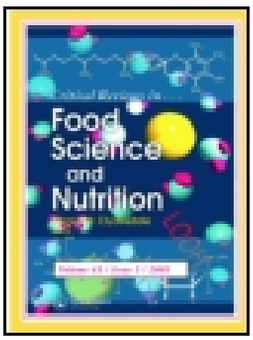

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Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

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**To cite this article:** Sandra Maria Barbalho, Ricardo de Alvares Goulart & Rodrigo Gallhardi Gasparini (2017): Associations between inflammatory bowel diseases and vitamin D, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2017.1406333

**To link to this article:** https://doi.org/10.1080/10408398.2017.1406333

Published online: 13 Dec 2017.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2017.1406333



# Associations between inflammatory bowel diseases and vitamin D

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**ABSTRACT**

Inflammatory Bowel Diseases (IBD) are increasing sharply, and the common medications are not effective for most patients. Vitamin D (VD) has been considerate to reduce inflammatory processes and may be helpful in IBD. The aim of this review was to perform an update on the potential role of VD in the IBD. We performed a search for articles associating VD and IBD published in MEDLINE-PubMed and EMBASE. The focused question used for the search was "What is the association between Inflammatory Bowel Disease and Vitamin D?" The exclusion criteria for this search were studies not in English, editorials, case reports, or poster presentations. VD prevents the inflammatory process such as negatively interfering with the release of Interleukin (IL)-1, IL-6, and Tumour Necrosis Factor-$\alpha$; enhancing the function of the intestinal epithelial barrier; decreasing the occurrence of apoptosis; stimulating Toll-Like Receptor-4; inducing the production of an antimicrobial peptide in Paneth cells. Furthermore, deficiency of VD is related to the severity of the symptoms and increased the risk of cancer and surgery. In conclusion, VD shows a potential role in the management of IBD, the supplementation is inexpensive, safe, and leads to improvement of the quality of life.

**KEYWORDS**

Inflammatory bowel disease; Ulcerative Colitis; Crohn's Disease; Vitamin D



## Introduction

The Inflammatory Bowel Diseases (IBD) include Ulcerative Colitis (UC) and Crohn's Disease (CD) that are the two primary entities defined as the chronic relapsing idiopathic inflammation of the gastrointestinal tract and with aetiology not wholly understood. The disruption of the equilibrium in the intestinal epithelial barrier leads to a higher permeability of the epithelial cells and enhanced uptake of microorganisms across the mucosa which triggers the activation of the immune system (Mohammed et al., 2017; Iida et al, 2017). The loss of homeostasis is not entirely understood, but it may be related to several aspects such as deficiency of Vitamin D (VD), and other factors as shown in Figure 1. Genetic factors may also be related to the incidence of the inflammatory conditions, which are considered to be a global burden (Liu et al., 2017; Zheng et al., 2017).

It has been estimated that millions of people worldwide suffer from IBD and are afflicted with recurrent symptoms of diarrhea, bleeding, abdominal pain, bowel obstruction, and other symptoms that reduce the quality of life and capacity for working (Rahbour et al., 2017; Reboredo et al., 2017).

UC is an inflammatory condition that manifests as a polymorphonuclear infiltration with the presence of oedema, cryptic abscesses, and congestion. Its stratified pattern of inflammation leads to proctitis, left-sided colitis, or pancolitis (Papamichael et al., 2017; Goulart et al., 2016). In CD patients, the inflammatory pattern involves an idiopathic transmural inflammation that permeates all the layers of the intestine wall. This scenario culminates in ulcerations and fistulisation in the abdominal wall and the perianal region. Figure 1 shows some aspects that differentiate UC and CD (Abautret-Daly et al., 2017; Jaime et al., 2017; Li et al., 2016).

Many authors have shown that Vitamin D (VD) is linked with gastrointestinal function, and its deficiency may play a potential role in IBD. It is a fat-soluble hormone that is obtained from the diet or synthesized in the skin under exposition to sunlight (Barbalho et al., 2016), and has been related to several aspects of immune system and inflammation pathways. It shows active signalization in the gut, exhibiting both immune-regulatory and immune-suppressive roles on inflammatory and inhibitory markers of IBD. It interferes with the immune response to the bacterial response, antigen presentation, and regulation of adaptive and innate immunity. Thus, VD may influence the incidence and progression of UC and CD (Bora et al., 2017; Ananthakrishnan et al., 2015; Yano et al., 2011).

Over 1.5 million people suffer from IBD in North America and 2 million in Europe (Burisch et al., 2013; Ng et al., 2017). As the number of patients has increased sharply in recent year the literature shows that there is an urgent need to reach a broader comprehension of the pathological processes involved in these diseases. As VD may profoundly influence

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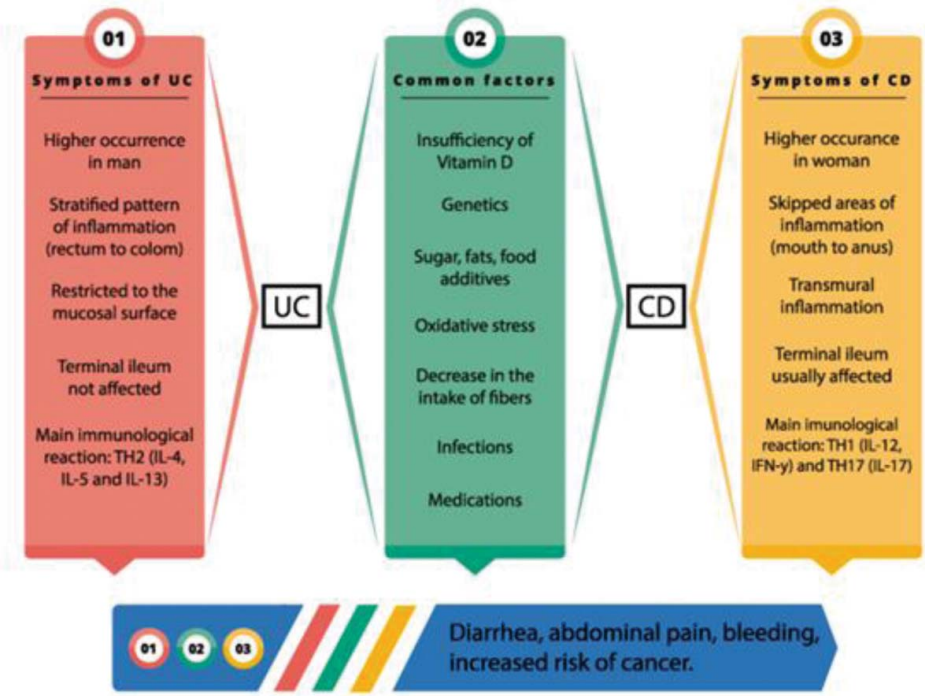


**Figure 1.** Ulcerative Colitis (UC) and Crohn's Disease (CD): symptoms, similar and non-similar aspects and consequences. TH2: T helper 2; IL- 4: Interleukin 4; IL- 5: Interleukin 5; IL-13: Interleukin 13; TH1: T helper 1; IL- 12: Interleukin 12; IFN-$\gamma$: Gamma-Interferon; TH17: T helper 17. Modified form Barbalho et al, 2016.

inflammatory processes, the aim of this review is to perform an update on the potential role of this vitamin in the IBD.

## Methods

### *Focused question*

The focused question used for this search was "What is the association between Inflammatory Bowel Disease and Vitamin D?"

### *Inclusion and exclusion criteria*

Recent studies associating Vitamin D and Inflammatory Bowel Disease published in MEDLINE-PubMed and EMBASE were included. Reviews and original articles in English were selected. The exclusion criteria for this search were studies not in English, editorials, case reports, or poster presentations.

### *Databases*

For this review, we have searched the MEDLINE-PubMed (National Library of Medicine, National Institutes of Health), and EMBASE databases for appropriate articles addressing the focused question.

As Vitamin D may be referred by other different terms, the following combinations of keywords were used: "Inflammatory Bowel Disease" and "Vitamin D", "calcidiol", " calcitriol", "1,25 (OH)2D3", "25(OH)D", "25 hydroxycholecalciferol", and "cholecalciferol". These terms were also combined with "Crohn's Disease" and "Ulcerative Colitis". With this list of references for these combinations of descriptors, we selected the most relevant articles to build our discussion and we separated studies in human models that were performed in the last five years (2013 up to September, 2017) to build Table 1. The screening of the studies was evaluated by each author and checked for agreement among all of them.

## Results

Several authors have been discussing the potential role of VD in the inflammatory processes and in IBD. For these reasons, many studies were consulted in order to provide information about the Pathophysiology of IBD, Metabolism of VD and the association of this vitamin with IBD. For original studies with humans, we have found eighteen original articles that fulfil the eligibility criteria for this review (these articles were selected in the last 5 years). These eighteen articles have included 8,838 patients (3,545 classified as CD patients; 2,440 as UC patients; and for 2,853 patients, no classification was reported in the studies). All the studies were performed at Universities and Healthcare Centers, and the size of the samples ranged from 10 to 3,217 patients aged between 8 to 79 years (male and female patients). Sixteen studies enrolled adult patients (Frigstad et al., 2017; Han et al., 2017; Narula et al., 2017; Pallav et al., 2017; Garg et al., 2017; Winter et al., 2017; Abreu-Delgado, Isidro, Torres, 2016; Santos-Antunes et al., 2016; Kabbani et al., 2016; Ghaly et al., 2016; Raftery et al, 2015a; Raftery et al., 2015b; Castro et al., 2015; Torki et al., 2015; Ananthakrishnan et al., 2014;) and two studies enrolled paediatric patients (Carlsen et al, 2017; Simek et al., 2016). These eighteen articles are found in Table 1.

**Table 1.** Main findings relating Vitamin D (VD) in Inflammatory Bowel Disease Patients after the evaluation of the 18 studies selected for this review in the last 5 years.

| Model | VD in the patients | Main findings related to VD | Reference |
|---|---|---|---|
| 3,217 IBD patients (55% CD) | VD < 20 ng/mL indicate increased surgery risk and hospitalization. | Supplementation of CD patients reduced risk or surgery. | Ananthakrishnan et al., 2013 |
| 2809 IBD patients with VD media of 26ng/mL (11 y of follow-up) | 7% developed cancer (n = 191; 41 cases of colorectal cancer). | Deficiency showed increased risk for cancer. Each 1-ng/mL increase in plasma was linked to 8% reduction in risk of colorectal cancer. | Ananthakrishnan et al., 2014 |
| 27 CD patients in remission | Three months of treatment with VD 2,000UI/d increased serum levels and cathelicidin. | Levels higher than 75nmol/L increased QoL scores and reduced CRP. | Raftery et al., 2015a |
| 119 CD patients | VD was inversely linked to the levels of CRP and FC. | VD levels were significantly inversely linked to intestinal inflammation. | Raftery et al., 2015b |
| 76 IBD patients (19 CD / 57 UC) | Patients in remission presented higher VD levels. SIBDQ scores < 50, disease activity and low QoL related to low levels. | Most IBD patients presented low levels of VD | Castro et al., 2015 |
| 85 UC and 48 CD patients | There is a link between VD levels and disease activity. | Patients presented low levels of VD. | Torki et al., 2015 |
| 34 pediatric IBD patients | Use of 5,000 or 10,000 IU/10 kg body weight/week was efficient and safe at normalizing VD levels. | Increase levels of VD were observed after 8 weeks of treatment. | Simek et al., 2016 |
| 56 CD and 12 UC patients | VD deficiency was associated with risk for adverse events in anti-TNF therapy and with the presence of antinuclear antibodies. | Deficiency of VD was shown in 93% of the patients. | Santos-Antunes et al., 2016 |
| 965 IBD patients: 62% CD; 38% UC. Follow up of 5 years. | Patients with low levels: needed more biologic narcotics, steroids, tomography scans, emergency, hospital admissions, and surgery. Presented worse disease activity scores, pain, and QoL. | Kabbani *et al.*, 2016 Supplementation: decrease healthcare utilization. Low levels: increased morbidity and severity of the disease. | Kabbani et al., 2016 |
| 309 CD patients | 12% were VD deficient; 35% were insufficient. | Higher VD-binding protein significantly correlated with increased risk of disease flare. | Ghaly et al., 2016 |
| 10 IBD and 10 non-IBD patients | IBD patients presented more insufficiency of VD. | Inflammation correlates negatively with colonic VDR expression in the diseased mucosa. | Abreu-Delgado, Isidro, Torres, 2016 |
| 408 IBD patients (53% CD and 44% UC) | 49% presented VD <50 nmol/L: 53% CD and 44% UC patients. In CD patients, VD was inversely linked to disease activity. | VD deficiency was linked with higher scores in disease activity. UC patients with VD deficiency showed elevated FC. | Frigstad et al., 2017 |
| 83 IBD patients | 89.2% exhibited suboptimal levels of VD. CD patients were linked to low levels of VD. | Korean IBD patients present insufficiency of VD. | Han et al. 2017 |
| 173 IBD patients with anti-TNF-$\alpha$ | There was the induction of remission with the use of VD. | Patients with the sufficiency of VD had 2.64 increased odds of remission at three months. | Winter et al. 2017 |
| 79 pediatric IBD patients (39 CD / 40 UC) | IMPACT score for QoL significantly associated with UC and CD-symptom score and inversely associated with VD levels. | IMPACT score for QoL and levels of VD associated with CF and other markers. | Carlsen et al., 2017 |
| 10,000IU/d and 1,000 IU/d (1 year in 39 remission CD patients) | 10,000 IU/day: VD levels from 73.5 nmol/L to 160.8 nmol/L. Both groups presented improvement in scores of anxiety and depression. | The rate of relapse was not significant differences between patients both doses. | Narula et al., 2017 |
| 5 patients with CD and 5 UC | Use of a dose adjusted 4-weekly (50,000-100,000 IU) to reach a target level of 100–125 nmol/L (12 weeks of treatment). | Oral VD reached the target levels, improved activity scores, but did not modify intestinal or systemic inflammation (fecal calprotectin and circulating markers). | Garg et al., 2017 |
| 211 IBD patients (129 CD and 82 UC) | CD patients were more likely to be VD deficient. | Patients with BMI > 30 kg/m$^2$ and African-American race were linked to VD deficiency in IBD patients. | Pallav et al. 2017 |

IBD: Inflammatory Bowel Disease; CD: Crohn's Disease; UC: Ulcerative Colitis; VD: Vitamin D; QoL: Quality of life; FC: Fecal calprotectin; CRP: C-Reactive Protein; SIBDQ: Short Inflammatory Bowel Disease Questionnaire.

## Discussion

### *Pathophysiology of IBD*

The chronic inflammatory process that affects IBD patients is associated with the disruption in the response of the immune system in the mucosa and epithelial barrier due to a plethora of known and unknown possible causes, such as genetic factors and environment (Iida et al., 2017). The recognition of an antigen occurs by the recruitment of protein adapters and cellular kinases that trigger the activation of signalling cascades that

lead to the activation of Mitogen-Activated Protein Kinase (MAPK) and Nuclear Factor-$\kappa$B (NF-$\kappa$B) (Yokota et al, 2017; Mohammed et al., 2017; Calderón-Gómez et al., 2016; Ordás, 2012; Elia et al., 2015).

Literature shows that over 200 loci with approximately 1500 potential associated genes were identified as being correlated with the pathology of IBD. NOD2 (Nucleotide-Binding Oligomerization Domain 2) was the first gene discovered for increasing the susceptibility for development of CD (Yano et al., 2011) and its functions are related to intracellular bacterial sensing, autophagy, control in the production of the antibacterial peptide in Paneth cells, and improvement of tolerance by decreasing action of TLR (Toll-Like Receptor). Dysfunction in NOD2 is linked to the development of CD and production of Tumor Necrosis Factor $\alpha$ (TNF-$\alpha$) and other proinflammatory cytokines as well as activation of caspase-1 resulting in the release of Interleukin (IL)-1$\beta$ and IL-18 (Cooney et al., 2010; Travassos et al., 2010).

The main panorama in IBD patients tends to substantially increase the inflammation process with a reduction in the activation of Regulatory T cells (Treg) and reduction in the release of anti-inflammatory cytokines such as IL-10 and Transforming Growing Factor-$\beta$ (TGF-$\beta$). In CD, the main immunological reaction occurs by TH1 (T Helper 1), which is activated by IL-12 and related with the release of Interferon-$\Upsilon$ (IFN-$\Upsilon$). There is also a higher production of TNF-$\alpha$ that is related to the disease activity (Bittner et al., 2017; Bamias et al., 2017; Fuss et al., 2004). In CD, TH17 is also activated and results in the release of IL-17 (Calderón-Gómez et al, 2016). This scenario is followed by a profound increase in the synthesis of inflammatory mediators such as chemokines, growth factors, prostaglandins, leukotrienes, and reactive oxygen species (ROS). These products are associated with intensification of inflammation, cell damage, destruction of the tissues, and manifestation of the clinical signs of the disease. There is also leukocytes recruitment from vascular space to the sites of the illness which is essential for the continuity of the inflammatory pathways (Bamias et al., 2017). Figure 2 summarizes the inflammatory pathways that occur in homeostasis and UC and CD.

Due to the high complexity of the aberrant intestinal inflammation, it is difficult to achieve a final therapeutic approach as it is observed with the use of standard drugs such as glucocorticoids that induce 50% of the patients to dependency or surgery, and many do not respond to these drugs (20–30%). Modern therapies such as the use of Anti-TNF drugs induce healing of the mucosa in only 30–50% of the individuals. The understanding of the pathophysiological process is necessary to improve the existent therapies or develop efficient new ones (Zhiwei et al., 2017; Rosen et al., 2015; Colombel et al., 2011). Alternative therapies such as the use of Vitamin D may help in the prevention or remission of inflammatory pathways.

## Vitamin D

Figure 3 summarizes the metabolism of VD. The primary circulating metabolite, the calcidiol (25-hydroxyvitamin D), is formed by hepatic hydroxylation through enzymes CYP2R1, and others such as CYP27A1, CYP2J2, and CYP3A4. The last one is expressed in colonic epithelial cells of humans and has upregulation by VD signaling. When produced by plants, it is named ergocalciferol (VD2). The skin may synthesize VD in amounts ranging up to 25,000 IU/day under UVB radiation exposition and can interfere in several biological processes (Reich et al., 2014).

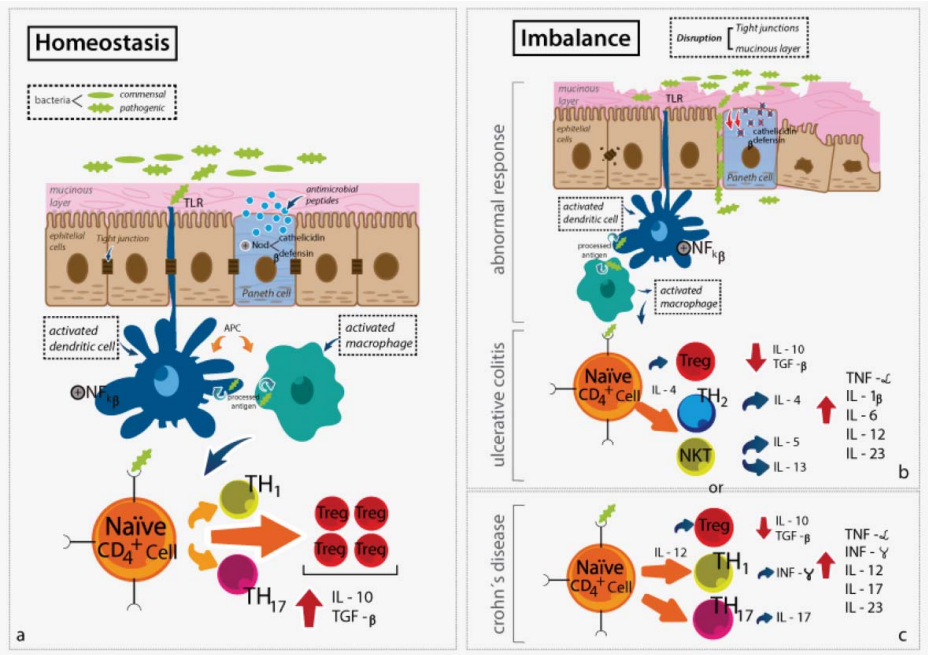


**Figure 2.** a) In homeostasis, there is an adequate inflammatory response to the antigens. TLR receptors are related to the recognition of microorganism; there is activation of NF-k$\beta$ that induces the release of inflammatory cytokines. Treg cells and release of IL-10 and TGF-$\beta$ mediate a resolution of this process. b and c) In the imbalance (disruption in tight junctions and/or mucinous layer) predominates the inflammatory response: Paneth cells decrease the production of cathelicidin and defensins; in UC the main response is mediated by TH2, and in DC the main response is mediated by TH1 and TH17 resulting in the release of several inflammatory cytokines. UC: Ulcerative Colitis; CD: Crohn's Disease; TH: T helper cell; NKT: Natural Killer T cells; IL: Interleukin TGF-$\beta$: Transforming Growing Factor $\beta$; NF-k$\beta$: Nuclear Factor k$\beta$.

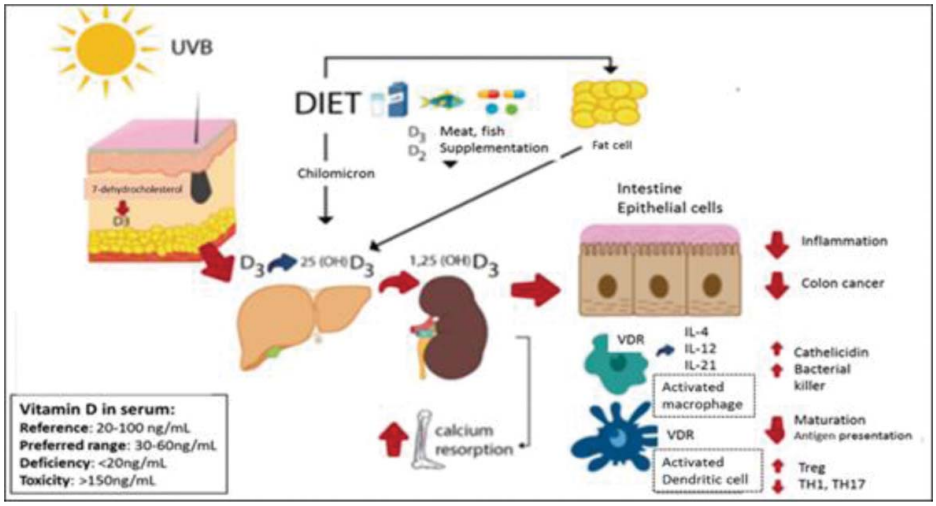


**Figure 3.** Vitamin D: metabolism, effects on the epithelial cells and reference values. Vitamin D may be obtained from the diet, supplementation or by an exposition of 7-dehydrocholesterol presented in the skin to sunlight. Activation of this compound by ultraviolet light and after modification in liver and kidney results in $1,25(OH)_2D_3$ that is associated with a reduction of inflammation processes in epithelial cells (reduction of the activation of TH1 and TH17). The actions of this vitamin require the activation of VDR (Vitamin D Receptor). Levels of Vitamin D in the serum are according to Abreu-Delgado, Isidro, Torres (2016). IL: Interleukin; Treg: Regulatory T cells, TH: T Helper Cell.

VDR (VD receptor) and 1-$\alpha$-hydroxylase (CYP27B1), which is the VD-activating enzyme, are expressed in almost all cells of the immune system (activated or naïve CD4+ and CD8+ T cells, B cells, neutrophils, dendritic cells, and macrophages), and in the intestine (Galone et al., 2017).

### Vitamin D and IBD

VD intensifies the chemotactic and phagocytic macrophage responses inducing the synthesis of antimicrobial peptides such as cathelicidin, and results in a decrease in the synthesis of inflammatory interleukins (IL-1, IL-6, IL-8), and TNF-alpha. VD/VDR also interferes in the function and balance of TH1 and cytokine patterns due to the enhancing of TH2 response. It is also associated with the inhibition of TH17 cells and the stimulation of Treg cells that are protective against autoimmunity due to the stimulation of the expression of the cytotoxic T-associated protein 4 (CTLA- 4) and Fork-head box P3 (FOXP-3), associated with the production of IL-10 (Figure 4). VDR is also needed to prevent the replication of quiescent CD8+ T cells and for the release of IFN-$\gamma$. Polymorphisms in the VDR result in abnormal answers in the immune system and, thus, are associated with IBD. $1,25(OH)_2D_3$/VDR also stimulates the transcription of NOD2 gene that is related with the production of $\beta$-defensin 2 and cathelicidin (Chun et al., 2014; Chen et al., 2014).

Besides being crucial for the production of T reg cells and in the disconnection of TH1 and TH17, $1,25(OH)_2D_3$ is also crucial for the expression of iNKT (invariant Natural killer T cells) and CD8$\alpha\alpha$ T cells, leading to the homeostasis of the gastrointestinal system. Insufficiency of VD results in dysbiosis and augmentation of inflammation markers, and a shift of the microbiome (Cantorna, 2016; Zator et al., 2014; Cantorna, 2012).

$1,25(OH)_2D_3$ is related to the upregulation of MAPK-1 which is crucial for the regulation of the release of inflammatory markers. It up-regulates MAPK-1 and, thus, negatively interferes with the release of IL-1, IL-6, and TNF-$\alpha$ (White et al., 2016; Ooi et al., 2013).

One of the first responses to the presence of the pathogens is the release of IL-1$\beta$. Transcription of the gene of this interleukin is a direct target of $1,25(OH)_2D_3$, and its secretion occurs by cooperation induced by this hormone and infection of macrophages (White et al., 2016). Another direct target of $1,25(OH)_2D_3$ is the gene encoding NOD2. The induction of this gene is also needed because its protein plays a role in autophagy and production of autophagosomes, which act in intracellular pathogens, damaged organelles, and proteins which will be destroyed by lysosomes. Insufficiency of VD also is linked with abnormal Paneth cells and a decrease in the release of ATG16L1 which will result in a reduction of the proteins that are necessary for autophagy. These roles of VD show that its insufficiency may increase the chances of occurrence of CD (Verway et al., 2013; Wang et al., 2010).

Furthermore, VD is linked with the action of Lithocholic Acid (LTC) that is produced from glycine and taurine-conjugated bile acids by the microbiome in the gut and is made a part of the enterohepatic cycle. LTC can interfere in TH cells by inhibiting the activation of TH1 in Jurkat T cells, and primary $CD4^+$ TH cells. This process is deeply mediated via VDR, which is well known to hedge TH1 inflammatory process. VDR is highly expressed in $CD4^+$ TH cells and is capable of binding to LTC (Makishima et al., 2002). In their study, Pols et al. (2017) showed this close association among VDR and LTC and showed that the signs of this acid acts predominantly but not exclusively via the VDR to inhibit TH1 differentiation in $CD4^+$ TH cells.

VD enhances the function of the intestinal epithelial barrier cells and induces its differentiation and decreases the occurrence of apoptosis particularly in inflammatory processes (Kuhne et al., 2014). It may also stimulate TLR-4, which is capable of recognizing LPS from gram-negative bacteria and indulges beneficial probiotic microorganisms rather than the pathogenic ones. It may also induce the production of

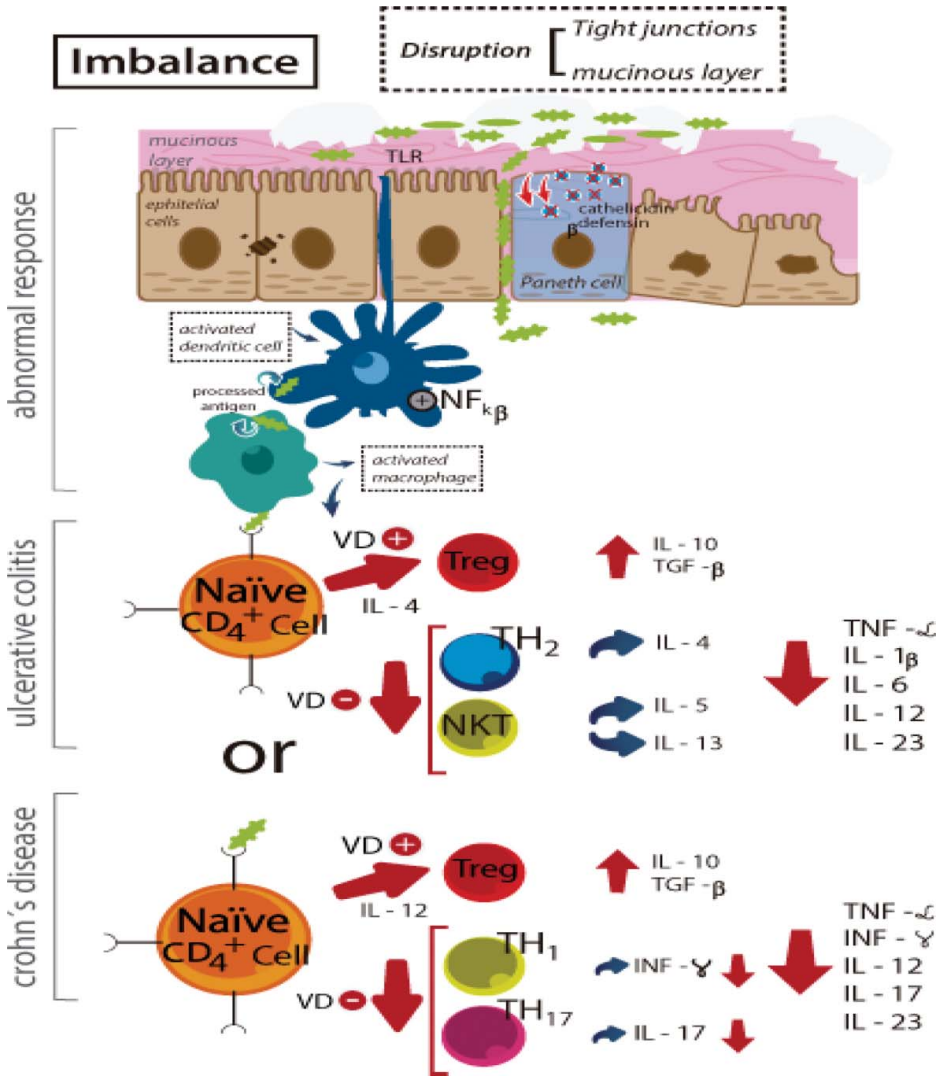


**Figure 4.** The abnormal inflammatory response in IBD increases the release of inflammatory cytokines. In Ulcerative Colitis, the use of VD activates Treg cells and reduce the activity of TH2 response. In Crohn's Disease VD activates Treg cells and reduce the activity of TH1 and TH17 response. +: activation; -: inhibition.VD: Vitamin D; IL: Interleukin; Treg: Regulatory T cells, TH: T Helper Cell; NKT: Natural Killer Cell; TNF- $\alpha$: Tumor Necrosis Factor $\alpha$; IFN-$\gamma$: Interferon $\gamma$.

antimicrobial peptides such defensins and cathelicidin antimicrobial peptide (CAMP) in Paneth cells. The release of these peptides may also stimulate NOD2, which is encoded by a direct VD target gene. Calcitriol interferes in NOD2 and in the production of defensins and CAMP while 1,25D augments CAMP expression (Yang et al., 2017; Dimitrov et al., 2017; Pols et al., 2017; Meeker et al., 2016; Wang et al., 2016; Wang et al., 2010).

VD also has as a direct target, the gene encoding IL-1$\beta$, NK, and innate lymphoid cells. NK regulates dendritic and T cell responses (Martinet et al., 2015). Furthermore, 1,25D augments the cytotoxic function of these cells and downregulates the expression of inflammatory cytokines (Al-Jaderi et al., 2013). Actions in Dendritic cells are also observed. 1,25D may induce the permanence of Dendritic cells in an immature state and produce effects of reduction of expression of pro-inflammatory cytokines and favor Treg production and production of IL-10 (Dimitrov et al, 2017; Bartels et al, 2013).

Some studies also link VD with the intensity of symptoms. Therefore, it may also be related to the therapeutics. In a review, Ardesia et al. (2015) concluded that the insufficiency of VD deficiency was related to 8–100% of CD patients and in 15–60% of UC individuals. They also showed that the decreased levels of this vitamin were associated in 73–100% of the patients in winter and 55–59% of the patients in the summertime. Authors also have concluded that the clinical scores of IBD activity seem to be inversely correlated to the levels of VD which are also associated with clinical outcomes such as surgery, *Clostridium difficile* infection, response to anti-TNF therapy, and death.

Many authors have shown the link between insufficiency of VD (<20 ng/mL) and the IBD prevalence and severity, particularly in CD. According to Ananthakrishnan et al. (2012), in The Nurses' Health Study, which evaluated 72,719 women for 12 years, it was found that 122 of the women developed CD. They concluded that low levels of the vitamin are related to the incidence of this pathology and worsening of the QoL (Kabbani et al., 2016; Ulitsky et al., 2011; Raftery et al., 2015a; Raftery et al., 2015b; Ananthakrishnan et al., 2013). Figure 5 shows that the sufficiency of VD is related with homeostasis in the

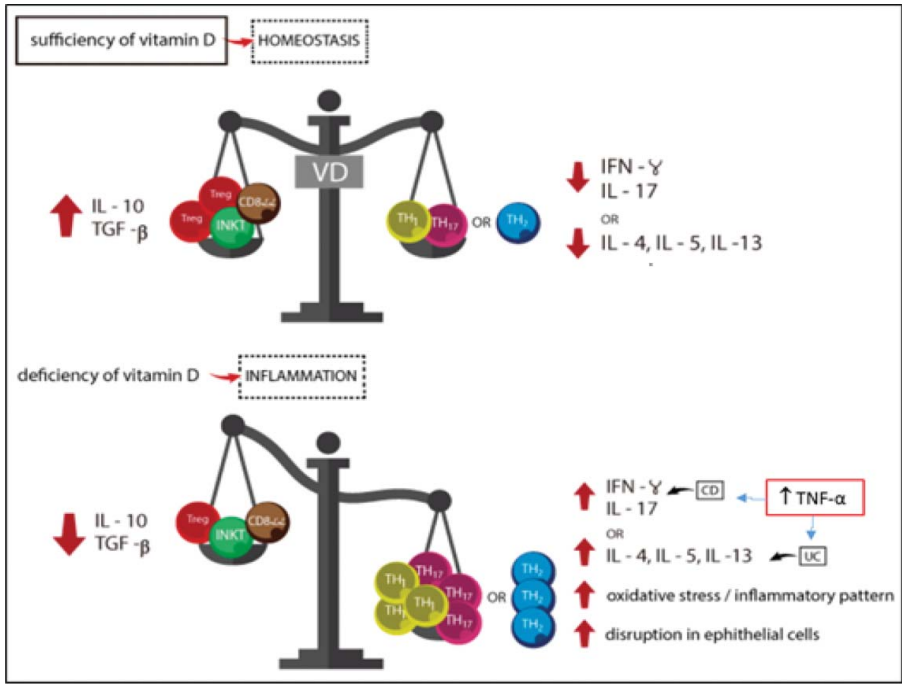


**Figure 5.** In the sufficiency of Vitamin D there is a balance among anti and pro-inflammatory cytokines, and in the insufficiency there is a predominance of the inflammatory pattern, occurrence of oxidative stress and disruption of the epithelial cells Vitamin D; IL: Interleukin; TGF-$\beta$: Transforming Growing Factor-$\beta$; Treg: Regulatory T cells, TH: T Helper Cell; iNKT: invariant Natural Killer Cell; TNF- $\alpha$: Tumor Necrosis Factor $\alpha$; IFN-$\gamma$: Interferon $\gamma$. Modified from Cantorna, 2016.



immune response and the insufficiency leads to the increase of pro-inflammatory conditions.

In Table 1 it is possible to see that several relevant studies had provided substantial evidence that the $1,25(OH)_2D_3$ may play a significant role in the treatment of IBD patients. These studies showed that insufficiency of VD was found to be common in these patients (Torki et al., 2015; Castro et al., 2015; Pallav et al., 2017; Narula et al., 2017). In adults, sufficient levels of VD in CD patients may reduce the risk of colorectal cancer (Anathakrishnan et al., 2014), surgery (Anathakrishnan et al., 2013; Kabbany et al., 2016), and disease activity (Torki et al., 2015; Ghaly et al., 2016; Frigstad et al., 2017; Garg et al., 2017). The improvement in the scores of quality of life (Raftery et al., 2015a; Castro et al., 2015; Kabbani et al., 2016), and anxiety and depression (Narula et al., 2017) are also observed. The diminished inflammation grade was observed due to the reduction of C Reactive Protein and Faecal Calprotectin, and increase in the levels of cathelicidin (Raftery et al., 2015a; Raftery et al., 2015b; Abreu-Delgado, Isidro, Torres, 2016). VD was also connected with the increase in remission (Winter et al., 2017). The deficiency of VD may also augment the occurrence of side effects of traditional therapies such as anti-TNF, the necessity of drugs such as steroids, and hospital admissions (Kabbani et al., 2016).

In children, VD was associated with improvement in the scores for quality of life (Carlsen et al., 2017). Lower VD status are seen mainly in African-Americans and doses of 5,000 or 10,000 IU/10 kg/weekly during six weeks is safe and effective at normalizing VD levels in pediatric IBD patients (Simek et al., 2016) (Table 1).

Nevertheless, the question that remains is, "What would be the optimal doses of VD that are to be used in the IBD patient?" Despite the need for more conclusive clinical studies, there are authors who establish the possible doses to be used. Ananthakrishnan (2016) purposes that the dose depends on whether a patient is insufficient or deficient in VD. For patients with mild insufficiency, he recommends 1000–2000 IU/day. For those who are more deficient, he recommends doses between 2000–4000 IU/day until subjects reach normal levels. After they have achieved normal levels, he recommends 1000 IU/day for maintenance. For subjects with VD levels less than 15–20 ng/mL, he recommends higher doses weekly (50,000 UI) for about three months until the patients reach normal levels.

Despite the findings of Ananthakrishnan (2016), the dosage and frequency of VD supplementation required by IBD patients are still matters that are fraught with controversies. For these reasons, well-conducted clinical trials are necessary and crucial for understanding the potential therapeutic and immunomodulatory effects of this hormone and more researchers should work in the establishment of doses that could improve symptoms but not cause undesirable side effects (Sharma et al., 2017; Elimrani et al., 2017).

In addition to human studies, many authors have also shown beneficial effects of VD in animal models and in cell isolates. These studies found that this vitamin may lead to the up-regulation of Treg cells, release of IL-10, TGF-$\beta$1, IL-4, and IL- 10. It may also down-regulate the monocyte differentiation into dendritic cells, IL-12 production, inflammation, and colorectal tumors in both C57BL/6J and $NOD2^{-/-}$mice, and bacterial translocation to extra-

intestinal tissues (Canning et al., 2001; Mattner et al., 2000; Khoo et al., 2011; Ryz et al., 2015; Elimrani et al., 2017)

## Conclusion

There is an increasing epidemiological data which show that VD supplementation can bring several benefits for IBD patients. Clinical studies provide evidence that the insufficiency of VD is related to the pathogenesis of IBD, episodic reactivation of the disease, pain, and increased risk of cancer, surgery, and hospitalization. If, on the one hand, a large number of publications demonstrate that conventional or last generation treatments are usually costly and are associated with several side effects, on the other hand, VD supplementation is inexpensive, safe, and leads to the improvement of the quality of life of the IBD patient due to a plethora of mechanisms that interfere with the inflammatory process. Therefore, professionals should consider the use of this vitamin in the treatment of IBD in proper doses and efficient ways of delivery.

## Disclosure statement

The Authors do not have conflict of interests, and this research did not receive any financial support.

## Author contributions

SMB, RAG, and RGG were responsible for the concept and design of this manuscript, and all contributed to and agreed on the final version of this review.

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