European Review for Medical and Pharmacological Sciences 2023; 27: 4678-4687

The potential therapeutic role of vitamin D in inflammatory bowel disease

L. BOCCUZZI[1], M. INFANTE[2,3], C. RICORDI[2]

[1]Rush University Medical Center, Chicago, IL, USA
[2]Diabetes Research Institute (DRI) and Clinical Cell Transplant Program, University of Miami Miller School of Medicine, Miami, FL, USA
[3]Section of Diabetes and Metabolic Disorders, UniCamillus, Saint Camillus International University of Health Sciences, Rome, Italy

Luciarita Boccuzzi and Marco Infante contributed equally to the present manuscript

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 system[1]. Patients affected by IBD experience different symptoms such as abdominal pain, diarrhea, nocturnal defecation, bloody stools, vomiting, weight loss and fatigue[1]. 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 wall[2,3]. 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)[3]. 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 colon[3]. In CD, there may also be histologic evidence of epithelioid granulomas[4]. 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 condition[5-8]. In the natural history of IBD, epigenetic factors can mediate the interactions between environment and genome[5]. In 2017, 6.8

Corresponding Author: Luciarita Boccuzzi, MD; e-mail: luciarita_boccuzzi@rush.edu

million cases of IBD have been reported worldwide[9]. The incidence of IBD has progressively increased over the last three decades especially in newly industrialized countries[9], 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[10,11]. 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[12,13], in view of the anti-inflammatory and immunomodulatory properties exerted by the biologically active form of vitamin D (calcitriol)[13,14]. 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[15], 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[16,17]. 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 (CYP27B1) catalyzes the conversion of 25(OH)D3 into 1,25-dihydroxyvitamin D3 [1,25(OH)2D3; a.k.a. calcitriol], which represents the biologically active metabolite of vitamin D[18]. Calcitriol binds to the nuclear vitamin D receptor (VDR), which forms a heterodimer with the retinoid X receptor (RXR) and subsequently binds to DNA sequences known as "vitamin D response elements" (VDREs), thus regulating the transcription of multiple genes[18]. 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[19]. 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[20,21]. Importantly, the expression of VDR has been documented in almost all human cells and tissues (including immune cells and intestinal mucosa)[22]. 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[13,23].

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[16]. 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)[16,24-27].

Several epidemiologic studies[27-32] have shown that 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[33] 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][33]. 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[34]. In addition, Abreu et al[33] 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[33]. 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[35].

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[13,36]. Remarkably, a prospective cohort study[37] 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[27,28,31,32,38-40] 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[13,36]. 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[41-44]. With specific regard to IBD, serum 25(OH)D levels have been found to positively correlate with serum and colonic cathelicidin in UC patients[45]. 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[45].

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[46], which regulate the intestinal permeability. Vitamin D has also been found to reduce intestinal epithelium permeability by decreasing lipopolysaccharide (LPS)-induced inflammation[47]. 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[48-50]. 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[51]. It has been suggested that such intestinal barrier dysfunction may trigger the onset of IBD and/or enhance disease progression[51]. 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 (Th)1 to Th2 cells ratio and Th17 to regulatory T cells (Tregs) ratio contribute to IBD pathogenesis[36]. Also, experimental studies found that predominance of pro-inflammatory M1 macrophages (as compared to anti-inflammatory M2 macrophages) plays a role in IBD pathophysiology[52]. As we previously mentioned, a growing body of evidence supports the anti-inflammatory and immunomodulatory properties of vitamin D[13,14,23]. Indeed, expression of functional

VDR has been found in almost all immune cells, especially antigen presenting cells (APCs) and T lymphocytes[53,54]. Moreover, 1α-hydroxylase is expressed by murine and human APCs[55,56] and it can be upregulated upon LPS and interferon gamma (IFN-γ) stimulation[57,58]. 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[59]; (ii) reduces macrophage surface expression of major histocompatibility complex (MHC)-class II molecules, thereby reducing the macrophage antigen-presentation and T-cell stimulatory ability[55,60]; (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)[61]; (iv) regulates the differentiation and function of dendritic cells, reducing their antigen-presenting capacity and rendering them more tolerogenic[62-66]; (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[67-69]; vi) upregulates Tregs[70].

VDR knockout and lack of 1α-hydroxylase have been shown to exacerbate the gastrointestinal tract inflammation in experimental models of IBD and colitis[71,72], 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 $VDR^{f/f}$ 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[73]. 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[74].

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[75] 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[76] 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[77], 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)[78]. With specific regard to IBD, Hlavaty et al[79] 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[76], 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)[76]. 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[80]. 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[76].

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[81]. In this regard, Garg et al[82] 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[83] 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[83]. A double-blind randomized placebo-controlled study[84] 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[85] 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[86] 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[87]. 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)[88].

It is also important to remind that vitamin D deficiency is a well-established risk factor for bone loss and osteopenia/osteoporosis[89]. Notwithstanding, vitamin D3 supplementation (at a dose of 2,000 IU/day) has also been shown to effectively correct vitamin D deficiency and sig-

nificantly improve trabecular bone mineral density in pediatric patients with IBD[90]. Finally, it is well-known that IBD patients have an increased risk of developing colorectal cancer in the long-term[91,92]. 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[93] 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[93].

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.

Funding

The authors received no honorarium, grant or financial support for the research, authorship, and/or publication of this article.

Authors' Contribution

Luciarita Boccuzzi and Marco Infante contributed equally to the present manuscript (conceptualization, writing and original draft preparation). Camillo Ricordi revised and edited the manuscript. All authors read, edited and approved the final version of the manuscript.

ORCID ID

Luciarita Boccuzzi: 0000-0002-3732-5533; Marco Infante: 0000-0003-2032-8735; Camillo Ricordi: 0000-0001-8092-7153.

Ethics Approval

Not applicable.

Informed Consent

Not applicable.

References

1) Fakhoury M, Negrulj R, Mooranian A, Al-Salami H. Inflammatory bowel disease: clinical aspects and treatments. J Inflamm Res 2014; 7: 113-120.
2) Zhang YZ, Li YY. Inflammatory bowel disease: pathogenesis. World J Gastroenterol 2014; 20: 91-99.
3) McDowell C, Farooq U, Haseeb M. Inflammatory Bowel Disease. 2022 Jun 27. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.

4) Johnson CM, Hartman DJ, Ramos-Rivers C, Rao BB, Bhattacharya A, Regueiro M, Schwartz M, Swoger J, Al Hashash J, Barrie A, Pfanner TP, Dunn M, Koutroubakis IE, Binion DG. Epithelioid Granulomas Associate With Increased Severity and Progression of Crohn's Disease, Based on 6-Year Follow-Up. Clin Gastroenterol Hepatol 2018; 16: 900-907.
5) Loddo I, Romano C. Inflammatory Bowel Disease: Genetics, Epigenetics, and Pathogenesis. Front Immunol 2015; 6: 551.
6) Saez A, Herrero-Fernandez B, Gomez-Bris R, Sánchez-Martinez H, Gonzalez-Granado JM. Pathophysiology of Inflammatory Bowel Disease: Innate Immune System. Int J Mol Sci 2023; 24: 1526.
7) Li X, Wei X, Sun Y, Du J, Xun Z, Li YC. High-fat diet promotes experimental colitis by inducing oxidative stress in the colon. Am J Physiol Gastrointest Liver Physiol 2019; 317: G453-G462.
8) Faye AS, Allin KH, Iversen AT, Agrawal M, Faith J, Colombel JF, Jess T. Antibiotic use as a risk factor for inflammatory bowel disease across the ages: a population-based cohort study. Gut 2023; 72: 663-670.
9) GBD 2017 Inflammatory Bowel Disease Collaborators. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020; 5: 17-30.
10) Piovani D, Danese S, Peyrin-Biroulet L, Nikolopoulos GK, Lytras T, Bonovas S. Environmental Risk Factors for Inflammatory Bowel Diseases: An Umbrella Review of Meta-analyses. Gastroenterology 2019; 157: 647-659.e4.
11) Cantorna MT. Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease. Prog Biophys Mol Biol 2006; 92: 60-64.
12) Infante M, Fabbri A, Della-Morte D, Ricordi C. The importance of vitamin D and omega-3 PUFA supplementation: a nonpharmacologic immunomodulation strategy to halt autoimmunity. Eur Rev Med Pharmacol Sci 2022; 26: 6787-6795.
13) Caprio M, Infante M, Calanchini M, Mammi C, Fabbri A. Vitamin D: not just the bone. Evidence for beneficial pleiotropic extraskeletal effects. Eat Weight Disord 2017; 22: 27-41.
14) Fabbri A, Infante M, Ricordi C. Editorial - Vitamin D status: a key modulator of innate immunity and natural defense from acute viral respiratory infections. Eur Rev Med Pharmacol Sci 2020; 24: 4048-4052.
15) Webb AR, Pilbeam C, Hanafin N, Holick MF. An evaluation of the relative contributions of exposure to sunlight and of diet to the circulating concentrations of 25-hydroxyvitamin D in an elderly nursing home population in Boston. Am J Clin Nutr 1990; 51: 1075-1081.
16) Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord 2017; 18: 153-165.
17) Schmid A, Walther B. Natural vitamin D content in animal products. Adv Nutr 2013; 4: 453-462.
18) Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. Physiol Rev 2016; 96: 365-408.
19) Jones G, Prosser DE, Kaufmann M. 25-Hydroxyvitamin D-24-hydroxylase (CYP24A1): its important role in the degradation of vitamin D. Arch Biochem Biophys 2012; 523: 9-18.
20) Cashman KD, van den Heuvel EG, Schoemaker RJ, Prévéraud DP, Macdonald HM, Arcot J. 25-Hydroxyvitamin D as a Biomarker of Vitamin D Status and Its Modeling to Inform Strategies for Prevention of Vitamin D Deficiency within the Population. Adv Nutr 2017; 8: 947-957.
21) Holick MF. The use and interpretation of assays for vitamin D and its metabolites. J Nutr 1990; 120 Suppl 11: 1464-1469.
22) Wang Y, Zhu J, DeLuca HF. Where is the vitamin D receptor? Arch Biochem Biophys 2012; 523: 123-133.
23) Gatti D, Idolazzi L, Fassio A. Vitamin D: not just bone, but also immunity. Minerva Med 2016; 107: 452-460.
24) Fletcher J. Vitamin D deficiency in patients with inflammatory bowel disease. Br J Nurs 2016; 25: 846-851.
25) Ananthakrishnan AN, Cagan A, Cai T, Gainer VS, Shaw SY, Churchill S, Karlson EW, Murphy SN, Kohane I, Liao KP, Xavier RJ. Common Genetic Variants Influence Circulating Vitamin D Levels in Inflammatory Bowel Diseases. Inflamm Bowel Dis 2015; 21: 2507-2514.
26) Taylor L, Almutairdi A, Shommu N, Fedorak R, Ghosh S, Reimer RA, Panaccione R, Raman M. Cross-Sectional Analysis of Overall Dietary Intake and Mediterranean Dietary Pattern in Patients with Crohn's Disease. Nutrients 2018; 10: 1761.
27) Blanck S, Aberra F. Vitamin d deficiency is associated with ulcerative colitis disease activity. Dig Dis Sci 2013; 58: 1698-1702.
28) Frigstad SO, Høivik M, Jahnsen J, Dahl SR, Cvancarova M, Grimstad T, Berset IP, Huppertz-Hauss G, Hovde Ø, Torp R, Bernklev T, Moum B, Jelsness-Jørgensen LP. Vitamin D deficiency in inflammatory bowel disease: prevalence and predictors in a Norwegian outpatient population. Scand J Gastroenterol 2017; 52: 100-106.
29) Fletcher J, Cooper SC, Ghosh S, Hewison M. The Role of Vitamin D in Inflammatory Bowel Disease: Mechanism to Management. Nutrients 2019; 11: 1019.
30) Suibhne TN, Cox G, Healy M, O'Morain C, O'Sullivan M. Vitamin D deficiency in Crohn's disease: prevalence, risk factors and supplement use in an outpatient setting. J Crohns Colitis 2012; 6: 182-188.
31) Rasouli E, Sadeghi N, Parsi A, Hashemi SJ, Nayebi M, Shayesteh A. Relationship Between

Vitamin D Deficiency and Disease Activity in Patients with Inflammatory Bowel Disease in Ahvaz, Iran. Clin Exp Gastroenterol 2020; 13: 419-425.

32) Law AD, Dutta U, Kochhar R, Vaishnavi C, Kumar S, Noor T, Bhadada S, Singh K. Vitamin D deficiency in adult patients with ulcerative colitis: Prevalence and relationship with disease severity, extent, and duration. Indian J Gastroenterol 2019; 38: 6-14.

33) Abreu MT, Kantorovich V, Vasiliauskas EA, Gruntmanis U, Matuk R, Daigle K, Chen S, Zehnder D, Lin YC, Yang H, Hewison M, Adams JS. Measurement of vitamin D levels in inflammatory bowel disease patients reveals a subset of Crohn's disease patients with elevated 1,25-dihydroxyvitamin D and low bone mineral density. Gut 2004; 53: 1129-1136.

34) Adams JS, Singer FR, Gacad MA, Sharma OP, Hayes MJ, Vouros P, Holick MF. Isolation and structural identification of 1,25-dihydroxyvitamin D3 produced by cultured alveolar macrophages in sarcoidosis. J Clin Endocrinol Metab 1985; 60: 960-966.

35) Redlich K, Smolen JS. Inflammatory bone loss: pathogenesis and therapeutic intervention. Nat Rev Drug Discov 2012; 11: 234-250.

36) Wu Z, Liu D, Deng F. The Role of Vitamin D in Immune System and Inflammatory Bowel Disease. J Inflamm Res 2022; 15: 3167-3185.

37) Ananthakrishnan AN, Khalili H, Higuchi LM, Bao Y, Korzenik JR, Giovannucci EL, Richter JM, Fuchs CS, Chan AT. Higher predicted vitamin D status is associated with reduced risk of Crohn's disease. Gastroenterology 2012; 142: 482-489.

38) Jørgensen SP, Hvas CL, Agnholt J, Christensen LA, Heickendorff L, Dahlerup JF. Active Crohn's disease is associated with low vitamin D levels. J Crohns Colitis 2013; 7: e407-e413.

39) Ulitsky A, Ananthakrishnan AN, Naik A, Skaros S, Zadvornova Y, Binion DG, Issa M. Vitamin D deficiency in patients with inflammatory bowel disease: association with disease activity and quality of life. JPEN J Parenter Enteral Nutr 2011; 35: 308-316.

40) Ananthakrishnan AN, Cagan A, Gainer VS, Cai T, Cheng SC, Savova G, Chen P, Szolovits P, Xia Z, De Jager PL, Shaw SY, Churchill S, Karlson EW, Kohane I, Plenge RM, Murphy SN, Liao KP. Normalization of plasma 25-hydroxy vitamin D is associated with reduced risk of surgery in Crohn's disease. Inflamm Bowel Dis 2013; 19: 1921-1927.

41) Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, Tavera-Mendoza L, Lin R, Hanrahan JW, Mader S, White JH. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. J Immunol 2004; 173: 2909-2912.

42) Gombart AF, Borregaard N, Koeffler HP. Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. FASEB J 2005; 19: 1067-1077.

43) Gombart AF. The vitamin D-antimicrobial peptide pathway and its role in protection against infection. Future Microbiol 2009; 4: 1151-1165.

44) Hewison M. Antibacterial effects of vitamin D. Nat Rev Endocrinol 2011; 7: 337-345.

45) Gubatan J, Mehigan GA, Villegas F, Mitsuhashi S, Longhi MS, Malvar G, Csizmadia E, Robson S, Moss AC. Cathelicidin Mediates a Protective Role of Vitamin D in Ulcerative Colitis and Human Colonic Epithelial Cells. Inflamm Bowel Dis 2020; 26: 885-897.

46) Sun J, Zhang YG. Vitamin D Receptor Influences Intestinal Barriers in Health and Disease. Cells 2022; 11: 1129.

47) Lee C, Lau E, Chusilp S, Filler R, Li B, Zhu H, Yamoto M, Pierro A. Protective effects of vitamin D against injury in intestinal epithelium. Pediatr Surg Int 2019; 35: 1395-1401.

48) Michielan A, D'Incà R. Intestinal Permeability in Inflammatory Bowel Disease: Pathogenesis, Clinical Evaluation, and Therapy of Leaky Gut. Mediators Inflamm 2015; 2015: 628157.

49) Camilleri M. Leaky gut: mechanisms, measurement and clinical implications in humans. Gut 2019; 68: 1516-1526.

50) Paray BA, Albeshr MF, Jan AT, Rather IA. Leaky Gut and Autoimmunity: An Intricate Balance in Individuals Health and the Diseased State. Int J Mol Sci 2020; 21: 9770.

51) Edelblum KL, Turner JR. The tight junction in inflammatory disease: communication breakdown. Curr Opin Pharmacol 2009; 9: 715-720.

52) Zhu W, Yu J, Nie Y, Shi X, Liu Y, Li F, Zhang XL. Disequilibrium of M1 and M2 macrophages correlates with the development of experimental inflammatory bowel diseases. Immunol Invest 2014; 43: 638-652.

53) White JH. Vitamin D metabolism and signaling in the immune system. Rev Endocr Metab Disord 2012; 13: 21-29.

54) Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. Nutrients 2013; 5: 2502-2521.

55) Overbergh L, Decallonne B, Valckx D, Verstuyf A, Depovere J, Laureys J, Rutgeerts O, Saint-Arnaud R, Bouillon R, Mathieu C. Identification and immune regulation of 25-hydroxyvitamin D-1-alpha-hydroxylase in murine macrophages. Clin Exp Immunol 2000; 120: 139-146.

56) Stoffels K, Overbergh L, Giulietti A, Verlinden L, Bouillon R, Mathieu C. Immune regulation of 25-hydroxyvitamin-D3-1alpha-hydroxylase in human monocytes. J Bone Miner Res 2006; 21: 37-47.

57) Overbergh L, Stoffels K, Waer M, Verstuyf A, Bouillon R, Mathieu C. Immune regulation of 25-hydroxyvitamin D-1alpha-hydroxylase in human monocytic THP1 cells: mechanisms of interferon-gamma-mediated induction. J Clin Endocrinol Metab 2006; 91: 3566-3574.

58) Kapetanovic R, Fairbairn L, Beraldi D, Sester DP, Archibald AL, Tuggle CK, Hume DA. Pig bone

marrow-derived macrophages resemble human macrophages in their response to bacterial lipopolysaccharide. J Immunol 2012; 188: 3382-3394.

59) Zhang Y, Leung DY, Richers BN, Liu Y, Remigio LK, Riches DW, Goleva E. Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. J Immunol 2012; 188: 2127-2135.

60) Korf H, Wenes M, Stijlemans B, Takiishi T, Robert S, Miani M, Eizirik DL, Gysemans C, Mathieu C. 1,25-Dihydroxyvitamin D3 curtails the inflammatory and T cell stimulatory capacity of macrophages through an IL-10-dependent mechanism. Immunobiology 2012; 217: 1292-1300.

61) Zhang X, Zhou M, Guo Y, Song Z, Liu B. 1,25-Dihydroxyvitamin D_3 Promotes High Glucose-Induced M1 Macrophage Switching to M2 via the VDR-PPARγ Signaling Pathway. Biomed Res Int 2015; 2015: 157834.

62) Piemonti L, Monti P, Sironi M, Fraticelli P, Leone BE, Dal Cin E, Allavena P, Di Carlo V. Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells. J Immunol 2000; 164: 4443-4451.

63) Penna G, Adorini L. 1 Alpha,25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. J Immunol 2000; 164: 2405-2411.

64) Gauzzi MC, Purificato C, Donato K, Jin Y, Wang L, Daniel KC, Maghazachi AA, Belardelli F, Adorini L, Gessani S. Suppressive effect of 1alpha,25-dihydroxyvitamin D3 on type I IFN-mediated monocyte differentiation into dendritic cells: impairment of functional activities and chemotaxis. J Immunol 2005; 174: 270-276.

65) Ferreira GB, van Etten E, Verstuyf A, Waer M, Overbergh L, Gysemans C, Mathieu C. 1,25-Dihydroxyvitamin D3 alters murine dendritic cell behaviour in vitro and in vivo. Diabetes Metab Res Rev 2011; 27: 933-941.

66) Saul L, Mair I, Ivens A, Brown P, Samuel K, Campbell JDM, Soong DY, Kamenjarin N, Mellanby RJ. 1,25-Dihydroxyvitamin D3 Restrains CD4+ T Cell Priming Ability of CD11c+ Dendritic Cells by Upregulating Expression of CD31. Front Immunol 2019; 10: 600.

67) Overbergh L, Decallonne B, Waer M, Rutgeerts O, Valckx D, Casteels KM, Laureys J, Bouillon R, Mathieu C. 1alpha,25-dihydroxyvitamin D3 induces an autoantigen-specific T-helper 1/T-helper 2 immune shift in NOD mice immunized with GAD65 (p524-543). Diabetes 2000; 49: 1301-1307.

68) Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HF, O'Garra A. 1alpha,25-Dihydroxyvitamin d3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. J Immunol 2001; 167: 4974-4980.

69) Bouillon R, Lieben L, Mathieu C, Verstuyf A, Carmeliet G. Vitamin D action: lessons from VDR and Cyp27b1 null mice. Pediatr Endocrinol Rev 2013; 10 Suppl 2: 354-366.

70) Jeffery LE, Burke F, Mura M, Zheng Y, Qureshi OS, Hewison M, Walker LS, Lammas DA, Raza K, Sansom DM. 1,25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. J Immunol 2009; 183: 5458-5467.

71) Froicu M, Weaver V, Wynn TA, McDowell MA, Welsh JE, Cantorna MT. A crucial role for the vitamin D receptor in experimental inflammatory bowel diseases. Mol Endocrinol 2003; 17: 2386-2392.

72) Liu N, Nguyen L, Chun RF, Lagishetty V, Ren S, Wu S, Hollis B, DeLuca HF, Adams JS, Hewison M. Altered endocrine and autocrine metabolism of vitamin D in a mouse model of gastrointestinal inflammation. Endocrinology 2008; 149: 4799-4808.

73) He L, Liu T, Shi Y, Tian F, Hu H, Deb DK, Chen Y, Bissonnette M, Li YC. Gut Epithelial Vitamin D Receptor Regulates Microbiota-Dependent Mucosal Inflammation by Suppressing Intestinal Epithelial Cell Apoptosis. Endocrinology 2018; 159: 967-979.

74) Charoenngam N, Shirvani A, Kalajian TA, Song A, Holick MF. The Effect of Various Doses of Oral Vitamin D3 Supplementation on Gut Microbiota in Healthy Adults: A Randomized, Double-blinded, Dose-response Study. Anticancer Res 2020; 40: 551-556.

75) Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011; 96: 53-58.

76) Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96: 1911-1930.

77) Charoenngam N, Holick MF. Immunologic Effects of Vitamin D on Human Health and Disease. Nutrients 2020; 12: 2097.

78) Lim K, Thadhani R. Vitamin D Toxicity. J Bras Nefrol 2020; 42: 238-244.

79) Hlavaty T, Krajcovicova A, Payer J. Vitamin D therapy in inflammatory bowel diseases: who, in what form, and how much? J Crohns Colitis 2015; 9: 198-209.

80) Fassio A, Adami G, Rossini M, Giollo A, Caimmi C, Bixio R, Viapiana O, Milleri S, Gatti M, Gatti D. Pharmacokinetics of Oral Cholecalciferol in Healthy Subjects with Vitamin D Deficiency: A Randomized Open-Label Study. Nutrients 2020; 12: 1553.

81) Nielsen OH, Hansen TI, Gubatan JM, Jensen KB, Rejnmark L. Managing vitamin D deficiency in inflammatory bowel disease. Frontline Gastroenterol 2019; 10: 394-400.

82) Garg M, Hendy P, Ding JN, Shaw S, Hold G, Hart A. The Effect of Vitamin D on Intestinal Inflammation and Faecal Microbiota in Patients with Ulcerative Colitis. J Crohns Colitis 2018; 12: 963-972.

83) Garg M, Rosella O, Rosella G, Wu Y, Lubel JS, Gibson PR. Evaluation of a 12-week targeted vitamin D supplementation regimen in patients with active inflammatory bowel disease. Clin Nutr 2018; 37: 1375-1382.

84) Raftery T, Martineau AR, Greiller CL, Ghosh S, McNamara D, Bennett K, Meddings J, O'Sullivan M. Effects of vitamin D supplementation on intestinal permeability, cathelicidin and disease markers in Crohn's disease: Results from a randomised double-blind placebo-controlled study. United European Gastroenterol J 2015; 3: 294-302.

85) Zhu T, Liu TJ, Shi YY, Zhao Q. Vitamin D/VDR signaling pathway ameliorates 2,4,6-trinitrobenzene sulfonic acid-induced colitis by inhibiting intestinal epithelial apoptosis. Int J Mol Med 2015; 35: 1213-1218.

86) Li J, Chen N, Wang D, Zhang J, Gong X. Efficacy of vitamin D in treatment of inflammatory bowel disease: A meta-analysis. Medicine (Baltimore) 2018; 97: e12662.

87) Mathur J, Naing S, Mills P, Limsui D. A randomized clinical trial of vitamin D3 (cholecalciferol) in ulcerative colitis patients with hypovitaminosis D3. PeerJ 2017; 5: e3654.

88) Zepeda M, Pérez J, Doepking C. Vitamin D supplementation in inflammatory bowel disease: a narrative review. Medwave 2022; 22: e8536.

89) Tański W, Kosiorowska J, Szymańska-Chabowska A. Osteoporosis - risk factors, pharmaceutical and non-pharmaceutical treatment. Eur Rev Med Pharmacol Sci 2021; 25: 3557-3566.

90) Hradsky O, Soucek O, Maratova K, Matyskova J, Copova I, Zarubova K, Bronsky J, Sumnik Z. Supplementation with 2000 IU of Cholecalciferol Is Associated with Improvement of Trabecular Bone Mineral Density and Muscle Power in Pediatric Patients with IBD. Inflamm Bowel Dis 2017; 23: 514-523.

91) Lakatos PL, Lakatos L. Risk for colorectal cancer in ulcerative colitis: changes, causes and management strategies. World J Gastroenterol 2008; 14: 3937-3947.

92) Lucafò M, Curci D, Franzin M, Decorti G, Stocco G. Inflammatory Bowel Disease and Risk of Colorectal Cancer: An Overview From Pathophysiology to Pharmacological Prevention. Front Pharmacol 2021; 12: 772101.

93) Ananthakrishnan AN, Cheng SC, Cai T, Cagan A, Gainer VS, Szolovits P, Shaw SY, Churchill S, Karlson EW, Murphy SN, Kohane I, Liao KP. Association between reduced plasma 25-hydroxy vitamin D and increased risk of cancer in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2014; 12: 821-827.