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Vitamin D, the gut microbiome and inflammatory bowel disease

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Abstract

Vitamin D has an important role in bone metabolism but recently has been recognized as an immunoregulator, and this has led to investigations on the effect of Vitamin D supplementation in various autoimmune diseases and its anti-inflammatory effects. There is some evidence that Vitamin D can regulate gastrointestinal inflammation. In addition, previous studies have shown that Vitamin D can affect the gut microbiome. The aim of this review is to evaluate the effect of Vitamin D on inflammatory processes, especially its relation to the inflammatory bowel disease (IBD) and gut microbiome. There is some evidence that Vitamin D can regulate gastrointestinal inflammation, with epidemiological studies showing that individuals with higher serum Vitamin D have a lower incidence of IBD, particularly Crohn's disease. Vitamin D changes transcription of cathelicidin and DEFB4 (defensin, beta 4) that can affect the gut microbiome. Several cell types of the immune system express Vitamin D receptor, and hence the use of Vitamin D in immune regulation has some potential. Furthermore, Vitamin D deficiency leads to dysbiosis of gut microbiome and reported to cause severe colitis. Vitamin D supplementation is low cost and available and can be a therapeutic option.

Keywords: Gut microbiome, inflammatory bowel diseases, Vitamin D

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic relapsing inflammatory bowel diseases (IBDs) that are increasing in prevalence. In the West, UC affects 120–200/100,000 people and CD affects up to 50–200/100,000 people.[1] IBD also frequently has extraintestinal manifestations; it has a prevalence of 15.4% and leads to a reduced quality of life in these patients.[2] The pathogenesis of IBD

is incompletely understood, and it may be due to inappropriate immune responses to the antigens that are present in the gastrointestinal tract.[3] Furthermore, there is a hypothesis that there is an immune dysregulation to normal intestinal microbiome.[4] There is also evidence that inadequate Vitamin D intake is associated with an increased risk for these diseases.[5,6,7]

In the past decade, there has been increasing evidence that Vitamin D is involved in other aspects of human health apart from bone health. Vitamin D has been shown to regulate innate and adaptive immune systems.[8] There appear to be links between Vitamin D status and autoimmune diseases, and Vitamin D insufficiency/deficiency is closely associated with obesity, which is an established risk factor for cardiovascular disease and it is an inflammatory status.[9] Vitamin D deficiency is associated with the onset and activity of IBD and the risk of its malignant transformation.[10,11] Hence, Vitamin D supplements have been suggested as an adjunctive treatment in IBD.[12,13,14] Vitamin D deficiency is also commonly present in IBD, with up to 95% patients with IBD being affected.[15] A large study comprising 3217 patients with CD and UC showed that 32% had Vitamin D deficiency ($25(OH)D_3$ level of <50 nmol/l].[16]

The most common factor accounting for Vitamin D deficiency in IBD patients, as is the case for most other patient groups, has been reported to be inadequate sun exposure, chiefly ultraviolet B radiation.[17] Sun exposure may be affected by outdoor activities, daylight hours, sunscreen use, skin pigmentation, dressing, and latitude. IBD patients often spend less time outdoors because of their disability. Moreover, many use sunscreen because they are often treated with thiopurine drugs that are associated with an increased risk of skin malignancy.[18,19] For these patients, dietary sources of Vitamin D are, therefore, important. The recommended daily allowance of Vitamin D according to Institute of Medicine is 600 IU between ages 1 and 70 years. The optimal intake of Vitamin D varies with individual,[20] and in some circumstances, higher doses are required.[21] Patients with IBD often have clinical features that limit oral absorption of Vitamin D. These include disturbance in bile acids circulation that can lead to malabsorption of fat-soluble vitamins including Vitamin D. Furthermore, disease of the terminal ileum and resection can have an impact on Vitamin D absorption.[22]

The interaction of the gut microbiome, the diet, and other environmental and genetic factors are thought to be important in the development of gastrointestinal disease.[23,24,25,26]

Genetic factors also have an impact on Vitamin D transport proteins and the formation of 25(OH)D_3, but these must be investigated in IBD patients.[27] Smoking is a risk factor for CD and is also associated with an increased risk of Vitamin D deficiency.[28,29] Corticosteroid use, long duration of IBD, and body mass index >30 can also lead to Vitamin D deficiency.[30,31]

In this study, Web of Science, PubMed, and Google Scholar have been systematically searched for randomized controlled trials (RCTs), systematic reviews of RCTs, and epidemiologic studies that investigate the concept of Vitamin D, the gut microbiome, and inflammatory bowel diseases.

VITAMIN D AND IMMUNITY

A potential link between vitamin D and the immune system was suggested when it was observed that Vitamin D affected leukemia cell differentiation.[32] It has now been confirmed that peripheral blood mononuclear cells have Vitamin D receptors (VDRs);[33,34] VDR is also found on other hematopoietic cells.[35] Furthermore, macrophage and dendritic cells (DCs) have been shown to elaborate active Vitamin D (1,25[OH]2D).[36,37] We have listed potential immune functions of Vitamin D in Table 1.

VITAMIN D AND INTESTINAL IMMUNITY

While the role of Vitamin D deficiency in the etiology of IBD is unclear, it has been shown to have some potentially beneficial effects *in vitro* and *in vivo*.

Vitamin D reduces the permeability of intestinal cells in animal models of colitis.[38,39] In VDR knock-out mice, dextran sodium sulfate induces colitis that is associated with decreased immunostaining of zonula occludens-1 and occluding proteins on epithelial cells of the colon and associated with decreased transepithelial resistance and increased permeability. The nucleotide-binding oligomerization domain-

containing protein 2 (NOD2) is an intracellular pattern recognition receptor. It activates NF-kB and increases Vitamin D-mediated transcription of cathelicidin and DEFB4 (defensin, beta 4).[40] If the innate immune system cannot control the microbiome, it could be lead to tissue inflammation.

NOD2 is thought to be important in CD susceptibility.[41] It is possible that Vitamin D modulates NOD2 and protects against CD with antibacterial responses.

Angiogenin-4 is another antimicrobial protein. It has bactericidal activity against intestinal microbiome. In mice with Vitamin D deficiency, several genes have been reported consistently to be upregulated or downregulated when compared with Vitamin D-sufficient mice.[42] Angiogenin-4 was one of these genes. This change was associated with increasing number of colonic bacteria up to 50 fold. Therefore, Vitamin D deficiency can lead to dysbiosis and it may, therefore, be a factor in the pathogenesis of CD.

DCs are antigen-presenting cells that express the VDR and can produce 1,25(OH)2D3.[43] Treatment of these cells with 25(OH)D3 and 1,25(OH)2D3 lead to a weakened capacity for antigen presentation. Therefore, the response of the DC to antigens become weaker and they cannot activate adaptive immune system effectively (tolerogenesis).[44,45] Furthermore, 1,25(OH)2D3-treated DCs express more interleukin (IL)-10, which is an anti-inflammatory and immunosuppressive cytokine.[46]

VITAMIN D AND INFLAMMATORY BOWEL DISEASE

The incidence of IBD has increased in recent years and has been estimated to affect 1/200 people in the developed countries.[47] IBD is a more severe disease in children and adolescents.

Although patients with CD have a significantly lower serum level of 25(OH)D as compared with control group, it is unknown whether this was cause or effect of IBD activity.[48] Furthermore, seasonal changes in serum 25(OH)D level are associated with CD activity.[49]

Genetic predisposition appears to be an important factor in the development of IBD, and 163 distinct genetic variants have been reported to be associated with IBD risk. Host–microbiome interactions have been implicated in risk of IBD and even progression of disease.[41]

However, few studies have investigated the association between Vitamin D deficiency and risk of IBD. The Nurses' Health Study has shown that participants in the highest quartile of Vitamin D had a lower risk of developing CD, but this was nonsignificant for UC (odds ratio [OR] for CD: 0.54; 95% confidence interval [CI]: 0.30–0.99; $P = 0.02$). The insignificant result for UC may have been because of smaller number of UC patients compared with CD patients.[10]

Cohort studies have found an association between CD activity and low serum $25(OH)D_3$ levels.[17,50,51] A cross-sectional study has reported that higher levels of fecal calprotectin (as a marker for intestinal inflammation) was associated with lower serum $25(OH)D_3$ level and it indicated that Vitamin D may be of potential value in treating intestinal inflammation.[52] However, some studies have not shown any significant association between serum $25(OH)D_3$ level and CD and UC activity;[53,54] these studies may be limited by the low number of participants.

A large multicentral IBD cohort has shown that serum $25(OH)D_3$ level <50 nmol/l has increased risk of surgery (OR: 1.76; 95% CI: 1.24–2.51) or hospitalization (OR: 2.07; 95% CI: 1.59–2.68).[16] This result suggests that Vitamin D deficiency may have an adverse effect on the course of IBD.

VITAMIN D AND THE GUT MICROBIOME

The gut microbiome has effects on the host immune system and has the potential to change disease development.

Guo *et al*. have shown that Vitamin D induces the expression of cathelicidin antimicrobial peptide (CAMP) gene [Figure 1]. CAMP expresses by immune and epithelial cells and enhances barrier function.[55] These results suggest that Vitamin D has antibacterial effects.

The intestinal microbiome is involved in the synthesis of secondary bile acids. Lithocholic acid (LCA) is a secondary bile acid that is hepatotoxic and toxic for intestinal cells and may also induce enteric cancer. Interestingly, LCA can bind to the VDR. When Vitamin D activates the VDR, it induces the expression of cytochrome CYP3A, which is involved in the detoxification of LCA in intestine and liver. [56,57] Some probiotics increase serum Vitamin D level. In a multicenter study, oral supplementation with *Lactobacillus reuteri* (NCIMB30242), a probiotic, increased serum 25(OH)D concentration.[58]

Some bacteria, for example, *Chlamydia trachomatis*, reduces VDR activity.[59] The probable mechanism for this is through bacterial capnine that inhibits ligand-binding pocket in the nuclear VDR. [60] The VDR response is inhibited by such bacteria and leads to upregulation of the miRNA, hsa-mir-21 by monocytes, thereby potentially blocking the immune responses that are stimulated by Vitamin D. [61]

A reduction in the production of $1,25(OH)_2D_3$ or expression of VDR may lead to gut inflammation and an increase in Proteobacteria colonization. This leads to a shift in the balance of the microbiome composition [Figure 1].

Deletion of the VDR in intestinal epithelial cells results to a defective autophagy in colitis. Defective autophagy has seen in IBD. There is an essential correlation between autophagy, VDR, and gut microbiome that is important for intestinal homeostasis, these have a role in pathophysiology of IBD. [62] These data suggest that Vitamin D is an important factor in determining the composition of the gut microbiome and inflammatory processes in IBD.

VITAMIN D AS A TREATMENT FOR IBD PATIENTS

It has been proposed that the benefits of supplementation with Vitamin D in IBD because it can regulate homeostasis in the gut. Vitamin D modifies epithelial cells' integrity, immune responses especially for innate immune system, and the diversity and the composition of the human gut microbiome.[63] In

Vitamin D/IL-10 deficient mice, administration of $1,25(OH)_2D$ was found to reduce the severity of colitis.[64]

In man, there have been few studies to evaluate the therapeutic effects of Vitamin D in IBD patients. In one clinical trial in CD patients, receiving 1200 IU/day of Vitamin D for 1 year, reduced the relapse rate from 29% to 13% when compared with placebo group.[14] However, this reduction was nonsignificant ($P = 0.06$) and was of insufficient power due to the small sample size. Miheller *et al*. have compared the effects of 1,25 dihydroxyvitamin D and 25 hydroxyvitamin D on disease activity of CD patients. Their results have shown that, after 6-week, Crohn's Disease Activity Index reduced significantly with 1,25 dihydroxyvitamin D.[65]

In CD patients, supplementation with 1000 IU/day of Vitamin D_3 until the serum level of 25(OH)D reached to 100 nmol/l was associated with a significant reduction in Crohn's Disease Activity Index scores. However, inflammatory markers did not change significantly.[13]

In addition to the effects of Vitamin D for treatment of IBD patients, it has effects on other medical treatments in these patients. Zator *et al*. evaluated the effect of the serum level of 25 hydroxyvitamin D and duration of responses to antitumor necrosis factor-α as a treatment in IBD patients. Interestingly, there was a significant association between Vitamin D insufficiency and early failure of treatment with antitumor necrosis factor-a (hazard ratio: 2.13; 95% CI: 1.34–4.39; $P = 0.04$).[12] Furthermore, in patients that did not receive Vitamin D supplements, this failure was stronger. This effect is due to the effects of suppression of the colon tumor necrosis factor-a genes by Vitamin D.

The studies support Vitamin D supplementation in IBD patients. However, this is important to investigate the Vitamin D doses according to some other factors such as the human gut microbiome or genetic factors.

CONCLUSION

Several cell types of the immune system express VDR, and hence the use of Vitamin D in immune regulation has some potential. Recent studies confirm an association between Vitamin D status and the development of IBD, particularly CD. There have been few clinical trials that have evaluated the effects of Vitamin D supplementation in the treatment of IBD. Vitamin D has been reported to have effects on the severity (increasing hospitalization and surgery) and pathogenesis of IBD. In animal studies, Vitamin D deficiency has been reported to cause severe colitis, but in man, it has not been proven that low serum level of Vitamin D is a consequence of disease or it is the cause of IBD. Therefore, further research is necessary in this field and for using Vitamin D as an adjunct therapy for IBD patients.

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Conflicts of interest

There are no conflicts of interest.

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Figures and Tables

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Table 1

Potential immune functions of Vitamin D

Author (year)	Potential immune function	Reference
Kizaki M, *et al*. (1991) Reichel H, *et al*. (1987)	Monocyte differentiation, antigen presentation, lysosomal enzyme activity, and the expression of reactive oxygen metabolites	[35,36]
Fritsche J, *et al*. (2003)	Downregulation of TLR in monocytes and dysregulation of immune response to LPS	[37]
Zhang YG, *et al*. (2013) Kong J, *et al*. (2007)	Suppresses TNF-α production and impaired proliferation and differentiation of lymphocytes	[38,39]
Wang TT, *et al*. (2010) Jostins L, *et al*. (2012)	Hyporesponsiveness with disturbance in dendritic cell differentiation, IL-12 secretion and inhibition of T lymphocyte activation	[40,41]
Lagishetty V, *et al*. (2010) Brennan A, *et al*. (1987)	Induce regulatory T-cell production	[42,43]
Penna G, *et al*. (2000)	Prevention of the GMCSF gene transcription	[44]
Hewison M, *et al*. (2003)Van Halteren AG, *et al*. (2002) Molodecky NA, *et al*. (2012) Carvalho AY, *et al*. (2013)	Inhibits pro-inflammatory cytokine production, induces production of IL-10 (an anti-inflammatory cytokine)	[45-48]

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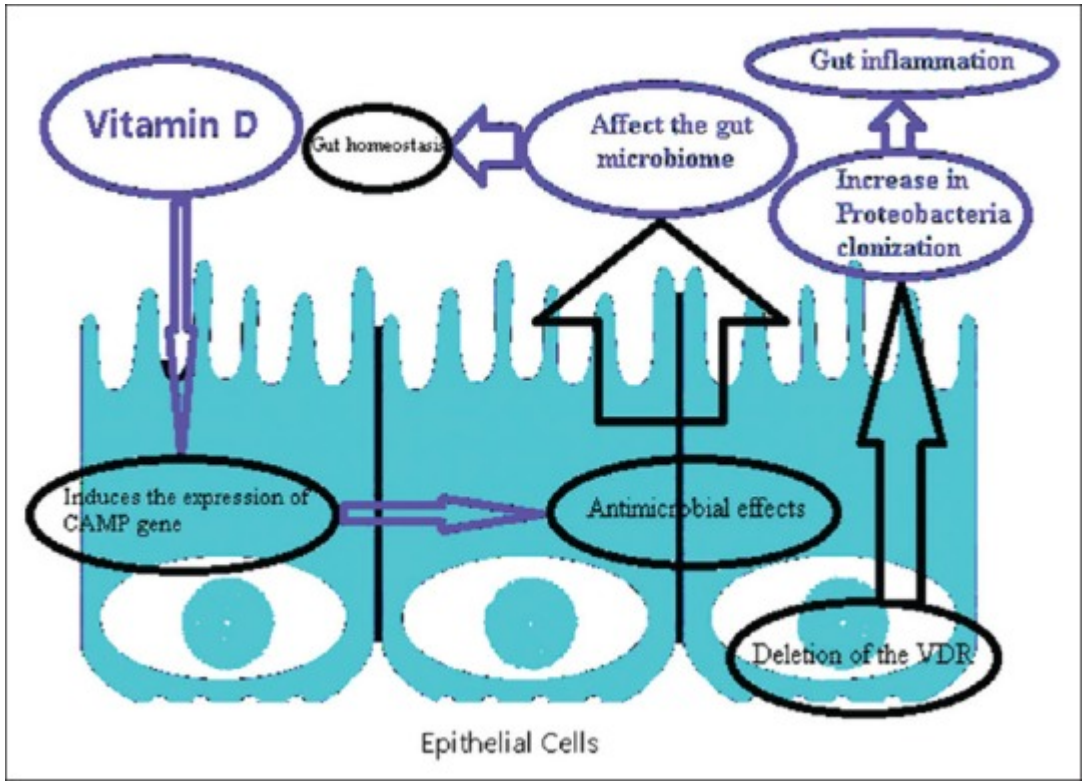
Figure 1



Interaction between Vitamin D and gut microbiome can affect gut homeostasis or gut inflammation. VDR: Vitamin D Receptor, CAMP: Cathelicidin antimicrobial peptide