The potential therapeutic role of vitamin D in inflammatory bowel disease

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Abstract. – Inflammatory bowel disease (IBD) is defined as a relapsing and remitting condition characterized by chronic inflammation at different sites in the gastrointestinal tract. Crohn’s disease (CD) and ulcerative colitis (UC) represents the two major forms of IBD. Even though IBD pathophysiology is still not fully understood, genetic factors, environmental factors, dysregulation of both innate and adaptive immune responses, alterations in gut microbiota composition, excessive consumption of saturated fats and cumulative antibiotic exposure have all been suggested to play a role in the development of this condition. Amongst the environmental factors, vitamin D deficiency has been suggested to participate in IBD pathophysiology. Indeed, vitamin D exerts several pleiotropic effects beyond its well-established regulation of bone and calcium homeostasis, including anti-infective, anti-inflammatory and immunomodulatory effects as well as maintenance of gastrointestinal barrier integrity and beneficial gut microbiota composition. In this narrative review, we discuss the role of vitamin D deficiency in IBD pathophysiology as well as the potential therapeutic use of vitamin D for the management of IBD.

Key Words: Inflammatory bowel disease, IBD, Vitamin D, Intestinal mucosal inflammation, Immunomodulation, Disease activity, Prevention, Treatment.

Introduction

Inflammatory bowel disease (IBD) is defined as a relapsing and remitting condition characterized by chronic inflammation at different sites in the gastrointestinal tract and arising from host-microbial interactions in genetically susceptible subjects. Notably, IBDs represent a group of chronic disorders characterized by inflammation of both small and large intestine, in which components of the digestive system are attacked by the immune system1. Patients affected by IBD experience different symptoms such as abdominal pain, diarrhea, nocturnal defecation, bloody stools, vomiting, weight loss and fatigue1. IBD encompasses two major conditions known as Crohn’s disease (CD) and ulcerative colitis (UC), which are differentiated by their location and depth of involvement in the intestinal wall2,3. UC usually only affects the colon, causing diffuse inflammation of the colonic mucosa, with histopathology showing the involvement of the mucosa and submucosa as well as the formation of crypt abscesses and mucosal ulcers. UC affects most frequently the rectum (proctitis), but it may extend into the sigmoid colon (proctosigmoiditis), beyond the sigmoid colon (distal ulcerative colitis), or include the entire colon up to the cecum (pancolitis)2. Conversely, CD can affect the entire gastrointestinal tract, from the mouth to the anus. CD is characterized by transmural ulceration of any portion of the gastrointestinal tract, most often affecting the terminal ileum and the colon3. In CD, there may also be histologic evidence of epithelioid granulomas4. Although the IBD pathophysiology is still not fully understood, genetic factors, environmental factors, dysregulation of both innate and adaptive immune responses, alterations in gut microbiota composition, excessive consumption of saturated fats and cumulative antibiotic exposure have all been suggested to play a role in the development of this condition5-8. In the natural history of IBD, epigenetic factors can mediate the interactions between environment and genome5. In 2017, 6.8
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millions of cases of IBD have been reported worldwide. The incidence of IBD has progressively increased over the last three decades especially in newly industrialized countries, thus implicating an important contribution of environmental factors to IBD pathophysiology. Amongst the environmental factors, vitamin D deficiency has been suggested to increase the risk of developing IBD, particularly in genetically susceptible individuals. This is in line with the fact that vitamin D deficiency has been suggested as a risk factor for development of various chronic inflammatory and autoimmune disorders, in view of the anti-inflammatory and immunomodulatory properties exerted by the biologically active form of vitamin D (calcitriol). The present narrative review explores the potential role of vitamin D deficiency in the IBD pathophysiology, as well as the potential beneficial effects of vitamin D supplementation in patients with IBD.

**Vitamin D Physiology and Metabolism**

In humans, vitamin D is mainly synthesized in the skin upon sunlight exposure. Nevertheless, approximately 20% of vitamin D is obtained through dietary sources, which provide the two major forms of vitamin D, namely vitamin D2 (a.k.a. ergocalciferol), contained in yeast and fungi, and vitamin D3 (a.k.a. cholecalciferol), contained in a few animal sources such as cod liver oil and fatty fish. Upon sunlight exposure [ultraviolet B (UVB) radiation exposure], the vitamin D precursor 7-dehydrocholesterol (7-DHC) contained in the skin is converted into cholecalciferol (vitamin D3). Subsequently, vitamin D3 is transported to the liver by vitamin D-binding protein (VDBP), an alpha-globulin primarily produced by the liver itself. In the liver, the enzyme vitamin D-25-hydroxylase (CYP2R1) catalyzes the conversion of vitamin D3 into 25-hydroxyvitamin D3 [25(OH)D3]. 25(OH)D3 is then transported to the kidneys, where the enzyme 1α-hydroxylase has also been demonstrated in intestinal macrophages and multinucleated giant cells, similar to what has been observed in granulomatous description of multiple genes. The mitochondrial enzyme 24-hydroxylase (CYP24A1) catalyzes the hydroxylation of 25(OH)D3 or 1,25(OH)2D3 on carbon 24 (C24), which results in the synthesis of the less active vitamin D metabolites 24,25(OH)2D3 and 1,24,25(OH)3D3, respectively. In humans, 25(OH)D3 (a.k.a. calcidiol or calcifediol) is the major circulating form of vitamin D, with total serum 25(OH)D concentrations representing the most reliable biomarker of vitamin D status. Importantly, the expression of VDR has been documented in almost all human cells and tissues (including immune cells and intestinal mucosa). Indeed, vitamin D has been shown to exert several pleiotropic extraskeletal effects beyond the well-established regulation of bone and calcium homeostasis, such as the regulation of innate and adaptive immune responses.

**Vitamin D Deficiency in Patients with IBD**

Vitamin D deficiency is deemed a pandemic afflicting more than one billion subjects across all age groups on a global scale. Patients with IBD are at increased risk of developing vitamin D deficiency due to different factors, including nutrient malabsorption, bile acid malabsorption, restricted dietary intake (with subsequent low dietary intake of vitamin D-rich foods such as dairy products), corticosteroid therapy, avoidance of sunlight exposure during immunosuppressive therapy, and genetic factors (single nucleotide polymorphisms in the vitamin D metabolic pathway). Vitamin D deficiency is highly prevalent in patients with IBD (particularly those requiring corticosteroid therapy), and is generally more pronounced in patients with CD as compared to patients with UC. Interestingly, Abreu et al. showed that patients with CD exhibit inappropriately high serum levels (>60 pg/mL) of the metabolically active form 1,25(OH)2D, as compared to UC patients. This finding may be explained by the fact that lamina propria mononuclear cells present in the intestinal mucosa of CD patients express the enzyme 1α-hydroxylase which, in the presence of the 25(OH)D substrate, may lead to an increased local synthesis of 1,25(OH)2D [extrarenal conversion of 25(OH)D into 1,25(OH)2D]3. Increased expression of 1α-hydroxylase has also been demonstrated in intestinal macrophages and multinucleated giant cells, similar to what has been observed in granulomatous...
diseases such as sarcoidosis. In addition, Abreu et al. found that elevated 1,25(OH)2D levels were independently associated with low bone mineral density (regardless of therapeutic glucocorticoid use). Yet, the elevated 1,25(OH)2D levels observed in CD patients may reflect the local (intestinal) attempt to produce higher levels of 1,25(OH)2D in order to sustain compensatory gastrointestinal anti-inflammatory responses in view of the increased severity of intestinal inflammation. In keeping with this hypothesis, 1,25(OH)2D levels have also been found to correlate with CD activity. Additionally, it is worth specifying that inflammation is associated with the overproduction of different cytokines, such as tumour necrosis factor (TNF), interleukin (IL)-1 and IL-6, whose upregulation causes an excessive bone degradation mainly through osteoclast hyperactivation.

Although vitamin D deficiency is common in IBD patients, it is still unclear whether an actual cause-and-effect relationship between hypovitaminosis D and IBD exists. In fact, vitamin D deficiency may represent a consequence, rather than a cause, of IBD, in view of the aforementioned factors (nutrient and bile acid malabsorption, restricted dietary intake, corticosteroid therapy, avoidance of sunlight exposure, genetic factors). On the other hand, preclinical and clinical evidence supporting the anti-inflammatory and immunomodulatory properties of vitamin D suggest a causal role of vitamin D deficiency in IBD pathophysiology. Remarkably, a prospective cohort study conducted on 72,719 women aged 40-73 years and enrolled in the Nurses’ Health Study documented that women with a predicted 25(OH)D level >30 ng/mL (determined through a 25-hydroxyvitamin D prediction score based on previous assessment of diet and lifestyle) exhibited a significant reduction in the risk of incident CD, as well as a non-significant reduction in the risk of UC. Moreover, various clinical studies conducted in IBD patients have documented an association between vitamin D deficiency and disease activity, relapsing disease course, higher inflammatory activity and greater risk of surgery and hospitalizations.

**Potential Therapeutic Role and Mechanisms of Action of Vitamin D in Patients with IBD**

The potential beneficial actions of vitamin D in patients with IBD have been inferred from the anti-infective, anti-inflammatory and immunomodulatory properties of calcitriol. Calcitriol has been shown to induce the transcription of antimicrobial peptides – such as cathelicidin and defensin β2 – in different human cell lines, including myeloid cells, monocytes/macrophages and neutrophils. With specific regard to IBD, serum 25(OH)D levels have been found to positively correlate with serum and colonic cathelicidin in UC patients. Moreover, treatment of human colon cells with 1,25(OH)2D has been shown to induce cathelicidin and IL-10, repress TNF-α, and suppress *Escherichia coli* growth.

Furthermore, vitamin D and VDR appear to play an important role in the maintenance of gastrointestinal barrier integrity and function by regulating the expression of proteins (such as claudin-2) associated with epithelial tight junctions, which regulate the intestinal permeability. Vitamin D has also been found to reduce intestinal epithelium permeability by decreasing lipopolysaccharide (LPS)-induced inflammation. Such vitamin D actions are potentially protective against the development and progression of IBD. In fact, intestinal barrier breakdown leads to increased intestinal permeability (“leaky gut syndrome”), which, in turn, promotes the exposure of the host body to the gut lumen content (including commensal bacteria) and triggers an aberrant immunologic response causing intestinal and systemic inflammation in many chronic inflammatory diseases, including IBD. Notably, IBD patients develop a loss of tight junction barrier function, which leads to increased epithelial permeability, augmented production of pro-inflammatory cytokines and immune dysregulation. It has been suggested that such intestinal barrier dysfunction may trigger the onset of IBD and/or enhance disease progression. Thus, therapies targeted to restore the intestinal barrier integrity and function may provide a valid therapeutic approach for IBD.

It is known that increased values of T helper (Th1) to Th2 cells ratio and Th17 to regulatory T cells (Tregs) ratio contribute to IBD pathogenesis. Also, experimental studies found that predominance of pro-inflammatory M1 macrophages (as compared to anti-inflammatory M2 macrophages) plays a role in IBD pathophysiology. As we previously mentioned, a growing body of evidence supports the anti-inflammatory and immunomodulatory properties of vitamin D. Indeed, expression of functional
VDR has been found in almost all immune cells, especially antigen presenting cells (APCs) and T lymphocytes. Moreover, 1α-hydroxylase is expressed by murine and human APCs and it can be upregulated upon LPS and interferon gamma (IFN-γ) stimulation. Calcitriol exerts different effects on innate and adaptive immune system, promoting immune tolerance and activating anti-inflammatory pathways. Of note, calcitriol: (i) inhibits the synthesis of pro-inflammatory cytokines by monocytes and macrophages; (ii) reduces macrophage surface expression of major histocompatibility complex (MHC)-class II molecules, thereby reducing the macrophage antigen-presentation and T-cell stimulatory ability; (iii) favours the shift of macrophage polarization from a pro-inflammatory phenotype (M1 or “classically activated” macrophages) towards an anti-inflammatory phenotype (M2 or “alternatively activated” macrophages); (iv) regulates the differentiation and function of dendritic cells, reducing their antigen-presenting capacity and rendering them more tolerogenic; (v) promotes the shift of T cells from an “effector” phenotype towards a “regulatory” and anti-inflammatory phenotype by increasing Th2 cells and decreasing Th1 and Th17 cell differentiation; (vi) upregulates Tregs.

VDR knockout and lack of 1α-hydroxylase have been shown to exacerbate the gastrointestinal tract inflammation in experimental models of IBD and colitis, thus suggesting that altered vitamin D metabolism and VDR signaling in the gastrointestinal tract impair the intestinal barrier integrity and function, as well as the local gastrointestinal anti-inflammatory and immunomodulatory responses. In a 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis model, mice carrying VDR deletion in gut epithelial cells or in colonic epithelial cells, as compared to VDR+/+ control mice, exhibited a more severe clinical colitis, characterized by more robust Th1 and Th17 responses and greater epithelial cell apoptosis leading to increased mucosal barrier permeability. These results suggest that gut epithelial VDR signaling modulates intestinal mucosal inflammation by suppressing epithelial cell apoptosis. Additionally, higher circulating vitamin D values in IBD patients may mitigate intestinal mucosal inflammation and reduce disease activity by modulating the composition of the gut microbiota, leading to an increase in beneficial bacteria and to a decrease in pathogenic bacteria.

**Recommendations for Prevention and Treatment of Vitamin D Deficiency in IBD Patients**

Currently, vitamin D deficiency is differently defined across various guidelines. According to the 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine (IOM), vitamin D deficiency is defined as a serum 25(OH)D concentration less than 20 ng/mL (<50 nmol/L). On the other hand, the Endocrine Society guidelines define serum 25(OH)D values between 20 and 29.9 ng/mL (50-74 nmol/L) as vitamin D insufficiency, serum 25(OH)D values less than 20 ng/mL (<50 nmol/L) as vitamin D deficiency, and serum 25(OH)D values equal to or above 30 ng/mL (≥75 nmol/L) as vitamin D sufficiency. However, it is worth specifying that such guidelines refer to the classic effects of vitamin D on skeletal health. Conversely, there are no specific recommendations or guidelines defining the optimal vitamin D status (indicated by serum 25-hydroxyvitamin D concentrations) with regard to the extraskeletal effects of vitamin D. Similarly, there are no specific recommendations or guidelines regarding the screening and management of vitamin D deficiency in IBD patients. Nevertheless, emerging evidence suggests that the serum 25(OH)D threshold required for the achievement of the extraskeletal vitamin D actions in vivo (including the anti-inflammatory and immunomodulatory properties) is approximately 40-50 ng/mL, which is slightly above the recommended threshold for bone health and well below the threshold >100 ng/mL (the latter defining hypervitaminosis D and increased risk of vitamin D toxicity). With specific regard to IBD, Hlavaty et al. suggested that achieving serum 25(OH)D levels between 30 and 50 ng/mL appears safe and may have substantial clinical benefits in terms of reduction of disease activity in IBD patients.

According to the Endocrine Society guidelines, the recommended vitamin D (vitamin D2 or vitamin D3) intake to achieve serum 25(OH)D concentrations above 30 ng/mL in vitamin D deficient patients varies across different age groups, as follows: i) 2,000 IU/day or 50,000 IU once weekly (for infants and toddlers aged 0-1 yr; and for children aged 1-18 yr), for at least 6 weeks.
followed by maintenance therapy of 400-1,000 IU/day (for infants and toddlers aged 0-1 yr) and of 600-1,000 IU/day (for children aged 1-18 yr); ii) 50,000 IU once a week or 6,000 IU daily (for all adults who are vitamin D deficient) for at least 8 weeks, followed by maintenance therapy of 1,500-2,000 IU/day. However, the same guidelines outline that higher vitamin D doses (two to three times higher, such as 6,000-10,000 IU/day) may be needed to treat vitamin D deficiency and achieve serum 25(OH)D concentrations >30 ng/mL in selected patients, such as those with obesity, malabsorption syndromes, IBD, as well as patients taking medications affecting vitamin D metabolism (e.g., corticosteroids). Importantly, high-dose vitamin D3 supplementation has been proven safe and effective in normalizing serum 25(OH)D concentrations in otherwise healthy vitamin D deficient subjects. In view of the potential benefits of vitamin D supplementation, screening for vitamin D deficiency in subjects at risk for hypovitaminosis D and in whom a prompt response to optimization of vitamin D status may be expected (including patients with malabsorption syndromes, patients with IBD and patients on corticosteroid therapy) appears reasonable, as it has also been suggested by the Endocrine Society guidelines on evaluation, treatment, and prevention of vitamin D deficiency.

**Potential Benefits of Vitamin D Supplementation in IBD Patients**

Assessment of vitamin D status and subsequent tailored vitamin D supplementation is recommended particularly in IBD patients on corticosteroid therapy, in order to prevent or treat corticosteroid-related hypovitaminosis D and its associated consequences such as bone loss, osteopenia and osteoporosis. Yet, growing evidence suggests that vitamin D may play a relevant role in ameliorating disease outcomes in IBD patients by virtue of its anti-inflammatory and immunomodulatory properties, and by virtue of its ability to alter fecal microbiota and repair intestinal mucosal barrier integrity and function. In this regard, Garg et al. showed that 8-week vitamin D3 supplementation (at a dose of 40,000 IU/week) led to a significant decrease in the levels of fecal calprotectin (a sensitive marker of intestinal inflammation) among vitamin D deficient patients with active UC. Furthermore, Garg et al. conducted another pilot study on patients with active IBD and a serum 25(OH)D concentration <75 nmol/L (<30 ng/mL), who received oral liquid vitamin D3 supplementation over a 12 week-period. Authors used a specific protocol with vitamin D3 dose adjusted 4-weekly, aiming to reach a target 25(OH)D level of 100-125 nmol/L (40-50 ng/mL). Authors noted that clinical disease activity (assessed according to symptom-based activity scores) consistently declined, although fecal calprotectin and circulating markers of inflammation did not. Moreover, there were no serious adverse events related to the administration of vitamin D3. A double-blind randomized placebo-controlled study conducted on 27 CD patients in remission showed that short-term (3-month) vitamin D3 supplementation (at a dose of 2,000 IU/day) led to significantly lower levels of C-reactive protein, higher plasma cathelicidin (LL-37) concentrations, and better quality of life (assessed using the validated Inflammatory Bowel Disease Questionnaire, a.k.a. IBDQ) in patients who achieved 25(OH)D concentrations ≥75 nmol/L (≥30 ng/mL) at 3 months. The use of vitamin D analogs (e.g., paricalcitol) may also hold promise for treating IBD, since evidence from murine studies shows that such compounds can attenuate the development of TNBS-induced colitis by inhibiting the excessive apoptosis of intestinal epithelial cells, which partly accounts for development of colonic inflammation and IBD. Of note, a meta-analysis of 18 randomized controlled trials involving 908 patients evaluating the therapeutic effect of vitamin D for treatment of IBD found that vitamin D supplementation was able to significantly reduce the relapse rate in IBD patients, although there was no significant difference between the low-dose and the high-dose vitamin D treatment. However, significant improvements in IBD outcomes after vitamin D supplementation have not been observed in other studies. It has been suggested that the variability in effects on disease outcomes observed across different studies evaluating the vitamin D3 supplementation in IBD patients may partly arise from the administered daily dose, with higher daily doses (≥2,000 IU/day) being associated with a greater likelihood of clinical benefits as compared to lower daily doses (<2,000 IU/day).

It is also important to remind that vitamin D deficiency is a well-established risk factor for bone loss and osteopenia/osteoporosis. Notwithstanding, vitamin D3 supplementation (at a dose of 2,000 IU/day) has also been shown to effectively correct vitamin D deficiency and sig-
significantly improve trabecular bone mineral density in pediatric patients with IBD. Finally, it is well-known that IBD patients have an increased risk of developing colorectal cancer in the long-term. Thus, it would be important to investigate whether vitamin D supplementation in IBD patients (particularly UC patients) may play a significant role in reducing the risk of colorectal cancer. In this regard, an observational study conducted by Ananthakrishnan et al in 2,809 IBD patients found that vitamin D deficiency—defined by a plasma 25(OH)D value lower than 20 ng/mL—was associated with an increased risk of metastatic and non-metastatic cancers (the association was stronger for colorectal cancer). With specific regard to colorectal cancer, each 1 ng/mL increase in circulating 25(OH)D value was associated with a 8% reduction in the risk of colorectal cancer.

Conclusions

Vitamin D exerts several pleiotropic effects that may be beneficial for prevention and treatment of IBD, including anti-infective, anti-inflammatory and immunomodulatory effects as well as maintenance of gastrointestinal barrier integrity and beneficial gut microbiota composition. Indeed, vitamin D deficiency is highly prevalent in patients with IBD due to different reasons, including nutrient and bile acid malabsorption, restricted dietary intake, corticosteroid therapy, avoidance of sunlight exposure, and genetic factors. Further prospective studies are needed to establish the existence of a true cause-and-effect relationship between hypovitaminosis D and IBD pathophysiology. Yet, screening for vitamin D deficiency appears reasonable in IBD patients, who are considered at high risk of hypovitaminosis D (particularly if they are on corticosteroid therapy). Preliminary evidence shows that vitamin D supplementation can significantly reduce intestinal mucosal inflammation and disease activity in IBD patients. Therefore, large randomized controlled trials are warranted to establish whether vitamin D supplementation can represent a safe and effective adjuvant therapeutic strategy to prevent IBD development, counteract IBD progression, induce and maintain disease remission, reduce IBD-related hospitalizations and surgery, enhance the response to biologic drugs used for IBD treatment, counteract IBD-related bone loss, and even reduce IBD-associated colorectal cancer risk. Since the current guidelines on the management of hypovitaminosis D only refer to the classic effects of vitamin D on bone and calcium homeostasis, future studies should aim to establish which is the optimal serum 25(OH)D level required for the achievement of the beneficial effects exerted by vitamin D in patients with IBD. Finally, such studies should also investigate which are the most appropriate dosing, formulation and route of administration of vitamin D supplementation in IBD patients.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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