrates protective links between vitamin D, colitis, and colitis-associated colon cancer, although studies attempting to demonstrate the usefulness of vitamin D as a therapy for these diseases in animal models have yielded mixed results, likely due to our lack of complete understanding of the model systems as well as the role of vitamin D in inflammation and gut homeostasis. As the use of vitamin D as a treatment in patients with IBD would be simple and inexpensive to implement, it is important that we continue to gain additional insights into its mechanisms of action to determine which patient populations may best benefit from this potential adjunctive therapy.

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**Figure 1 Vitamin D metabolism.**  Vitamin D can be obtained either through exposure to sunlight where ultraviolet b (UVB) interaction in the skin converts 7-dehydrocholesterol to Vitamin D or through absorption from the diet. Vitamin D must undergo several hydroxylation steps to become an active metabolite, 1,25-dihydroxyvitamin D.  The first hydroxylation step occurring mainly in liver by 25-hydroxylase produces 25-hydroxyvitamin D, the main circulating form of vitamin D. The second hydroxylation step catalyzed by 1α-hydroxylase occurs in many target tissues including kidney, intestinal epithelial cells and immune cells and generates the active form of vitamin D, 1,25-dihydroxyviatmin D. This latter form of vitamin D is a ligand for a transcription factor, vitamin D receptor (VDR), which is present in most cell types. VDR bound with 1,25-dihydroxy vitamin D translocates to the nucleus where it dimerizes with retinoid X receptor (RXR). The dimers have the ability to activate transcription of various genes containing a specific promoter region known as vitamin D response elements (VDRE) by binding to the region and recruiting transcriptional machinery.

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| **Table 1 Vitamin D and mouse models of inflammatory bowel disease** |
| **Strain** | **Model** | **Vitamin D metabolite / analog** | **Dose, Route** | **Treatment window and duration** | **Serum Vit D measure** | **Outcome** | **Ref.** |
| **Vitamin D Supplementation** |  |  |  |   |  |
| Protection |   |   |   |   |   |  |
| *Il10-/-* | Spontaneous | 1,25(OH)2D3 and D3 | 0.005 μg 1,25(OH)2D3/dor 5 μg D3/d, diet0.2 μg 1,25(OH)2D3/d, diet | 3 wk of age; maintained throughout study.At the first sign of IBD (diarrhea), lasted for 2 wk | ND | Ameliorated IBDEffective at blocking the progression and ameliorating the symptoms in established disease. | [40] |
| *Il10-/-* | Spontaneous | 1,25(OH)2D3 | 20 ng/d, diet | 4 wk of age; maintained throughout study | ND | Significantly reduced spontaneous colitis. More effective protection with combined treatment with calcium | [113] |
| C57BL/6 | DSS (0.5-3.5%), 5 d | 1,25(OH)2D3 | 50 ng/d, diet or10 ng, intrarectally | Diet given 1 wk prior to DSS treatment; maintained throughout study. Intrarectal administration given 1 d prior to DSS; given every other day | ND | Decreased DSS-induced colitis. Intrarectal administration more effective than dietary delivery. | [106] |
| Balb/c | DSS (3%), 7 d | ZK191784 (1,25(OH)2D3 analog) | 100 μg/kg/d, orally | 3 d prior or at the start of DSS treatment; given daily. | ND | Significantly decreased DSS-induced colitis. | [115] |
| C57BL/6 | DSS (3%), 7 d | 1,25(OH)2D3 | 0.5 μg/kg, IP | 1 d prior to DSS treatment; given daily up to 11 d | ND | Decreased inflammation and tissue damage following DSS treatment; Increased weight loss likely due to hypercalcemia. | [41] |
| C57BL/6 | DSS (2%), 7 d | 1,25(OH)2D3 | 0.2 μg/25 g BW/d, oral gavage | After DSS treatment | ND | Decreased clinical disease, colonic inflammation and intestinal permeability following DSS treatment. | [117] |
| *Cyp27b1-/-*and *Vdr-/-* | DSS (3.5%), 5 d | 1,25(OH)2D3 | 50 ng/d, diet | 2 wk prior to DSS treatment; maintained throughout study | ND | *Cyp27b1-/-*mice more susceptible to DSS induced colitis; supplementation with 1,25(OH)2D3 partially ameliorated disease. | [91] |
| C57BL/6 | DSS (3%), 7 d | NA | Adoptive transfer of CYP27B1 over-expressing monocytes | Adoptive transfer on 5th day of DSS treatment | ND | CD11b+/Gr1+ monocytes overexpressing CYP27B1 trafficked to the inflamed colon and ameliorated DSS-induced colitis | [114] |
| C57BL/6 | DSS (2%), 5 d of treatment followed by 2 d of regular water throughout study | 1,25(OH)2D3 | 0.2 μg/25g BW/d, oral gavage | 2 wk after initiation of DSS treatment; maintained throughout study | ND | Vitamin D decreased clinical disease and colonic inflammation following DSS treatment. Vitamin D treatment significantly decreased mononuclear cell infiltrates present in the spleen and mesenteric lymph node following DSS. | [139] |
| *Smad3-/-* | *Helicobacter bilis* | D3 | 1000 IU/kg or 5000 IU/kg, diet | 2 wk prior to *H. bilis* infection; maintained throughout study | 25(OH)D | Higher vitamin D significantly decrease colonic inflammation | [39] |
| Balb/c | TNBS (100 mg/kg) | 1,25(OH)2D3 | 0.2 μg/kg, IP | Given 2 h before and 3 d post (acute) or 3, 4 and 5 d post TNBS (interventional) | ND | Significantly reduced colitis; greater protection with concurrent treatment with dexamethasone. | [140] |
| C57BL/6 | TNBS (100 mg/kg) | Paracalitriol (1,25(OH)2D3 analog) | 0.5 μg/kg, IP | Given 30 min before and 1, 3 and 5 d post TNBS | ND | Ameliorated TNBS colitis and protected against epithelial barrier disruption | [116] |
| Neutral |   |   |   |   |   |   |  |
| *Il10-/-* | Spontaneous colitis | D3 | 25 IU/kg or 5000 IU/kg, diet | Before conception; maintained throughout study | 25(OH)D | No significant difference in inflammation score | [109] |
| *Rag-/-* | Adoptive transfer of *Il10-/-* T cells + piroxicam (7 d) | D3 | 1000 IU/kg or 5000 IU/kg, diet | After peroxicam treatment ends; for 12 d | 1,25(OH)2D, 25(OH)D | Vitamin D supplementation during active colitis did not alter colonic inflammation; increased trabecular bone deterioration. | [108] |
| Exacerbation |   |   |   |   |   |  |
| C57BL/6 | *Citrobacter rodentium* | 1,25(OH)2D3 | 0.5 μg/kg, IP | 1 d prior to treatment; daily | ND | Increased colonic ulceration and bacterial burdens compared to controls. | [41] |
|  |  |  |  |  |  |  |  |
| **Vitamin D Deficiency** |
| *Il10-/-* | Spontaneous | NA | Vit D deficient diet | Maintain throughout study | ND | Increased mortality and more rapid disease development compared to vitamin D sufficient animals. | [40] |
| C57BL/6 | DSS (2.5%), 6 d | NA | Vit D deficient diet | 6 wk prior to DSS treatment; maintained throughout study | 25(OH)D | Exacerbated DSS colitis and increased bacterial loads within the colonic tissue. | [105] |
| *Il10-/-* | AOM + DSS (2%), 7 d | NA | Vit D deficient diet | 3 wk of age; maintained throughout study | 25(OH)D | Increased mortality and disease severity in AOM/DSS colitis. | [141] |
| *Smad3-/-* | *Helicobacter bilis* | NA | Vit D deficient diet | 2 wk prior to infection; maintain throughout study | 25(OH)D | Did not alter IBD development or severity | [39] |
| *Il10-/-* | DSS (2%), 9 days or *E. coli* | NA | Vit D deficient diet | Maintain throughout experiment | 1,25OH)2D and 25(OH)D | Decreased survival and increased intestinal permeability following DSS treatment; increased susceptibility to infection with invasive *E. coli*. | [103] |
| **Other (genetically altered VDR)** |
| hVDR Tg | TNBS, DSS, and adoptive T cell transfer | NA | NA | NA | ND | Overexpression of VDR in the intestinal epithelial cells protected against TNBS, DSS and adoptive T cell transfer -induced colitis. | [77] |
| hVDR Tg *Il10-/-* | Spontaneous | NA | NA | NA | ND | Overexpression of VDR in the intestinal epithelial cells protected against spontaneous disease in *Il10-/-* mice. | [142] |
| *Vdr-/-* | DSS (0.5-3.5%), 5 d | NA | NA | NA | ND | Increased sensitivity, mortality and disease severity in response to DSS | [107] |
| *Vdr-/-* | DSS (2-2.5%), 7 d | NA | NA | NA | ND | More sensitive to DSS inducted colitis resulting in severe mucosal ulcerations, impaired mucosal wound healing, decreased epithelial barrier function and increased mortality. | [102] |
| *Vdr-/-* | *Salmonella typhimurium* | NA | NA | NA | ND | Administration of probiotics (*Lactobacillus rhamnosus* and *Lactobacillus plantarum)* increased VDR protein expression in colon epithelial cells. Probiotic administration protected against *Salmonella*-induced colitis in wild type but not *Vdr-/-* mice. | [138] |
| VDRΔIEC | DSS (5%), 7 d | NA | NA | NA | ND | Loss of intestinal epithelial VDR exacerbated DSS colitis, altered paneth cell development and changed autophagy gene expression. | [137] |
| *Vdr-/-* and *Il10-/-/ Vdr-/-* | Adoptive T Cell Transfer and Spontaneous | NA | NA | NA | ND | *Il10-/-/ Vdr-/-* mice developed more severe IBD and increased mortality compared to *Il10-/-* mice. Adoptive transfer of *Vdr-/-* CD4 T cells into *Rag-/-* mice induced severe IBD. | [143] |
| *Il10-/-/ Vdr-/-* | Spontaneous | NA | NA | NA | ND | *Il10-/-/ Vdr-/-* mice developed more severe IBD compared to *IL10-/-*mice | [106] |
| *Il10-/-/ Vdr-/-* | Spontaneous and Adoptive T cell Transfer | NA | NA | NA | ND | Adoptive transfer of *Il10-/-/ Vdr-/-* CD4 T cells into *Rag-/-* mice induced severe colitis. Loss of VDR results in decreased T cell homing to the gut and decreased CD4/CD8αα intraepithelial lymphocytes | [89] |
| *Vdr-/- Il10-/-/ Vdr-/-*, and *Rag-/-* | Adoptive T Cell Transfer | NA | NA | NA | ND | Adoptive transfer of *Il10-/-/ Vdr-/-* CD8 T cells into *Rag-/-* mice induces severe colitis. *Vdr-/-* CD8 T cells exacerbate CD4/CD45RBhigh cell-induced colitis. | [144] |

AOM: Azoxymethane; BW: body weight; Cyp27b1: 1α-hydroxylase; D3: Vitamin D3;DSS: dextran sodium sulfate; IBD: Inflammatory bowel disease; IP: Intraperitoneal; NA: not applicable; ND: not done; TNBS: 2,4,6-Trinitrobenzenesulfonic acid; Vit: Vitamin; VDR: vitamin D receptor.

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| **Table 2. Vitamin D and mouse models of colitis-associated colon cancer** |
| **Strain** | **Model** | **Vitamin D metabolite / analog** | **Dose, Route** | **Treatment window and duration** | **Serum Vit D measure** | **Outcome** | **Ref.** |
| **Vitamin D Supplementation** |  |  |  |  |  |
| A/J | AOM + DSS (3%), 7 d | Ro26-2198 (analog) | 0.01 μg/kg/d, subcutaneous pump | 1 wk prior to AOM | ND | Delayed onset of clinical colitis, decreased cellular proliferation and decreased dysplasia following AOM/DSS. | [43] |
| CF1 | AOM + DSS (2.5%) × 7 d | D3, 25(OH)D, 1,25(OH)2D3 and 1,25(OH)2D5 | 500 μg D3 /kg diet , - 500 μg 25(OH)D/kg diet, 2.5 μg 1,25(OH)2D3/kg diet , and 25μg 1,25(OH)2D5/kg diet | 1 week prior to AOM + DSS treatment and maintained throughout study | ND | D3, 25(OH)D, and 1,25(OH)2D5 significantly decreased tumor incidence. 1,25(OH)2D3 induced significant weight loss compared to other treatments; not included in final analysis. | [118] |
| C57BL/6 | AOM + DSS (2%), 4 d × 3 cycles | D3 | 100, 400, 1000, 2500 or 5000 IU/kg, diet | 2.5 wk prior to AOM + DSS treatment. | 25(OH)D | Vitamin D supplementation significantly decreased dysplasia in a dose dependent manner | [42] |
| *Smad3-/-* | *Helicobacter bilis* | D3 | 1000 IU/kg or 5000 IU/kg, diet | 1 wk prior to infection; maintain throughout study | 25(OH)D | Higher vitamin D significantly decreased tumor incidence | [39] |
| **Vitamin D Deficiency** |  |  |  |  |  |
| *Smad3-/-* | *Helicobacter bilis* | NA | Vit D deficient diet | 2 wk prior to infection; maintain throughout study | 25(OH)D | No change in dysplasia score or tumor incidence. | [39] |
| **Other (VDR Knockout)** |  |  |  |  |  |
| *Vdr-/-* | AOM + DSS (1.5%), 5 d × 3 cycles | NA | NA | NA | ND | Increased inflammation and tumor burdens; increased activation of EGFR and ErbB2 signaling | [145] |

AOM: Azoxymethane; D3: Vitamin D3;DSS: dextran sodium sulfate; EGFR: Epidermal growth factor receptor; ErbB2: Receptor tyrosine-protein kinase erbB-2; NA: not applicable; ND: not done; Vit: vitamin.