Journal Pre-proof

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PII: S0965-2299(19)30294-8

DOI: https://doi.org/10.1016/j.ctim.2019.08.023

Reference: YCTIM 2189

To appear in: *Complementary Therapies in Medicine*

Received Date: 3 March 2019

Revised Date: 27 August 2019

Accepted Date: 28 August 2019

Please cite this article as: Parizadeh SM, Jafarzadeh-Esfehani R, Hassanian SM, Mottaghi-Moghaddam A, Ghazaghi A, Ghandehari M, Alizade-Noghani M, Khazaei M, Ghayour-Mobarhan M, Ferns GA, Parizadeh SMR, Avan A, Vitamin D in inflammatory bowel disease: from biology to clinical implications, *Complementary Therapies in Medicine* (2019), doi: https://doi.org/10.1016/j.ctim.2019.08.023

Vitamin D in inflammatory bowel disease: from biology to clinical implications

Seyed Mostafa Parizadeh[1*], Reza Jafarzadeh-Esfehani[2,*], Seyed Mahdi Hassanian[1,*], Ali Mottaghi-Moghaddam[1], Anahita Ghazaghi[1,3], Maryam Ghandehari[1,3], Mohadese Alizade-Noghani[1], Majid Khazaei[1], Majid Ghayour-Mobarhan[1,4], Gordon A. Ferns[5], Seyed Mohammad Reza Parizadeh[1#], Amir Avan[1,4,6,#]

Affiliations

1) Metabolic syndrome Research center, Mashhad University of Medical Sciences, Mashhad, Iran
2) Department of Medical Genetics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
3) Student Research Committee, Faculty of Medicine, Islamic Azad University, Mashhad branch, Mashhad, Iran
(4) Department of Modern Sciences and Technologies, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
(5) Brighton & Sussex Medical School, Division of Medical Education, Falmer, Brighton, Sussex BN1 9PH, UK.
(6) Cancer Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

#Corresponding Author:

Amir Avan, PhD; and Seyed Mohammadreza Parizadeh, PhD, Metabolic Syndrome Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. Tel:+9851138002298, Fax: +985118002287; Email: avana@mums.ac.ir

*Equally contributed as first author.

Highlights:

- Vitamin D deficiency is a major concern in general population as well as in IBD patients.
- The main focus of most of present clinical studies are on the inflammatory state rather than evaluation clinical outcomes.
- The exact dose of vitamin D supplementation in IBD patients has not been studied systematically in clinical trials which requires further studies with greater sample size with more emphasizes on every vitamin D sources especially the sun exposure.

Abstract

Inflammatory bowel disease (IBD) is a chronic immune-mediated inflammatory disorder of the gastrointestinal tract consisting two principal categories, ulcerative colitis (UC) and Crohn's disease (CD). The precise etiology of IBD remains unknown. Vitamin D is an important micronutrient that plays a critical biological role in various processes in human tissues. However, the relationship between disruption of the gut microbiota and the development of IBD is unclear. Some studies suggest that IBD is the cause of disrupted gut microbiota while others propose that gut microbiota itself can lead to development of IBD. Regardless of this complexity, it has emerged that vitamin D is an immunoregulatory factor that plays a significant role in the pathogenesis of IBD by affecting the gut microbiome and the inflammatory response. It has been reported that 38.1% of CD patients and 31.6% of UC patients suffer from vitamin D deficiency (VDD). In this review, we aimed to evaluate the association between VDD and IBD, summarizing recent clinical studies examining the effect of low vitamin D and the role of vitamin D supplementation on IBD clinical outcomes.

Keywords: vitamin D; inflammatory bowel disease; Crohn's disease; ulcerative colitis; supplementation; sun exposure

Introduction

Inflammatory bowel disease (IBD) is a chronic immune-mediated inflammatory disorder of the gastrointestinal (GI) tract with relapsing and remitting periods. IBD comprises two principal categories; ulcerative colitis (UC) and Crohn's disease (CD) (94). Epidemiologic studies indicate that millions of people suffer from IBD globally (9). The common clinical manifestations of IBD patients include: diarrhea, weight loss, anemia, hematochezia and extra-intestinal

manifestations (9). The exact etiology of IBD remains unknown, however it is believed that genetic factors such as a mutation of the nucleotide-binding oligomerization domain-containing protein 2 (NOD2) gene, gut microbiome, immune and environmental factors have important roles in its pathogenesis (45, 9). Inflammation is considered as the main etiology in pathogenesis of IBD. The role of the immune system in the inflammation and progression of IBD has recently been proposed. While TH-1 is mostly associated with CD, TH-2 is reported to be associated with UC (65). IBD has also been associated with developing different types of cancer. Chronic intestinal inflammation is responsible for developing colorectal cancer. Small bowel carcinoma as well as intestinal lymphoma are other two main malignancies in IBD (6). While majority of different factors has been related to development of IBD, one of the fat-soluble vitamins has become the era of interest for most recent studies. It has been emerged that vitamin D as an immunoregulatory factor play a significant role in IBD pathogenesis by contributing to the composition of the gut microbiome and the inflammatory response(91).

Vitamin D is an important micronutrient that plays a critical biological role in various processes in human tissues (73). Vitamin D can be obtained from dermal synthesis following ultraviolet B (UVB) exposure, dietary intake and supplementation. A large number of people especially IBD patients have vitamin D insufficiency or deficiency worldwide (21). It has been reported that 38.1% of CD patients and 31.6% of UC patients suffer from vitamin D deficiency (VDD) (21). Regarding the effect of vitamin D in regulation of hundreds of genes and immune system response, recent studies have revealed a relationship between vitamin D status with the development and progression of different chronic autoimmune disorders (7). In this review, we aim to evaluate the association between VDD and IBD, and summarizing the recent clinical

studies examining the effect of low vitamin D intake and the role of vitamin D supplementation on IBD clinical outcomes.

Source and metabolism of vitamin D and its role in the regulation of immunity system and pathogenesis of autoimmune disease

UV light, dietary intake and supplementation are three main sources of Vitamin D (Figure 1). Two major forms of vitamin D are Vitamin D2, also known as ergocalciferol, and vitamin D3, also known as cholecalciferol (22). The greater portion of vitamin D is derived by dermal synthesis during UVB exposure (61, 73). Salmon and mackerel, mushrooms and cod liver oil are common natural sources of vitamin D (61). Daily sun exposure for about a quarter of an hour produces up to 10,000 IU vitamin D (88). Cholesterol is converted to 7-dehydrocholesterol in the plasma membrane of epidermal cells. Subsequently, 7-dehydrocholesterol is converted to pre-vitamin D which will be further converted to vitamin D (61). Then, vitamin D is released into the circulation bound to Vitamin D Binding Protein (VDBP) (61). Vitamin D is transported to the liver and kidney which further be converted to 25-hydroxyvitamin D (25(OH)D) and 1,25(OH)2D (73). The minimum level of 25(OH)D which is required for normal physiological functions is about 30 ng/mL (73).

Vitamin D deficiency may therefore be a result of limited sun exposure, kidney and hepatic dysfunction, malabsorption and inadequate intake (61).

The discovery of vitamin D receptors on different body cells, especially on immune cells, has led to the idea of possible linkage between nutrition and immune system (76). Immune cells express the 25(OH)D3-1alfa-hydroxylase (CYP27B1) which is the rate limiting enzyme for

biologically active vitamin D production (32). The further linkage of vitamin D and immune system has become clearer after discovering the effect of supplementation on animal model of immune disease such systemic lupus erythemathosis (48). As mentioned earlier, vitamin D can be obtain from both UV exposure and dietary source. These two sources are not easy to control in clinical trial studies that have attempted to relate the exact source of vitamin D with different immune disease. Regardless of such difficulties in conducting clinical research on the linkage between vitamin D and autoimmune disease, determination of the possible role of vitamin D in immune system has been a focus of interest. A relationship between vitamin D status and immune function became more likely when VDRs were shown to be present on immune cells. Moreover, it has been demonstrated that Vitamin D deficiency is associated with an increased risk of infectious diseases (31). Scientists has focused their efforts on evaluating the role of vitamin D on different parts of immune system's cells including innate and adaptive immune cells. Early effects of vitamin D on the innate immune system was evaluated by assessing macrophages function in fighting against against microbial agents including mycobacterium tuberculosis. Calcitriol can boost phagocytic function and activate B2 defensins which are antimicrobial peptides (104). The immunogenic effects of vitamin D on other innate immune system cells including dendritic cells has also been investigated. It has been shown that calcitriol can modulate such antigen presenting cells to tolerogenic states and decreases their MHC-II and co-stimulatory molecules which will further result in increased expression of tolerogenic interleukins (80, 26). The expression of MHC-II antigens by cells of the immune system can be reduced by treatment with 1,25(OH)2D3 which will further results in decreased T cell stimulation. Furthermore, treatment with 1,25(OH)2D3 may result in increased T helper cytokines which also have

immunoregulatory effects (98). The tolerogenic capacities of antigen presenting cells (APCs) rely on their ability to express the CYP27B1 enzyme. By use of this enzyme, these cells can achieve high concentration of activated vitamin D which is important for developing their immunomodulatory effects (8). The production of both B and T lymphocytes and T cell maturation is also regulated by 1,25(OH)2D3 (98). Calcitriol can inhibit differentiation, proliferation and memory cell generation as well as inducing apoptosis of B cell lymphocytes. The sum of these effects on B cells is crucial for modulating auto reactive antibody production during development of an autoimmune process (17). In addition to B cells, T cells are also take affect from various ways. In addition to the indirect effect of vitamin D which is because of APCs and mentioned earlier, vitamin D also has some direct effects on T cells. Calcitriol can suppress T helper lymphocytes production, and negatively regulate the production of pro-inflammatory cytokines, which include IL-2, IL-9 and TNF-α (75). Along with suppression of these cytokines, other anti-inflammatory cytokines such as IL10 are increased. Another category of immune cell which are important in maintaining an anti-inflammatory state are regulatory T cells. These cells are activated either directly by calcitriol or indirectly by 25(OH)D (75). The effect of vitamin D on immune disease has been evaluated in various studies and investigations of the molecular pathways involved in the regulatory effects of vitamin D on immune system, has been supported by the results of clinical studies (62, 51, 72, 97). Evaluation of vitamin D intake or sun exposure and prevalence of immune disease has provided valuable insights about the effects of vitamin D on autoimmunity. However, the exact causative effect cannot be extracted from most of such studies (20). Only a few prospective studies have assessed baseline vitamin D levels prior to development of autoimmune disease (58, 63, 18). It seems that such studies are more likely to

provide valuable information about the possible relationship between serum vitamin D and autoimmune disease. Alongside with these studies, those that have evaluated the relationship between vitamin D receptor polymorphisms and autoimmunity are also promising(102). Different polymorphisms are reported to have different protective or predisposing effects. Other evidence suggesting the possible role for vitamin D can be derived from those studies which have evaluated the therapeutic effect of vitamin D on autoimmune diseases although the results of these studies have been equivocal (5, 74, 4).

The relation between vitamin D and gut microbiota

This complex microbial system of the gut microbiota is now considered as an important factor in health. Changes in the gut microbiota may result in alteration of human body function including metabolism and especially the immunity. The gut microbiota can be disrupted in several ways (95). Diet and obesity as well as developing specific disease are considered major factors affecting the gut microbiota. It is likely that IBD and gut microbiota do not have a clear cause and effect relationship. IBD is a chronic disease and is one of the factors which is thought to be important in altering the microbiota (35). However, recent studies have also highlighted the role of gut microbiota in developing mucosal lesions in IBD patients (54). Moreover, IBD is closely related to vitamin D metabolism in experimental studies (4, 57). Studies in selective intestinal VDR knock-out mice has shown some interesting findings regarding the effect of VDR in IBD pathogenesis. Wu et al. demonstrated that VDR acts as a master regulator of homeostasis in intestinal tissue (107). VDR knock-out mice will show decreased lysozyme which will further result in defective autophagy which is important in maintain effective gut homeostasis (79). Moreover, VDR knock-out mice have defective Paneth cells in their intestine (107). Disruption of

lysozyme and Paneth cell function results in a defective granule exocytosis pathway and inability to secrete antimicrobial peptides (107). The antimicrobial peptide is a key role player in formation of specific gut microbiome. So, disruption of this pathways by defective VDR can be both cause IBD development and gut microbiota disruption (107). It has also been shown that CYP27B1 or VDR knockout mice are prone to develop colitis. Interestingly, sequencing of fecal DNA from these mice has shown the alteration in gut microbiota which can be partially reversed by administration of 1,25(OH)D (68). Bora et al. conducted an experimental study on mice to investigate the effect of the gut microbiota on vitamin D status. This study also highlights the effect of fibroblast growth factor (FGF) on serum vitamin D. Parathyroid hormone will be inhibited by FGF23 and induce Cyp24A1. Cyp24A1 will result in decrease in 1.25(OH)D production. In this study, germ free mice have low levels of serum 25(OH)D and 1,25(OH)D; after returning to a conventional environment these mice were found to return to normal levels of 25(OH)D and 1,25(OH)D (12). Monocolonalization by specific organisms has provided the same results. Citrobacter rodentium have increase both 25(OH)D and 24,25(OH)D levels in germ free mice and also colonialization with eight commensals has provided the same results. Germ free mice have high level of FGF which will be regulated after conventionalization. Colonialization has suppressed FGF23 levels and therefore increased vitamin D levels. Neutralization of FGF23 in germ free mice without conventionalization will also result in increased 1,25(OH)D levels. According to their study, the gut microbiota induces inflammation in the intestine and therefore inhibits FGF23 which is involved in the regulation of vitamin D (12). $1,25(OH)_2D_3$ affects the expression of different genes such as B2 defensines (DEFB2/HBD2) which has antimicrobial effects (103). 1,25(OH)D also induces expression of cathelicidin antimicrobial peptides (CAMP)

which will response against microbial pathogens alongside with B2 defensines and NOD2/CARD15/IBD1. NOD2/CARD15 in monocytes will detect breakdown products of bacterial peptidoglycans. Cells which receive 1,25(OH)D will show synergic induction of HBD2 and CAMP if there is functional copy of NOD2 gene. Recently, the highly polymorphic HBD2 locus variations as well as attenuated NOD2 function has been linked to IBD and especially the CD (10). VDR status plays an important role in gut microbiota. VDR knockout mice have altered gut microbiota (39). Also, there are clinical trials available on human with IBD which indicates the role of vitamin D on gut microbiota. It has been reported that vitamin D supplementation in CD patients will alter gut microbiota while this effect is absent in healthy individuals (82). Consequently, gut microbiota alteration and decrease in butyrate-producing bacteria alongside with increased level of other microbes will have great impact on the intestine and body health (52, 16).

Role of serum concentration of vitamin D in clinical outcomes of inflammatory bowel disease

Several studies have evaluated the association between serum vitamin D with the presence of IBD which are summarized in Table 1. We have tried to narratively review the related literature and consider the most relevant articles addressing the relation between vitamin D status and development of IBD. We do not feel there is strong evidence of a relationship between vitamin D status and the development of IBD. Several studies have demonstrated that healthy subjects have significantly higher vitamin D level in comparison to IBD patients (42, 25, 36). Also, a recent meta-analysis has confirmed the conclusion of these studies and stated that CD and UC have lower vitamin D levels (53). However, results of other studies showed that although there was difference in vitamin D levels between IBD patients and healthy subjects, this difference was not statistically significant (92, 33, 13, 99). Different vitamin D status assessment strategy and

also considering different cut off points for vitamin D status assessment is a possible explanation for these controversial findings (50).

Whilst the relationship between vitamin D status and IBD has been evaluated, the possible effect of other factors affecting the level of this micronutrient has been also assessed in IBD patients. The results of 2 large cohort study has shown that there is a relation between sun exposure and IBD (66, 44). According to these cohort results, low sun exposure which can be also seen in higher latitude regions is related to higher prevalence of UC and CD. Moreover, low sun exposure has been related to higher rate of hospitalization and bowel surgery(49, 89). Such studies emphasizes the importance of vitamin D in IBD patient's life.

The relation between severity of disease, inflammation and disease recurrence and vitamin D status has been also an interesting topic which evaluated in many studies. Dumitrescu et al. has provided unique evidence about the relation between disease severity and Vitamin D status. They have reported that patients with moderate to severe IBD had lower vitamin D level compared to IBD patients with mild disease (24). Garg et al. evaluated 71 IBD patients and found an inverse association between vitamin D level and intestinal inflammation (28). Similarly, Meckel et al. and Raftery et al. in their cross-sectional studies investigated 230 UC and 119 CD patients, respectively. Both of these studies found an inverse correlation between serum vitamin D and intestinal inflammation (56). In an assessment of 182 CD patients, a negative association between serum vitamin D concentration and disease activity (41). Fifty UC patients investigated in a cohort conducted by Dolatshahi and colleagues. Consistent with previous studies, an inverse association was observed between vitamin D level and disease activity (23). These results were confirmed in further studies (96, 81, 1, 27, 84). In addition to increased disease activity, a relationship between vitamin D deficiency and higher risk of relapse was found by Frigstad and co-workers (27). Moreover, it has been stated that VDD could affect treatment response in IBD patients. Winter et al. revealed that VDD will affect response to anti-TNF-a therapy (106). Nevertheless, Middleton et al. found that there was no significant association between vitamin D concentration and disease severity in CD patients (59). On the other hand, Ananthakrishnan et al. revealed that level

of vitamin D in IBD patients was correlated with risk of incidence of colorectal cancer. This study showed that per 1 ng/mL increment in vitamin D level resulted in 8% decrement in risk of CRC in IBD patients (3).

Role of vitamin D supplementation therapy in clinical outcomes of inflammatory bowel disease

There are several clinical trials that have investigated low dose or high dose vitamin D supplementation therapy in patients with IBD (Table 2). As mentioned in previous section, the vitamin D status is related to quality of life. This fact has been confirmed in clinical trials conducted by Raftery et al., Mathur et al. (77, 55). They have proposed that administration of at least 2000IU of Vitamin D3/day will increase the life quality of IBD patients. Even though, vitamin D deficiency is related to increase in surgery rate in UC and CD patients. Considering 50000 IU vitamin D2/week will result in lower surgery rate in those who CD patients who had vitamin D deficiency(2). In addition, some trials has considered even greater amount of Vitamin D supplementation for controlling the disease and reducing the inflammation. Most of these studies evaluated the effect of administration of vitamin D on the levels of inflammatory markers and disease activity index in these patients. The main different between these studies could be addressed in their chosen methodology. While the most evident difference between these studies is the dose of Vitamin D, some studies have tried different administration root as well as considering different forms of vitamin D. Sharifi et al. assessed the effects of intramuscular

administration of 300,000 IU vitamin D3 in 86 UC patients. After ninety days follow up they found significant reduction in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in these patients (85). Mathur et al. evaluated lower dose of vitamin D supplementation in 18 UC patients with a serum 25(OH)D level <30 ng/ml. In this study patients were categorized into two groups and received orally 2000 or 4000 IU vitamin D3 per day for 90 days. The results showed a non-significant reduction in serum hs-CRP level with both regimens (55). Reftery et al. reported that oral use of 2000 IU vitamin D3 daily for 3 months in 27 CD patients was significantly effective in reducing CRP level (77). Miheller et al. have compared the efficacy of giving different form of Vitamin D in IBD patients. They found that giving alfacalcidiol, the active form of vitamin D, was more potent in CRP reduction in comparison with cholecalciferol (60).

The effect of supplementation on disease recurrence has been also evaluated but the results are still controversial. Jørgensen et al. investigated disease relapse in 94 CD patients. They concluded that vitamin D supplementation therapy insufficiently reduces disease relapse in these patients (40). Similarly, Narula assessed the effect of vitamin D3 treatment on CD relapse and found that there was no significant difference in disease relapse between two groups of CD patients receiving 1000 or 10000 IU vitamin D per day (64).

Role of solar UVB exposure and dermal synthesis of vitamin D in clinical outcomes of inflammatory bowel disease

There have been increasing evidence that residence in different latitude affects the incidence and also disease activity of IBD patients. Khalili et al. in their cohort study conducted in the United States evaluated 175912 women. Findings of this study showed that there is an association between increased incidence of both CD and UC and residence in higher latitude regions or in

other words in regions with low sun exposure (44). A meta-analysis has investigated 28 studies in pediatric population. Results of this meta-analysis confirmed correlation between latitude and incidence of CD (37). Jantchou et al. in a study in France, reported that high levels of sunlight exposure were associated with decreased incidence of CD but not UC (38). Another study conducted in France found similar results (66). Limketkai et al. in the United States investigated the relationship between solar UVB exposure and IBD severity and hospitalization. Results of this study revealed that lower sunlight exposure correlated with increased need for hospitalization and bowel surgery and also higher disease severity (49). Stein et al. reported similar findings (89).

Limitations of the current studies

As shown in tables 1 and 2, many studies have investigated the relationship between vitamin D status and supplementation in IBD patients. There are limitations of these studies which has to be addressed in the future researches. Various studies used different serum vitamin D measurement techniques, and the cut off values used in these studies differed and hence there may be detection errors. The other limitation would be the dose of vitamin D used in each of the mentioned intervention studies. While most of the clinical trials used controlled doses of vitamin D supplements, other sources of vitamin D are not generally controlled in most of the studies. Also, it seems that despite of the great number of clinical trials, still most of these trials are using different doses of supplementation. It seems that different drawing an exact dose of supplementation in IBD patients still need further research. The last limitation is some studies with limited sample size. Addressing all of these issues in further research and conducting more controlled and larger trials will help support a more reliable conclusion regarding the role of vitamin D in IBD patients.

Conclusion

IBD is common GI immune mediated disease that is related to many adverse clinical outcomes. Vitamin D as an important micronutrient which is also important in immune

regulation. Studies have highlighted the fact that vitamin D deficiency is a major concern in general population as well as in IBD patients. Ensuring adequate Vitamin D levels by different routes seems to be effective for overcome IBD complication and in some cases response to therapies. However, there are limited randomized clinical trials for many other aspects of vitamin D supplementation in IBD patients. The main focus of most of present clinical studies are on the inflammatory state rather than evaluation the clinical outcomes. Also, the exact dose of vitamin D supplementation in IBD patients has not been studied systematically in the clinical trials which requires further studies with greater sample size with more emphasizes on every vitamin D sources especially the sun exposure. Moreover, evaluation of more accurate effect of sun light by using skin sensors will provide more promising results in studies about vitamin D.

Grant

This study was supported by grant awarded (Seyed Mostafa Parizadeh, Seyed Mohammad Reza Parizadeh, Amir Avan) by the Mashhad University of Medical Sciences.

Conflict of interest

The authors have no conflict of interest to disclose

Acknowledgment

the authors would like to thank Mashhad University of medical sciences for supporting the present review**.**

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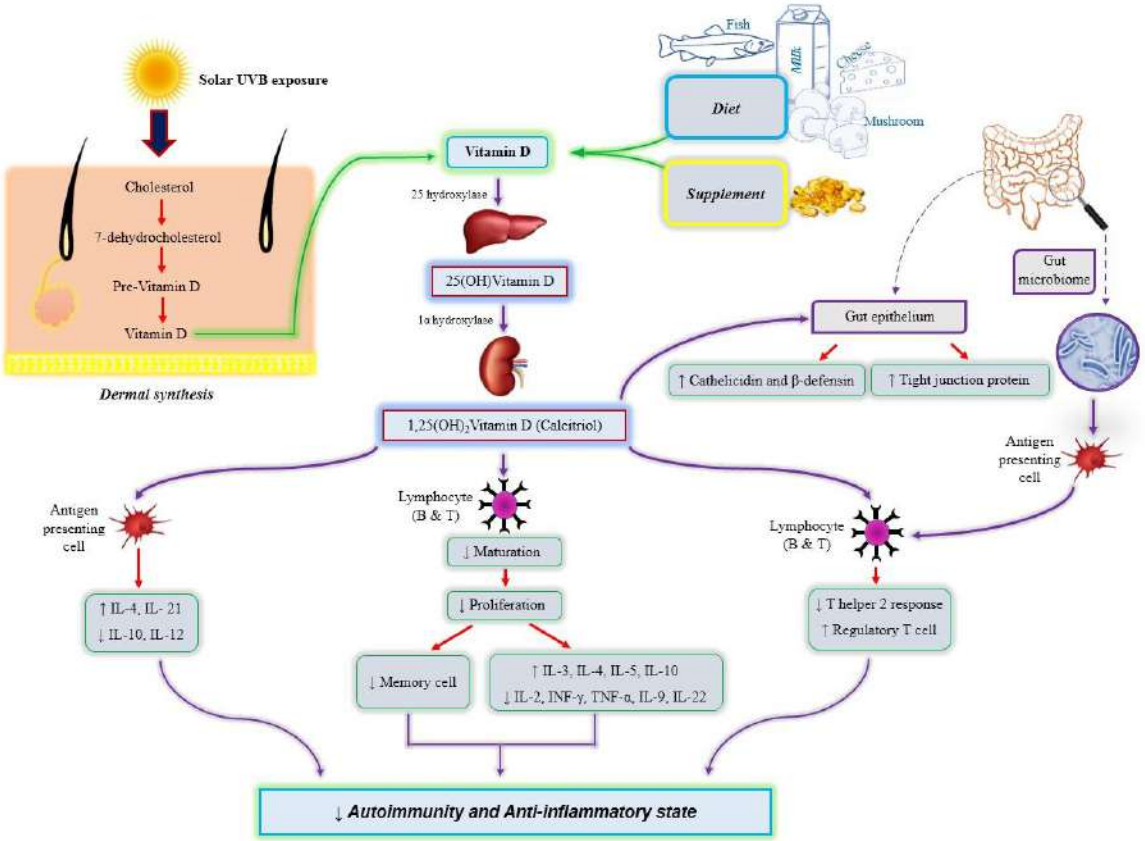

Figure 1. This figure illustrates the role of vitamin D in regulating immune system and its possible effects on developing IBD. Three main sources of vitamin D are illustrated in this figure which are supplementation, UV exposure and dietary intake. Calcitriol has major effects on immune system cells and gut epithelium. It can modulate both B and T lymphocytes and also antigen presenting cells. The main effect will take place by alteration production of different cytokines and inflammatory factors. These changes will result in alteration of immune system as well as producing memory and helper cells that are important in developing immune mediated diseases such as IBD. Also, vitamin D has important effects on gut epithelium by alternating β-defencine and tight junctions. Vitamin D will also affect T helper-2 and T regulatory cell responses to antigen producing cells which have up taken the gut microbiota.

Table 1. Summary of the most relevant studies investigating serum vitamin D status and sun exposure in inflammatory bowel disease

Author and year	Study type	Population	Vitamin D status assessment	Main findings

Joseph et al., 2009. (42)	Case-control	34 CD and 34 controls	RIA	Significantly lower vitamin D level in CD patients compared to controls
Suibhne et al., 2012 (67)	Case-control	81 CD and 70 controls	RIA	Association between VDD and longstanding disease and smoking in CD patients
Garg et al., 2013 (28)	Case-control	71 IBD and 23 controls.	Electrochemiluminescent	Inverse association between intestinal inflammation and vitamin D level
Grunbaum et al., 2013 (33)	Case-control	55 IBD and 48 controls	RIA	No significant difference in vitamin D level between IBD patients and healthy controls
Han et al. 2017 (36)	Case-control	83 IBD	LCMS	Significantly higher prevalence of vitamin D insufficiency or deficiency in IBD patients compared to controls
Opstelten et al., 2018 (69)	Case-control	241 IBD	LCMS	No association between serum vitamin D level and dietary intake of vitamin D and development of CD or UC
Vernia et al., 2018 (101)	Case-control	292 IBD and 540 controls	Sunlight exposure questionnaire	Significantly lower sun exposure in IBD patients in comparison to healthy controls
Strisciuglio et al., 2018 (90)	Case-control	33 IBD age 2-15	ELISA	Significantly lower VDBP in IBD patients compared to healthy controls. Furthermore, significant indirect association between CRP and VDBP
Veit et al., 2014 (99)	Cohort	58 IBD and116 controls	Chemiluminescent	No significant difference in vitamin D concentration between IBD patients and healthy controls
Nerich et al., 2011 (66)	Cohort	57098525 participants	-	Correlation between low sun exposure and increased incidence of CD but not UC
Khalili et al., 2012 (44)	Cohort	175912 women participants	-	Correlation between residence in higher latitude regions (low sun exposure) and increased incidence of both CD and UC
Ananthakrishnan et al., 2013 (2)	Cohort	3217 IBD	LCMS	Significant correlation between low level of vitamin D and elevated risk of hospitalization and surgery requirement
Jantchou et al., 2013 (38)	Cohort	91870 women participants	-	Correlation between higher sun exposure and decreased incidence of CD but not UC

Tan et al., 2014 (93)	Cohort	231 IBD and 122 controls	ELISA	VDD was common in Chinese IBD patients and is strongly associated with the severity of the disease
Ghaly et al., 2016 (30)	Cohort	309 CD	LCMS	Significantly association between elevated VDBP and higher risk of disease flare, however serum vitamin D level was not able to predict IBD flare
Stein et al., 2016 (89)	Cohort	220103 IBD	-	Correlation between lower sun exposure and higher rate of hospitalization
Ananthakrishnan et al., 2014 (3)	Cohort	2809 IBD	RIA and HPLC	Per 1 ng/mL increment in vitamin D level resulted in 8% decrement in risk of CRC in IBD patients
Dumitrescu et al., 2014 (24)	Cohort	47 IBD	Chromatography	Lower level of vitamin D in moderate to severe IBD patients compared to IBD patients with mild disease
Carlsen et al., 2017 (14)	Cohort	79 IBD age 10-17	ELISA	Significant direct correlation between patient's quality of life and vitamin D concentration
Santos-Antunes et al., 2016 (81)	Cohort	68 IBD	ELISA	Association between VDD and anti-TNF therapy failure
Kabbani et al., 2016 (43)	Cohort	965 IBD	HPLC	Association between VDD and higher IBD severity
Frigstad et al., 2017 (27)	Cohort	408 IBD	HPLC	Association between VDD and higher disease activity
Alrefai et al., 2017 (1)	Cohort	201 CD	HPLC	Correlation between VDD and increased disease activity
Gubatan et al., 2018 (34)	Cohort	70 UC	ELISA	Association between vitamin D and anti-inflammatory cytokines
Limketkai et al., 2014 (49)	Cohort	1034199 IBD	-	Correlation between lower sun exposure and increased need for hospitalization, bowel surgery and also higher disease severity
Winter et al., 2017 (106)	Cohort	173 IBD	HPLC	VDD affects initial response to anti-TNF-α therapy
Schaffler et al., 2017 (83)	Cohort	208 IBD	HPLC	High prevalence of VDD among IBD patients
Venkata et al., 2017 (100)	Cohort	880 CD	RIA	Protective effect of normal vitamin D in CD patients

Tajika et al., 2004 (92)	Cross-sectional	33 CD and 15 controls	Competitive protein binding assay	No significant difference in vitamin D level between IBD patients and healthy controls
El-Matary et al., 2011 (25)	Cross-sectional	60 IBD	Competitive protein binding assay	Significantly lower level of vitamin D in IBD in comparison with healthy participants
Jørgensen et al., 2013 (41)	Cross-sectional	182 CD and 62 controls	Chromatography	Negative association between vitamin D level and disease activity
Middleton et al., 2013 (59)	Cross-sectional	116 CD and 40 controls	Competitive protein binding assay	No association between vitamin D level and CD disease severity and history of surgery
de Bruyn et al., 2014 (13)	Cross-sectional	101 CD and 41 controls	Chemiluminescent	No statistically significant difference in vitamin D level between healthy controls and IBD patients
Kini et al., 2014 (46)	Cross-sectional	29 CD	Mass spectrometry	Insignificantly association between seasonal serum vitamin D level and disease activity
Raftery et al., 2015 (78)	Cross-sectional	119 CD	LCMS/MS	Significant inverse association between vitamin D level and intestinal inflammation
Castro et al., 2015 (15)	Cross-sectional	76 IBD	Immunoassay	Significantly lower level of vitamin D in CD patients compared to UC. Furthermore patients who were in clinical remission had higher vitamin D concentration than those with active disease
Torki et al., 2015 (96)	Cross-sectional	133 IBD	RIA	Correlation between insufficiency and deficiency of vitamin D and IBD activity
Meckel et al., 2016 (56)	Cross-sectional	230 UC	RIA	Inverse association between serum vitamin D and mucosal inflammation
Dolatshahi et al., 2016 (23)	Cross-sectional	50 UC	HPLC	Correlation between low vitamin D level and more disease activity
Ye et al., 2017 (109)	Cross-sectional	131 CD	RIA	Inverse association between vitamin D concentration and endoscopic disease activity and could be used as potential biomarker for assessing CD activity
Frigstad et al., 2017 (27)	Cross-sectional	408 IBD	LCMS	Correlation between VDD and higher inflammation and IBD activity and also higher risk of relapsing

Scolaro et al., 2018 (84)	Cross-sectional	60 IBD	ELISA	Association between VDD and IBD activity
Lee et al., 2018 (47)	Cross-sectional	102 pregnant with IBD and 574 pregnant women without IBD	LCMS	Dose of vitamin D supplementation in current guidelines seems be inadequate for pregnant women with IBD
Lu et al., 2015 (53)	Meta-analysis	21 studies	-	Lower vitamin D levels in both CD and UC patients compared to controls
Holmes et al., 2015 (37)	Meta-analysis	28 studies investigated pediatric CD	-	Correlation between higher latitude and increased incidence of CD in pediatrics

VDD: vitamin D deficiency; IBD: inflammatory bowel disease; CD: crohn's disease; UC: ulcerative colitis; CRC: colorectal cancer; ELISA: enzyme-linked immunosorbent assay; RIA: radioimmunoassay; HPLC: high-performance liquid chromatography; LCMS: liquid chromatography mass spectrometry; VDBP: vitamin D binding protein; CRP: C-reactive protein

Table 2. Summary of the most relevant clinical trials investigating vitamin D supplementation in inflammatory bowel disease

Author and year	**Population**	**intervention**	**follow duration**	**Vitamin D assay**	**Main findings**
Miheller et al., 2009 (60)	37 CD	Group A: Orally 0.5 µg alfacalcidiol/day Group B: Orally 1000 IU vitamin D3/day	12 months	NM	More reduction but not significant in DAI and CRP level with treatment by active form of vitamin D (alfacalcidiol) compared with colecalciferol
Jørgensen et al., 2010 (40)	94 CD	Orally 1200 IU vitamin D3/day	12 months	NM	Insignificantly reduction in disease relapse with vitamin D supplementation
Bendix-Struve et al., 2010 (11)	108 CD	Group A: Orally 1200 IU vitamin D3/day plus 1200 mg Ca/day Group B: placebo + 1200 mg Ca/day	12 months	LCMS	Elevation in IL-6 level and increasing in CD4+ T cell proliferation with vitamin D supplementation
Pappa et al., 2012 (71)	71 IBD aged 5-21	Arm A: Orally 2000 IU vitamin D2/day Arm B: 2000 IU vitamin D3/day	6 weeks	Chemiluminescent	Oral using of 2000 IU vitamin D3 per day and 50000 IU vitamin D2 per week had are more beneficial in increasing serum vitamin D level

		Arm C: 50000 IU vitamin D2/week All participants also received 800 mg Ca/day (<11 years) or 1200 mg Ca/day (≥11 years)			compared to daily oral use of 2000 IU vitamin D2
Yang et al., 2013 (108)	18 CD	Orally 1000 IU vitamin D3/day	24 weeks	ELISA	Significantly reduction in DAI with vitamin D supplementation therapy
Ananthakrishnan et al., 2013 (2)	3217 IBD	50000 IU vitamin D2/week	-	LCMS	Vitamin D in sufficiency was associated with increased surgery rate in both UC and CD patients. Lower requirement of surgery in CD patients with treated Vitamin D insufficiency.
Pappa et al., 2014 (70)	63 IBD aged 8-18	Arm A: Orally 400 IU vitamin D2/day plus 800 mg Ca/day (<11 years) or 1200 mg Ca/day (≥11 years) Arm B: Orally 1000 IU vitamin D2/day in the summer/fall and 2000 IU vitamin D2/day in the winter/spring All participants also received 800 mg Ca/day (<11 years) or 1200 mg Ca/day (≥11 years)	12 months	Chemiluminescent	Daily doses of vitamin D up to 2000 IU was well tolerated but was failed to maintain optimal vitamin D status. Receiving higher doses of vitamin D was related to decrease in inflammatory markers
Wingate et al., 2014 (105)	83 CD aged 8-18	Group A: Orally 400 IU vitamin D3/day Group B: Orally 2000 IU vitamin D3/day	6 months	Chemiluminescent	No significant differences in ESR, CRP and DAI between two groups
Raftery et al., 2015 (77)	27 CD	Orally 2000 IU vitamin D3/day	3 months	LCMS	Significantly lower CRP and higher quality

					of life and non-significantly lower DAI in CD patients with 25(OH)D≥75 nmol/L
Dadaei et al., 2015 (19)	108 IBD	Orally 50000 IU vitamin D3/week	12 weeks	ELISA	Insignificantly decrease in serum level of TNF-α which was correlated with DAI
Shepherd et al., 2015 (86)	76 children with IBD	Orally single dose of 200000 IU vitamin D3 in Age<3, 400000 IU in Age:3–12, and 800000 in Age>12	6 months	Chemiluminescent	Oral administration of these single high-dose of vitamin D supplement was safe and effective for maintaining vitamin D in sufficient levels for a period of six months
Sharifi et al., 2016 (85)	86 UC	Intramuscular single dose of 300 000 IU vitamin D3	90 days	ELISA	Significantly reduction in ESR and CRP with vitamin D supplementation in UC patients
Garg et al., 2017 (29)	10 IBD	Specific protocol with dose adjusted 4-weekly	12 weeks	NM	Amelioration in symptom-based activity score, however serum markers of inflammation was not decreased
Mathur et al., 2017 (55)	18 UC	Orally 2000 or 4000 IU vitamin D3/day	90 days	NM	Significantly increase in quality of life with higher dose regimen and insignificantly decrease in CRP level with both regimens
Narula et al., 2017 (64)	34 CD	Orally 1000 or 10000 IU vitamin D3/day	12 months	Chemiluminescent	Insignificantly differences in clinical relapse between two groups
Simek et al., 2017 (87)	32 IBD aged 8-21	Arm A: Orally 5000 IU vitamin D3/10 kg/week Arm B: Orally 10000 IU vitamin D3/10 kg/week	6 weeks	LCMS	Both 6 weeks vitamin D regimens were safe and effective in normalizing vitamin D status for 12 weeks. Maintenance vitamin D therapy is recommend in pediatric IBD
Tan et al., 2018 (94)	124 IBD	Arm A: Orally 150000 IU vitamin D3/3	12 months	ELISA	Daily oral administration of 1667 IU vitamin D3 is sub-optimal for IBD

		months plus Ca 600 mg/day Arm B: Orally Ca 600 mg/day Arm C: vehicle control group			patients with vitamin D insufficiency or VDD. Although the DAI was reduced by IBD treatment and remission was achieved, however, vitamin D status was not improved in Arm C.

IU: international unit; IBD: inflammatory bowel disease; CD: crohn's disease; UC: ulcerative colitis; Ca: calcium; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IL-6: interleukin-6; ELISA: enzyme-linked immunosorbent assay; LCMS: liquid chromatography mass spectrometry; DAI: disease activity index; NM: not-mentioned