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Review Article

Review Article

Role of Vitamin D in the Natural History of Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease [IBD], including ulcerative colitis and Crohn's disease, is a chronic and unpredictable condition characterised by alternating periods of remission interspersed with relapses. In recent years, accumulating support for an immunomodulating effect of vitamin D on both the innate and the adaptive immune systems has been presented. Through the vitamin D receptor, the active form of vitamin D, 1,25$[OH]_2$D, induces antimicrobial peptide secretion, decreases dendritic cell activity, and promotes Th2 and regulatory T cell development and activity. In addition, vitamin D promotes an increased ratio of anti-inflammatory cytokines to pro-inflammatory cytokines. Studies in IBD point to a role for vitamin D in ameliorating disease outcome. Suboptimal circulating levels of 25-hydroxyvitamin D are common in IBD and appear to be associated with an increased risk of flares, IBD-related hospitalisations and surgeries, an inadequate response to tumour necrosis factor [TNF] inhibitors, a deterioration in quality of life, and low bone mineral density. With only few available randomised double-blind, placebo-controlled studies investigating therapeutic effects of vitamin D related to IBD, further research is necessary to determine the true therapeutic potential of vitamin D, as well as to define its optimal range in serum to achieve and maintain quiescence of disease. This review aims to summarise the latest knowledge on the extraskeletal effects of vitamin D in IBD, and outlines the potential deleterious consequences of vitamin D deficiency in this patient cohort.

Key Words: Biologics; immunomodulation; inflammatory bowel disease; therapy; vitamin D

1. Introduction

Ulcerative colitis and Crohn's disease are the two major entities under the umbrella term of inflammatory bowel disease [IBD][1,2] which has emerged as a public health challenge worldwide.[3] IBD is a multifactorial disease with a complicated pathogenesis still incompletely understood. However, four main factors are known to interact and contribute to the chronic intestinal inflammation: intestinal antigens, genetic susceptibility, an overly reactive immune response, and various environmental triggers.[4,5]

It is well-known that patients with IBD have an increased risk of osteopenia and osteoporosis, and several factors including malabsorption of calcium and/or vitamin D caused by flaring disease or previous surgery, diminished food intake, and medications which inhibit bone formation or increase bone turnover interfering with calcium absorption and normal mineralisation of bone.[6–8] However, when focusing on vitamin D in calcium homeostasis and bone health,[9] both disease and non-disease-related elements are proposed to contribute to low levels of vitamin D in IBD. These include inadequate sunlight exposure, an impaired enzymatic activation, lower bioavailability, increased catabolism or excretion, insufficient physical activity, and smoking.[10–13]

However, the discovery that vitamin D might additionally have distinct immunological functions has initiated a huge interest in its possible pathogenic influence on the clinical course of IBD. Vitamin D, which is a critically essential nutrient, is involved in cell proliferation and differentiation and in immunomodulation, and can

influence the gut microbiome.[14–17] Recent data indicate that it also improves iron recycling through downregulatory effects on hepcidin, with resulting higher haemoglobin levels in patients with IBD.[18,19] As epidemiological studies have documented that vitamin D deficiency is frequent in IBD,[20,21] it is presumed that its supplementation may counteract a number of inflammatory-related complications.[12,13,15,22] Consistent with this hypothesis, a number of clinical studies have linked vitamin D levels with meaningful clinical outcomes in patients with IBD in recent years.[23–25] Independently of other variables, lower vitamin D levels are associated with a greater risk of clinical relapse, for example.[25–27] More robust causative evidence has emerged from interventional studies of vitamin D supplementation.[28–30] Cumulatively, this body of work supports a potential role for vitamin D as a therapeutic agent in patients with IBD.

The aim of the present review is to summarise updated data on the potential role of vitamin D in the pathophysiology of IBD as identified in Box with Search Strategy, with an emphasis on its impact on disease outcomes, and to provide practical guidance for its clinical use.

Box with Search Strategy

Literature was identified through searches on PubMed, EMBASE, and SCOPUS. Both MeSH terms and text words were used in combination: 'Inflammatory Bowel Diseases' [Mesh] OR IBD [Text Word] OR 'inflammatory bowel disease' [Text Word] AND 'Vitamin D' [Mesh] OR 'vitamin d' [Text Word] OR Cholecalciferol [Text Word] OR Hydroxycholecalciferols [Text Word] OR Calcifediol [Text Word] OR Dihydroxycholecalciferols [Text Word] OR '24,25-Dihydroxyvitamin D 3' [Text Word] OR Calcitriol [Text Word] OR Ergocalciferol [Text Word] OR '25-Hydroxyvitamin D 2' [Text Word] OR Dihydrotachysterol [Text Word] OR 'Vitamin D' [Mesh] in combination with 'Recommended Dietary Allowances' [Mesh] OR Recommended Dietary Allowances [Text Word] AND deficiency [Text Word] OR 'deficiency' [Subheading]. The search included original studies in humans, review articles, letters, and editorials. To narrow down the amount of articles and to specify the topic of the search with emphasis on novelty, the following criteria were applied to the search strategy: inclusion criteria: articles in English only; articles published since 2010; articles presenting evidence on the efficacy of vitamin D on IBD outcome; and studies focused on vitamin D as a therapeutic agent. Exclusion criteria were: articles focused on IBD in children; and manuscripts presenting animal studies only. Further, references were selected based on relevance and were additionally scrutinizsd manually to identify any supplementary references. Finally, recent studies were prioritised over older studies. The reference list was updated in February 2018.

2. Physiological Role of Vitamin D

2.1. Vitamin D and its effects on skeletal health

In humans the fat-soluble vitamin D is present in two main forms, vitamin D2 [ergocalciferol, from plant sources] and vitamin D3 [cholecalciferol, from animal sources]. Both are absorbed as a dietary vitamin in the small intestine or endogenously synthesised in the skin in response to ultraviolet light exposure [Figure 1],[8,11,31] which is the main source, facilitated when the sun's ultraviolet B [UVB] rays convert 7-dehydrocholesterol to pre-vitamin D3.

After its endogenous synthesis or intestinal absorption, vitamin D is transported to the liver where it is metabolised by the enzyme 25-hydroxylase to form 25-hydroxy-vitamin D (25[OH]D); 25[OH]D is the major circulating vitamin D metabolite and is used to define vitamin D status. However, 25[OH]D is not the active form, as the enzyme 1-α-hydroxylase converts 25[OH]D into its active form, 1,25-dihydroxy-vitamin D ($1,25[OH]_2D$) in the kidney. This process is tightly regulated by parathyroid hormone [PTH], calcium and phosphate levels, and fibroblast growth factor.[11] Circulating 25[OH]D is also the form in which vitamin D is stored in the liver and adipose tissue.[32]

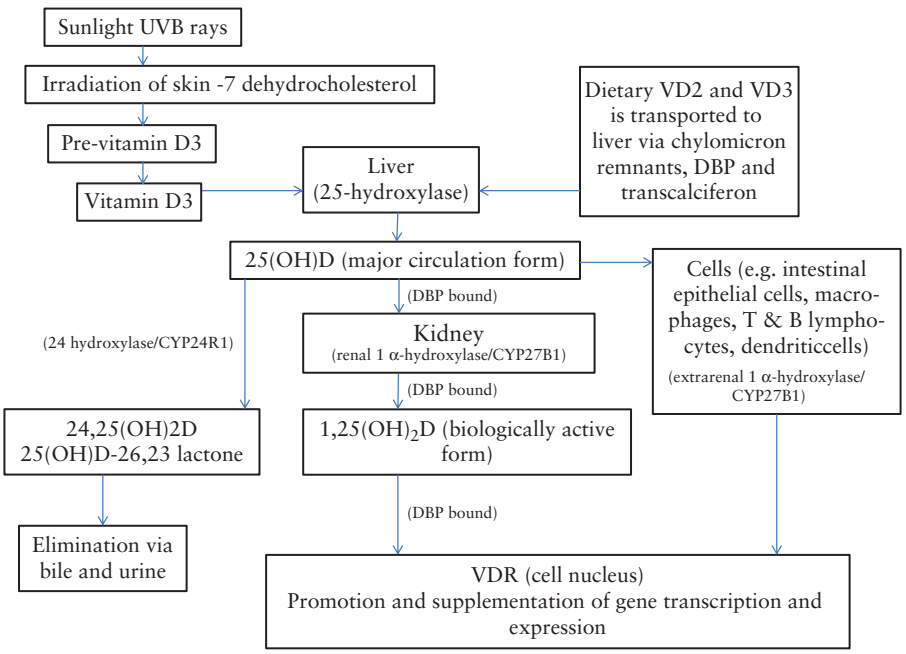

Figure 1. Synthesis and metabolism of vitamin D. BDP, vitamin D-binding protein; VD2, vitamin D2; VD3, vitamin D3; VDR, vitamin D receptor; UVB, ultraviolet B [shortwave] rays.

Both 25[OH]D and 1,25$[OH]_2$D are catabolised into the inactive metabolites 24,25$[OH]_2$D and 1,24,25$[OH]_3$D by 24-hydroxylase, which in turn is excreted through the urine and bile[12] [Figure 1].

In recent years, several studies have revealed that the production of 1,25[OH]D by 1-α-hydroxylase does not solely occur in renal tissue, but also in a number of cells in other tissues, including intestinal macrophages and the immune system.[8,11] This is of major interest, as plasma levels of 25[OH]D, accordingly, are of direct importance to the metabolism of cells in different tissues and do not only function as a substrate for the renal 1-α-hydroxylase. In the circulation, the different vitamin D metabolites are largely transported by being bound to vitamin D-binding protein [DBP] and albumin,[33] although a small fraction remains free in the circulation.[34] According to 'the free hormone hypothesis', only the non-protein-bound fraction of hormones, such as 25[OH]D, is able to enter cells and exert intracellular biological effects.[35] However, current data are conflicting on whether free 25[OH]D or protein-bound vitamin D are most closely correlated with bone mineral density [BMD].[36] As IBD sometimes also may cause low plasma protein levels, it is of interest in future studies to investigate whether measurement of free vitamin D levels is a better way to determine vitamin D status than total levels.

Unlike the tightly regulated activation of vitamin D in the kidney, it is unknown how the activation of vitamin D in non-renal tissues is regulated. Pathways regulating calcium homeostasis may dominate during states of depletion, with non-renal pathways only engaged once stores are replete. Relevant to IBD, circulating cytokines and inflamed tissues can promote extra-renal conversion of 25[OH] to 1,25[OH] vitamin D,[37] a process which may also be affected by an impact of inflammation on PTH levels.[38]

The active metabolite of vitamin D executes its potential beneficial actions on cells through the vitamin D receptor [VDR], which functions as a transcription factor to control gene expression and is present in several organs, including skeletal muscle, immune cells, and the intestine.[12,15] Consequently, vitamin D is involved in a wide range of physiological processes.[16] The binding of 1,25$[OH]_2$D to the nuclear VDR results in a VDR-complex. In turn, this complex forms a heterodimer with the retinoid X receptor [RXR], which either promotes or suppresses gene transcription by binding vitamin D response elements [VDRE] and the recruitment of transcription factors and coregulatory proteins.[31,39] Recent experimental data show that loss of VDR expression in macrophages and granulocytes may increase mucosal pro-inflammatory cytokine expression, thus emphasising a role for vitamin D/VDR signalling in controlling the mucosal immune response in IBD.[40]

In recent years, research studies have identified a crucial role for vitamin D in the regulation of both innate and adaptive immunity [Table 1].

2.2. The innate immune system

The epithelial lining of the gut acts as an important physical barrier for the host against luminal content, including food antigens and the microbiota.[41] Thus, tight junctions and adherent junctions between the epithelial cells are essential to maintain a continuous barrier,[42] as leakage through altered junctions will increase intestinal permeability, which may give rise to inflammation.[43] Studies have shown that a pore-forming transmembrane protein, claudin-2, increases intestinal permeability by inducing cation-selective channels in the tight junctions.[44] Patients with IBD have an increased expression of channel-forming claudin-2 as compared with heathy controls.[45] The expression of claudin-2 is stimulated by interferon [IFN]-γ, a pro-inflammatory cytokine, whereas the protein tyrosine phosphatase N2 [PTPN2] inhibits its expression. In this context, the 1,25$[OH]_2$D-VDR complex can induce transcription of the gene coding for *PTPN2*, resulting in an inhibition of claudin-2, protecting the intestinal barrier[12] and maintaining the differentiated adhesive phenotype of intestinal epithelial cells.[46]

When activated by pathogens, the intestinal epithelium and macrophages produce cathelicidin, which is an antimicrobial peptide,[47,48] as well as defensins which maintain and protect the intestinal barrier integrity.[12,49] Vitamin D (1,25$[OH]_2$D) leads to an increase in cathelicidin levels in macrophages, via vitamin D response elements [VDREs] in the promoter region of the cathelicidin gene.[50] Conversely, when 25[OH]D levels are low, an upregulation of cathelicidin is absent,[31] which adds further evidence of the role of vitamin D in enhancing the innate immune defenses.[11] Further, an intervention study in patients with ulcerative colitis demonstrated that high doses of vitamin D3 led to increased levels of cathelicidin in peripheral blood cells.[51]

Mutations of the gene *NOD2* is associated with a higher risk of developing Crohn's disease,[52,53] as well as a more complicated disease course,[54] as the anti-inflammatory feature of the NOD2 weakens in these carriers.[55] In this context, vitamin D has been found to be a direct inducer of the expression of NOD2 and its downstream pathway, and a synergistic effect on antimicrobial peptide expression by

Table 1. Effects of vitamin D on the innate and adaptive immune system [animal studies separate from human studies].

	Innate immune system	Adaptive immune system
In vitro or animal studies	Low levels of VDR are associated with chronic inflammation and downregulated expression of ATG16L1[57,60]	Dendritic cells have a reduced response to lipopolysaccharide when stimulated with 25[OH]D3,[65] resulting in a decreased activation of T cells[66]
	1,25$[OH]_2$D-VDR complex contributes to maintain the differentiated adhesive phenotype of intestinal epithelial cells[46]	When the VDR on dendritic cells is bound by 1,25$[OH]_2$D, IL-10 production is promoted and it favours a Th2 lymphocyte development over Th1, leading to an anti-inflammatory state[31]
	1,25$[OH]_2$D leads to an increase in cathelicidin in macrophages[50]	1,25$[OH]_2$D3 stimulation of CD4+ T cells increase IL-10 production[68] and apoptosis of activated Th1 cells, reducing pro-inflammatory mediators[70–72]
	Vitamin D acts as an inducer of NOD2 expression[56]	Vitamin D promotes transcription factors c-maf and GATA3, leading to maturation of Th2 cells[70]
	VDR regulates ATG16L1[59]	
	Vitamin D downregulates the IL-23 receptor pathway in lymphoid cells[61]	Vitamin D increases production of anti-inflammatory cytokines IL-4, IL-10, and TGB-β[70]
Human studies	When 25[OH]D levels are low an upregulation of cathelicidin is absent,[31] whereas high levels increase calthelicidin[51]	Circulating B cells can through an autocrine mechanism regulate the immune response by the production of 1,25$[OH]_2$D3[67]

VDR, vitamin D receptor.

vitamin D pre-treatment and successive muramyl dipeptide [MDP] activation has been reported.[56]

ATG16L1 is a gene essential in the process of autophagy and thereby in maintaining intestinal homeostasis, especially in Crohn's disease.[57] ATG16L1 is expressed in intestinal epithelium, dendritic cells, and T and B cells, thus affecting not only the innate but also the adaptive immune system,[5,57,58] and recently VDR was shown to transcriptionally regulate this gene.[59] Thus, in experimental models of colitis, low levels of VDR are associated with chronic inflammation and a downregulated expression of ATG16L1.[57,60] Finally, it has lately been shown that activated group3 innate lymphoid cells [ILC3s], which are tissue-resident lymphocytes functionally resembling TH17/22 cells in the adaptive system, are rendered responsive to vitamin D by upregulating VDR, which causes downregulation of the IL-23R pathway and simultaneous shifts of the ILC3 cytokine production to proinflammatory cytokines, e.g. IL-6 and IL-8. Hence, targeting VDR could have a therapeutic potential in IBD that might directly affect ILC3 functions crucial in orchestrating innate immune responses.[61]

Taken together, these emerging data establish a modulatory role for vitamin D to restore the mutualistic interplay between the microbiota and the epithelium in IBD.[62,63]

2.3. The adaptive immune system

Dendritic cells link the innate immune system to the adaptive immune system by presenting antigens to T cells and inducing an adaptive response through T cell-secreted cytokines.[64] Dendritic cells have a reduced response to lipopolysaccharide when stimulated with 25[OH]D3,[65] which results in a decreased activation of T cells,[66] thus preventing over-activation of the inflammatory response. Dendritic cells also express VDR, and when the receptor is bound by $1,25[OH]_2D$, dendritic cells inhibit the inflammatory response by promoting IL-10 production and inhibiting IL-12 production. This change in cytokine production favours the Th2 lymphocyte development over Th1 lymphocyte development, leading to an anti-inflammatory state.[31] Other mechanisms through which vitamin D may exert its modulating role include an increased production of the anti-inflammatory cytokine IL-10 in $CD4^+$ T cells from Crohn's disease when stimulated with $1,25[OH]_2D3$,[67,68] as well as apoptosis of activated Th1 cells, reducing pro-inflammatory mediators [TNF-α, IFN-γ, ICAM-1].[69–72] Very lately it has been revealed in a prospective cohort of patients with ulcerative colitis in remission, that high serum vitamin D correlates with greater serum anti-inflammatory to pro-inflammatory cytokine ratios, and that such anti-inflammatory cytokine phenotypes are associated with increased presence of histological mucosal healing and decreased risk of clinical relapse.[73] Vitamin D also promotes the transcription factors c-maf and GATA-3, leading to the maturation of Th2 cells.[70] In addition to T cell regulation, the production of anti-inflammatory cytokines, including IL-4, IL-10, and TGF-β, is increased by vitamin D.[70] Cumulatively, these effects suppress initiation and persistence of adaptive responses to exogenous triggers, a critical feature of chronic inflammation in IBD.[70]

3. Thresholds for Vitamin D Supplementation

The discovery of non-renal production of $1,25[OH]_2D$ suggests that circulating levels of 25[OH]D serve as a substrate for both renal and non-renal conversion to $1,25[OH]_2D$. In this context, the amount of 25[OH]D in circulation required for physiological processes and bone health may be influenced by the extent of non-renal conversion of 25[OH]D to $1,25[OH]_2D$ at the tissue level. However, the levels of serum 25[OH]D necessary for the local immunological effects noted above are uncertain, as non-renal tissue levels of $1,25[OH]_2D$ may not correlate with serum 25[OH]D levels.[37]

Serum levels of 25[OH]D are considered the best indicator of body stores and circulatory status of vitamin D, but the threshold for levels of 'deficiency' are largely based on physiological levels required for bone health alone, and even these remain a contentious issue in the scientific literature. Some expert recommendations, including a statement from the Endocrine Society, consider serum 25[OH]D levels below 50 nmol/L [20 ng/mL] as deficiency and levels in the range of 50–75 nmol/L [20–30 ng/mL] as insufficiency.[22] On the other hand, the US Institute of Medicine [IOM] [now the National Academy of Medicine] defines deficiency as a serum 25[OH]D level below 30 nmol/L [12 ng/mL], and insufficiency as 25[OH]D levels in the range of 30–50 nmol/L [12–20 ng/mL].[15,74,75] This cut-off is, however, based on population-based studies in the USA focused on bone health. The IOM suggest a daily Recommended Dietary Allowance [RDA] of 600 IU for adults aged 70 years or younger and 800 IU for those older,[75] which assumes minimal or no sun exposure. The daily tolerable upper limit of the IOM recommendation is set to 4000 IU[75]. Nevertheless, in a recent paper,[74] previous members of the IOM Committee on Dietary Reference Intakes for Vitamin D and Calcium points to some misconceptions in using the RDA cut-points in clinical practice, as they may lead to overprescribing of vitamin D. Thus, high dosages might potentially harm individuals whose intake is pushed above the tolerable upper intake level (with resulting 25[OH]D serum concentrations higher than 125 nmol/L).[74,76] Instead, the Estimated Average Requirement [EAR], reflecting the most likely requirement for the population, should be considered. The EAR is set at 400 IU daily for a person aged 70 years or younger and 600 IU for persons older than 70, equivalent to a serum 25[OH]D level of 16 ng/mL [40 nmol/L] for bone health. The issue of whether higher levels are needed for immune-mediated [i.e. extraskeletal] properties remains controversial,[31,77] and no consensus exists.[12,13,17] It has been suggested that immunomodulatory or other non-skeletal effects require concentrations higher than 75 nmol/L.[22,78] Above this level, PTH reaches a nadir, and renal 1α-hydroxylase is suppressed,[79] which may encourage production of 1,25[OH]D via non-renal pathways.[80]

Nonetheless, clinical studies in patients with IBD [Table 2] often use the RDA as the definition of 'inadequacy', which in real-world situations could lead to an overestimation of people being vitamin D deficient.[74] This highlights the limitation of using cut-off points determined for bone health from older populations to determine the need for supplementation in patients with IBD.[76] Before patients take vitamin D supplements they should, however, be calcium replete, as $1,25[OH]_2D$ mobilises calcium stores from bone.[81–84] Although most research has emphasised the possible benefits of vitamin D, it should be noted that supplemental intake of greater than 4000 IU per day increases the risk of hypervitaminosis D, which is associated with an increased risk of fractures and falls,[85] as well as renal calculi.[86] Recent epidemiological data have also pointed to an increased risk of pancreatic cancer, prostate cancer, and all-cause mortality correlated with high 25[OH]D serum levels.[75]

The known and purported benefits of sufficient vitamin D have caused some people to believe that taking doses higher than the RDA has even more value. Lately, investigators used a US Health and Nutrition Survey Database to identify about 5000 participants for each 2-year cycle of dietary assessment [from 1999 to 2014], for a total of 39 243 participants [mean age 47].[76] In the 2013–2014

Table 2. Cross-sectional and observational studies since 2010 of the association between 25[OH] vitamin D levels and outcomes in IBD.

Author	Year	Study design	Number of patients	Vitamin D variable, definition of deficiency	Outcome	Results
Jørgensen[28]	2010	Prospective	94 CD	25[OH]D, < 50 nmol/L	CDAI [clinical relapse]	Relapse rate among those treated with vitamin D3 for 12 months insignificantly [p = 0.06] reduced the risk of relapse compared with placebo
Hassan[92]	2012	Cross-sectional	60 IBD [26 CD, 34 UC]	25[OH]D, ≤25 nmol/L[a]	Truelove and Witts and CDAI	Vitamin D deficiency was not associated with disease activity [p = 0.23]
Ananthakrishnan[26]	2013	Retrospective	3217 IBD [1763 CD, 1454 UC]	25[OH]D, <50 nmol/L[a]	IBD-related surgery and IBD-related hospitalisations	Low plasma 25[OH]D is associated with increased risk of surgery and hospitalisations in IBD, whereas normalisation of the 25[OH]D level is associated with a reduction in the risk of surgery in CD, but not in UC
Jørgensen[94]	2013	Cross-sectional	182 CD	25[OH]D, <50 nmol/l	CDAI and CRP	25[OH]D level was inversely associated with disease activity, CDAI [p <0.01], and CRP [p<0.05]
Hlavaty[96]	2014	Cross-sectional	220 IBD [141 CD, 79 UC]	25[OH]D, <50 nmol/L[a]	SIBDQ	Vitamin D deficiency correlates with health-related quality of life in winter/spring [p = 0.04]
Zator[101]	2014	Retrospective	101 IBD [74 CD, 27 UC]	25[OH]D <75 nmol/L[a]	Durability of maintenance TNF inhibitor therapy stratified by reason for cessation	Low plasma 25[OH]D at induction of TNF inhibitors is associated with poorer response and earlier cessation of therapy
Pappa[29]	2014	Cross-sectional	63 IBD [37 CD, 26 UC]	25[OH]D <50 nmol/L[a]	PCDAI and PUCAI	Oral vitamin D2 doses up to 2000 IU were inadequate to maintain 25[OH]D of minimum 32 ng/mL but were well tolerated
Ham[95]	2014	Retrospective	37 CD [20 active, 17 in remission]	25[OH]D not defined	HBI	Correlation between 25[OH]D levels and beneficial response to TNF inhibitors
Raftery[93]	2015	Cross-sectional	119 CD	25[OH]D, <50 nmol/L	CRP and CDAI	25[OH]D was insignificantly associated with CRP [p = 0.073] and CDAI [p = 0.687]
Frigstad[24]	2016	Cross-sectional	408 IBD [230 CD, 178 UC]	25[OH]D, < 50 nmol/l	HBI, SCCAI, faecal calprotectin and relapse	Vitamin D deficiency was inversely associated with HBI [p <0.05] and clinical relapse in CD. Significant association was found between vitamin D deficiency and faecal calprotectin in UC [p <0.05], but not between SCCAI and UC [p = 0.23]
Dolatshahi[97]	2016	Cross-sectional	50 UC	25[OH]D, not defined	Truelove and Witts	Lower 25[OH]D levels was associated with higher disease activity [p = 0.04]
Kabbani[25]	2016	Prospective	965 IBD [597 CD, 368 UC]	25[OH]D, <50 nmol/L	Medication use, health care use, HBI score, UCAI, SIBDQ score. and surgery	Low 25[OH]D was associated with more steroid, biologics, and narcotics use, CT scans, emergency department visits, hospitalisations, and surgery. Patients with low 25[OH]D had worse disease activity scores and quality of life [p <0.05]
Winter[100]	2016	Retrospective	173 IBD [116 CD, 57 UC] patients treated with anti-TNF-α therapy	25[OH]D, <22.5–82.5 nmol/L[a]	Remission while receiving anti-TNF-α therapy	Normal 25[OH]D levels had a 2.64-fold increased odds of remission after 3 months of therapy with TNF-α inhibitors compared with patients with low 25[OH]D levels [p = 0.0067]
Gubatan[98]	2017	Prospective	70 UC	25[OH]D, not defined	Relapse	Mean baseline level of 25[OH]D was lower in UC with relapse than patients without [p = 0.001]

CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; HBI, Harvey-Bradshaw Index; IBD, inflammatory bowel disease; SCCAI, Simple Clinical Colitis Activity Index; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; TNF-α, tumour necrosis factor alpha; UC, ulcerative colitis; UCAI, Ulcerative Colitis Activity Index.

[a]Converted from nmol/L to ng/mL by dividing by a factor 2.5.

survey, the prevalence of daily supplemental intake ≥1000 IU vitamin D was 18.2%, and the prevalence of intake ≥4000 was 3.2%. It was observed that the intake increased significantly from the 1999–2000 survey [0.3%] to the 2013–2014 survey.[76] However, as hypervitaminosis D, as mentioned, is linked with serious side effects, caution is advised and clinicians should be asking patients specifically about their supplemental vitamin D use.

4. Relationship of Vitamin D Levels to Natural History of IBD

Given the noted impact of malabsorption and inflammation on serum vitamin D levels,[24,87,88] it is no surprise that vitamin D deficiency seems to occur more frequently in IBD than in the general population.[13,87,89,90] Prevalence rates of vitamin D deficiency in IBD range from 16% to 95%, and it seems to occur more commonly in Crohn's disease than in ulcerative colitis.[11,13,89–91]

4.1. Disease activity and outcomes

Studies of dietary supplementation of vitamin D support a beneficial effect of vitamin D in IBD. In the Nurses' Health Study cohort of 72 719 individuals, women with the predicted highest vitamin D levels had a significantly lower risk of incident Crohn's disease.[23] Nevertheless, observational studies focusing on vitamin D and its effects on the clinical course and outcome in IBD are conflicting [Table 2]. Thus in one study, 60 patients with IBD were included, of whom 95% had vitamin D deficiency defined as <29 ng/mL.[92] The patients were divided into active or quiescent disease, but no association between vitamin D and disease activity was revealed. Another study had similar findings in a cohort of 119 patients with Crohn's disease.[93] Additionally, this latter trial assessed the systemic inflammatory burden by measuring C-reactive protein [CRP], and no correlation with serum level of vitamin D was found [Table 2].

In contrast, a cross-sectional study[94] reported an inverse association between serum 25[OH]D and disease activity in 182 patients with Crohn's disease. Patients with Crohn's Disease Activity Index [CDAI] levels below 150 [i.e. quiescent disease] had a median serum level of 25[OH]D higher than patients with mild or moderate disease: 64 nmol/l [remission], 49 nmol/l [mild], and 21 nmol/l [moderate disease activity], respectively [p = 0.01]. A subsequent trial also revealed that serum 25[OH]D levels inversely correlated with Harvey-Bradshaw disease activity in 37 patients with Crohn's disease.[95] Furthermore, a recent outpatient population of 408 patients with IBD revealed that 49% of these patients had a 25[OH]D serum concentration below 50 nmol/L (230 were diagnosed with Crohn's disease and 178 with ulcerative colitis; 53% of Crohn's disease patients had low 25[OH]D concentrations versus 44% of ulcerative colitis).[24] In this study, vitamin D deficiency was prevalent in IBD and appeared to be linked to an increased disease activity, as the risk of relapse was almost doubled in patients with Crohn's disease and vitamin D concentrations below 50 nmol/L, and it was deducted that correction of vitamin D deficiency would be beneficial for controlling the disease.[24] Another cross-sectional study has supported this association by noting higher health-related quality of life in a cohort of 220 patients with IBD during periods of raised vitamin D levels[96] [Table 2]. Further, a study exclusively performed on 50 patients with ulcerative colitis supported the association between lower levels of serum 25[OH]D and disease activity.[97] Here patients receiving glucocorticoids were excluded because of the interaction of glucocorticoids with vitamin D metabolism. Patients were divided into two groups, and a significantly higher concentration of serum 25[OH]D was found in the group with mild disease activity as compared with the moderate disease activity group.[97]

The limitation of many studies has been their retrospective or cross-sectional correlation of vitamin D with disease activity indices, which does not answer the causation question. To address this, a recent prospective study of 70 patients with ulcerative colitis in clinical remission, followed for 12 months, reported that a serum level of 25[OH]D of 87.5 nmol/L or less during periods of clinical remission was associated with an increased risk clinical relapse over the subsequent 12 months.[98] Similarly, a prospective 5-year longitudinal study involving 965 IBD patients [62% with Crohn's disease and 38% with ulcerative colitis][25] found an association between vitamin D and health-related outcome. Low 25[OH]D levels [i.e. <75 nmol/l] were observed in 30% of patients at study entry, and were highest among young males.[25] During the 5-year follow-up, patients with low 25[OH]D levels required significantly more glucocorticoids, initiation of biologic treatment, narcotics for pain control, computed tomography scans, emergency department visits, hospitalisations, and surgery, than did those with normal 25[OH]D levels.[25] To control for the effect of disease severity on 25[OH]D levels, the investigators conducted a subgroup analysis of patients in clinical remission at study entry. In this group more patients with low versus normal 25[OH]D levels required glucocorticoids [51% and 37%, respectively] and IBD-related surgery [34% and 22%, respectively].[25] Moreover, patients with low vitamin D levels who were administered vitamin D supplementation progressively reduced their health care use during the 5-year follow-up, whereas those with low 25[OH]D levels who did not receive supplementation converseely increased their health care use. This extensive study with a comprehensive IBD cohort was able to associate low 25[OH]D to a multiplicity of outcomes, and thus it adds substantial information to the increasing amount of evidence connecting 25[OH]D levels with outcomes in IBD.[27] Another comprehensive prospective study of 3217 patients with IBD showed that low 25[OH]D is associated with higher risk of IBD-related surgery and hospitalisations.[26] Interestingly, the authors also reported that patients with Crohn's disease who normalised their 25[OH]D level (deficiency was defined as 25[OH]D <20 ng/mL) at the same time reduced the risk of surgery as compared with those who remained deficient, whereas no such an effect was observed in ulcerative colitis. Higher levels of 25[OH]D seem even to have a protective effect on infections with *Clostridium difficile* in IBD as well.[99]

4.2. Response to biologics

Although most of the patients included in the previous studies received medication, not many of the studies explored the relationship between 25[OH]D levels and the probability of remission while on a certain medication. Nevertheless, in a subgroup of 37 patients with Crohn's disease, an early increase of serum 25[OH]D was observed in those responding to tumour necrosis factor [TNF] inhibitors,[95] and recently a similar observation was noticed in ulcerative colitis as well.[100] Moreover, in a single-centre cohort study of 101 patients with IBD, pre-treatment levels of 25[OH]D influenced durability of TNF inhibitors.[101] This trial supported the relevance of both correcting and maintaining adequate vitamin D levels in IBD above 75 nmol/l to reduce the risk of flares and to optimise response to targeted medical regimens.[26,101] Finally, a recent retrospective study on 384 patients with IBD treated with TNF inhibitors concluded that IBD patients with normal 25[OH]D levels at

the initiation of treatment with TNF inhibitors had a 2.64 increased chance of reaching remission within 3 months as compared with those patients with low vitamin D concentrations.[100]

5. Vitamin D as a Therapy for IBD

Experimental studies in mice have previously shown vitamin D to reduce the severity of colitis.[102,103] However, in humans, vitamin D deficiency or impaired signalling might worsen colitis through multiple effects, including alterations of the gut microbiome,[59,60,83,104–106] and vitamin D supplementation has been reported to increase both bacterial richness and bacterial diversity.[107]

Nevertheless, only a few randomised controlled trials have examined the effects of vitamin D supplementation on outcome of IBD. In a small placebo-controlled, randomised trial of Crohn's disease in remission, 94 patients were randomly divided into two groups: one group receiving 1200 IU vitamin D3 daily, and the other receiving placebo. The trial concluded that dietary supplementation with vitamin D3 daily for 12 months modestly increased the participants' 25[OH]D levels and reduced the proportion of patients with clinical relapse from 29% to 13%.[28] Although this difference was not statistically significant [$p = 0.06$], the study did support the rationale for further studies.

In a study of 63 children and adolescents aged 8–18 years with IBD and a baseline 25[OH]D greater than 50 nmol/L, participants were randomised to receive one of two daily oral vitamin D2 regimens: either 400 IU [Arm A], or 1000 IU if between May 1 and October 31 or 2000 IU if between November 1 and April 30 [Arm B] for 12 months. The main outcome was the probability of maintaining 25[OH]D at a minimum 80 nmol/L at all trimonthly visits for the 12 months.[29] Although it was revealed that patients in Arm B had significantly lower levels of circulating IL-6 and CRP [$p < 0.05$], the daily doses of vitamin supplementation in both arms were inadequate to maintain the predefined serum 25[OH]D concentrations of 80 nmol/L or above at the follow-up visits, though doses were safe and well tolerated. The findings of an association between intake of higher doses of vitamin D and reduced inflammatory surrogate markers may, however, indicate that vitamin D repletion and supplementation regimens should be based on body weight.[29,108]

Supplementing all patients with the same amount of vitamin D might, however, result in patients with a low basal level not reaching the therapeutic threshold. Nevertheless, this was not relevant in an intervention study on 18 patients with Crohn's disease,[30] which applied a design focusing on achieving 25[OH]D levels of 100 nmol/L, instead of receiving a fixed daily dose of vitamin D. After 6 months, the authors reported a highly significant reduction in CDAI scores. Unfortunately this study had certain limitations, including a very small study cohort and the lack of a control group.[30]

A randomised controlled trial included 90 patients with quiescent ulcerative colitis.[51] The study design was different from other studies as it only intervened once by administering 300 000 IU vitamin D3 intramuscularly or 1 mL saline [placebo]. Systemic inflammation, measured as level of serum CRP, was assessed 3 months after intervention, presenting a decrease in the group receiving vitamin D3.[51] Another randomised, double-blind placebo-controlled trial in 34 patients with quiescent Crohn's disease compared the effect of high-dose vitamin D3 supplementation of 10 000 IU daily [$n = 18$ patients] versus 1000 IU daily [$n = 16$]. The cohort was supplemented for a full year, after which the study reported similar rates of clinical relapse in both treatment groups, although high-dose supplementation significantly improved 25[OH]D levels.[109]

To address some of the problems with under-dosing of vitamin D in intervention trials, a recent prospective pilot study of 10 patients with active IBD and a serum 25[OH]D level below 75 nmol/L had 'treat-to-target' dosing of vitamin D to get 25[OH] levels up to 125 nmol/L. Subjects were dose-adjusted 4-weekly to aim for a target level of 100–126 nmol/L. Per-oral doses used in the protocol were 5000–10 000 U/day. Over the 12 weeks of the study, the mean increase was 20 ng/mL, with most patients needing at least one 4-week period of 10 000 U/day. Target or near-target was achieved in all participants over 12 weeks and, though a signal for hypercalciuria was noted in one patient, the regimen was well tolerated and symptom-based activity scores improved.[110]

The available studies have confounders or limitations. These may include variations in: cut-off levels of serum 25[OH]D values used to define 'deficiency'; study populations and designs; inclusion and exclusion criteria; activity scores applied; treatment doses; and outcomes. Direct comparisons between studies are further complicated by the lack of a standardisation between various assays used to measure 25[OH]D levels.[111] However, results seem to support the concept of vitamin D having anti-inflammatory effects in IBD [Figure 2].[24,26]

6. Conclusions and Recommendations

Laboratory, epidemiological, and clinical studies support the concept that vitamin D may in part determine the development of, and course of, IBD beyond its classical key role in bone health and calcium homeostasis.

It is as yet unclear whether vitamin D deficiency is a causative factor for IBD or a risk factor, but vitamin D deficiency seems to be prevalent in IBD and to be inversely linked to disease activity, more frequent relapses, higher postoperative recurrence, poorer quality of life, and failure of response to biologics, as compared with normal or high levels of 25[OH]D in IBD. However, there is a need for the definition of the optimal therapeutic level of 25[OH]D in IBD and to clarify how vitamin D modifies levels of inflammation; its exact effect on disease severity, and if vitamin D deficiency is associated with any specific clinical phenotypes. Thus, it is likely that higher concentrations of serum 25[OH]D may be required in active IBD to achieve the immunological effects noted *in vitro*. Finally, a number of challenges occur when designing future trials to examine the importance of vitamin D supplementation, as placebo arms may be exposed to either the therapeutic intervention from vitamin D-enriched food or to sun exposure, blurring whether the intervention actually causes the expected effect.[13,112] Furthermore, leaving vitamin D deficiency untreated might even be unethical.

Nevertheless, this manuscript highlights a broad array of data supporting the importance of ensuring at least adequate [>75nmol/L] serum vitamin D levels in patients with IBD. This may improve clinical outcomes, such as relapse rate and mucosal inflammation, in addition to its benefits on bone health. Animal models, as well as epidemiological studies and intervention studies, have all provided a scientific rationale for this approach. The primary area lacking data is appropriately sized, randomised controlled trials of vitamin D supplementation, adjusted to obtain such adequate levels in an intervention cohort. Due to a lack of an industry sponsor to fund such complex studies, these are unlikely to emerge from investigator-initiated studies. In this setting, and in light of the accumulated literature reviewed here, we recommend that

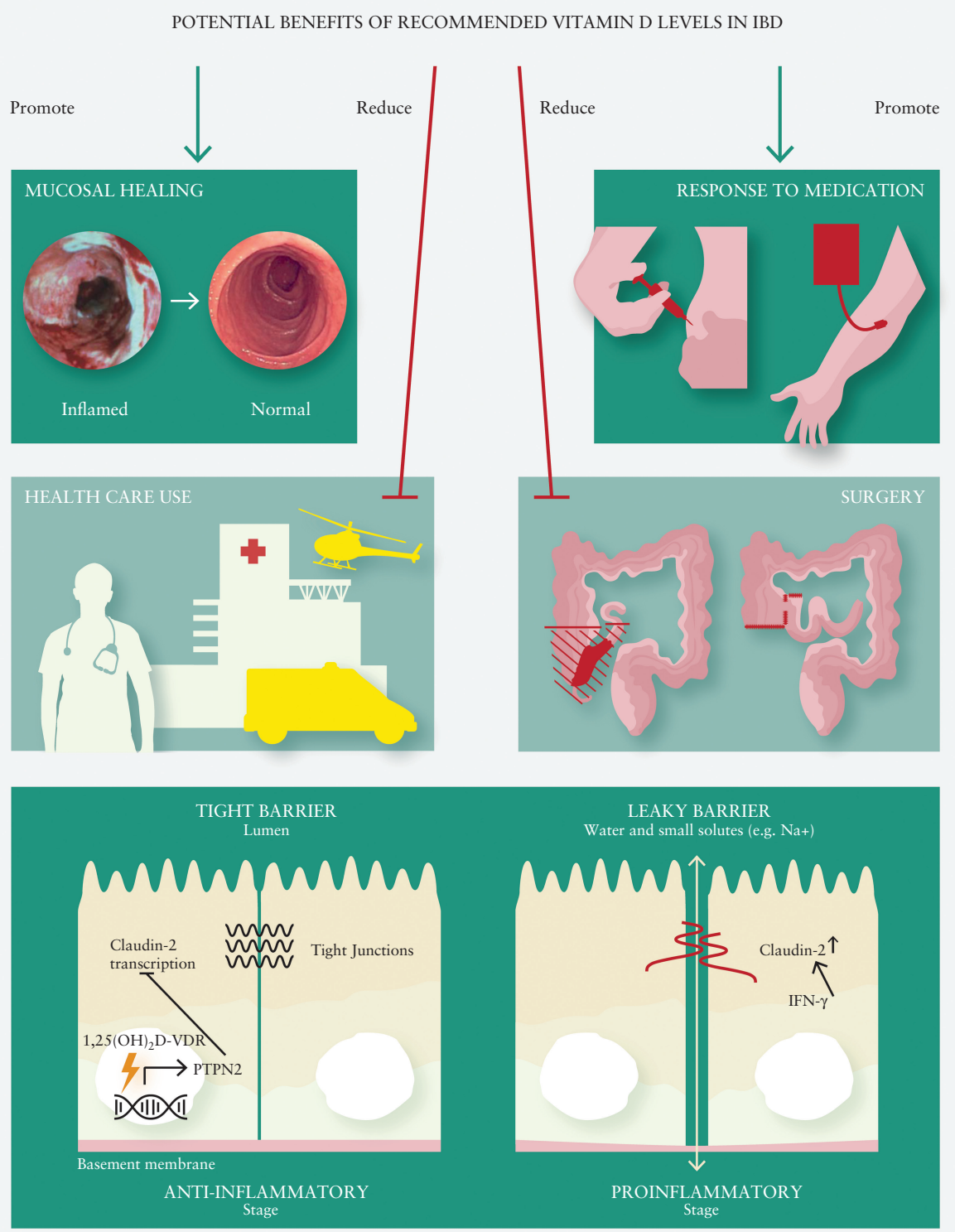

Figure 2. Effects of vitamin D on various clinical settings of importance for managing patients with inflammatory bowel disease [IBD]. Green arrows indicate stimulating effects; red lines indicate inhibiting effects.

physicians and other health care professionals check the 25[OH]D serum levels of their patients with IBD regularly. To avoid vitamin D insufficiency it is of importance to consider vitamin D supplementation which, unlike other current IBD therapies, is relatively affordable and accessible. This may increase the probability of clinical remission and response to conventional therapeutic strategies, and in this way may lead to better patient outcomes as well as reduced health care expenses.

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Conflict of Interest

None of the authors reported a conflict of interest related to the study.

Author Contributions

OHN wrote the manuscript; LR and ACM revised the manuscript. All authors read and approved the final manuscript.

Take-home Points

- A rationale for vitamin D supplementation comes from the extensively studied features of vitamin D in the innate and adaptive immune system of relevance for IBD.
- Optimising vitamin D levels is relevant not solely for therapeutic response, but also in reducing risk of relapse and risk of surgery and to improving response to medication and quality of life.
- A main challenge in studies of vitamin D in IBD is to clarify what target of 25[OH]D in serum shouldd be achieved, as most current recommendations are based on the effects of vitamin D on bone health of the general population, and not on effects involved in the immune regulation of specific chronic diseases like IBD.
- The evidence for vitamin D supplementation as an anti-inflammatory therapeutic agent is insufficient, i.e. there is an unmet need for well-designed clinical studies to determine whether the anti-inflammatory effects of vitamin D translate into clinical benefits for IBD patients.
- In trial design, a challenge is the appropriate treatment of the control group, as vitamin D deficiency should not be left untreated.
- Until further high-level evidence becomes available, the current evidence base seems to suggest beneficial effects of maintaining a replete vitamin D status among patients with IBD, i.e. serum 25[OH]D levels below 75 nmol/L should be avoided.

References

1. Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet* 2012;**380**:1590–605.
2. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. *Lancet* 2017;**389**:1756–70.
3. Ng SC, Shi HY, Hamidi N, *et al*. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2017;**390**:2769–78.
4. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. *Nature* 2011;**474**:307–17.
5. Atreya R, Neurath MF. IBD pathogenesis in 2014: molecular pathways controlling barrier function in IBD. *Nat Rev Gastroenterol Hepatol* 2015;**12**:67–8.
6. Larsen S, Bendtzen K, Nielsen OH. Extraintestinal manifestations of inflammatory bowel disease: epidemiology, diagnosis, and management. *Ann Med* 2010;**42**:97–114.
7. Targownik LE, Bernstein CN, Leslie WD. Risk factors and management of osteoporosis in inflammatory bowel disease. *Curr Opin Gastroenterol* 2014;**30**:168–74.
8. White JH. Vitamin D deficiency and the pathogenesis of Crohn's disease. *J Steroid Biochem Mol Biol* 2018;**175**:23–8.
9. Reid IR, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. *Lancet* 2014;**383**:146–55.
10. Nerich V, Jantchou P, Boutron-Ruault MC, *et al*. Low exposure to sunlight is a risk factor for Crohn's disease. *Aliment Pharmacol Ther* 2011;**33**:940–5.
11. Mouli VP, Ananthakrishnan AN. Review article: vitamin D and inflammatory bowel diseases. *Aliment Pharmacol Ther* 2014;**39**:125–36.
12. Garg M, Lubel JS, Sparrow MP, Holt SG, Gibson PR. Review article: vitamin D and inflammatory bowel disease – established concepts and future directions. *Aliment Pharmacol Ther* 2012;**36**:324–44.
13. O'Sullivan M. Vitamin D as a novel therapy in inflammatory bowel disease: new hope or false dawn? *Proc Nutr Soc* 2015;**74**:5–12.
14. Gominak SC. Vitamin D deficiency changes the intestinal microbiome reducing B vitamin production in the gut. The resulting lack of pantothenic acid adversely affects the immune system, producing a 'pro-inflammatory' state associated with atherosclerosis and autoimmunity. *Med Hypotheses* 2016;**94**:103–7.
15. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;**357**:266–81.
16. Rosen CJ. Clinical practice. Vitamin D insufficiency. *N Engl J Med* 2011;**364**:248–54.
17. Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. *BMJ* 2014;**348**:g2035.
18. Nielsen OH, Soendergaard C, Vikner ME, Weiss G. Rational management of iron-deficiency anaemia in inflammatory bowel disease. *Nutrients* 2018;**10**:E82–107.
19. Syed S, Michalski ES, Tangpricha V, *et al*. Vitamin D status is associated with hepcidin and hemoglobin concentrations in children with inflammatory bowel disease. *Inflamm Bowel Dis* 2017;**23**:1650–8.
20. Ananthakrishnan AN. Vitamin D and inflammatory bowel disease. *Gastroenterol Hepatol* 2016;**12**:513–5.
21. Fabisiak N, Fabisiak A, Watala C, Fichna J. Fat-soluble vitamin deficiencies and inflammatory bowel disease: systematic review and meta-analysis. *J Clin Gastroenterol* 2017;**51**:878–89.
22. Holick MF, Binkley NC, Bischoff-Ferrari HA, *et al*. Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011;**96**:1911–30.
23. Ananthakrishnan AN, Khalili H, Higuchi LM, *et al*. Higher predicted vitamin D status is associated with reduced risk of Crohn's disease. *Gastroenterology* 2012;**142**:482–9.
24. Frigstad SO, Høivik M, Jahnsen J, *et al*. Vitamin D deficiency in inflammatory bowel disease: prevalence and predictors in a Norwegian outpatient population. *Scand J Gastroenterol* 2017;**52**:100–6.
25. Kabbani TA, Koutroubakis IE, Schoen RE, *et al*. Association of vitamin D level with clinical status in inflammatory bowel disease: a 5-year longitudinal study. *Am J Gastroenterol* 2016;**111**:712–9.
26. Ananthakrishnan AN, Cagan A, Gainer VS, *et al*. Normalization of plasma 25-hydroxy vitamin D is associated with reduced risk of surgery in Crohn's disease. *Inflamm Bowel Dis* 2013;**19**:1921–7.
27. Ananthakrishnan AN. Editorial: vitamin D and IBD: can we get over the 'Causation' hump? *Am J Gastroenterol* 2016;**111**:720–2.
28. Jørgensen SP, Agnholt J, Glerup H, *et al*. Clinical trial: vitamin D3 treatment in Crohn's disease - a randomized double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2010;**32**:377–83.
29. Pappa HM, Mitchell PD, Jiang H, *et al*. Maintenance of optimal vitamin D status in children and adolescents with inflammatory bowel disease: a randomized clinical trial comparing two regimens. *J Clin Endocrinol Metab* 2014;**99**:3408–17.
30. Yang L, Weaver V, Smith JP, Bingaman S, Hartman TJ, Cantorna MT. Therapeutic effect of vitamin D supplementation in a pilot study of Crohn's patients. *Clin Transl Gastroenterol* 2013;**4**:e33.
31. Basson A. Vitamin D and Crohn's disease in the adult patient: a review. *JPEN J Parenter Enteral Nutr* 2014;**38**:438–58.
32. Heaney RP, Armas LA, Shary JR, Bell NH, Binkley N, Hollis BW. 25-Hydroxylation of vitamin D3: relation to circulating vitamin D3 under various input conditions. *Am J Clin Nutr* 2008;**87**:1738–42.
33. Bikle DD, Gee E, Halloran B, Kowalski MA, Ryzen E, Haddad JG. Assessment of the free fraction of 25-hydroxyvitamin D in serum and its regulation by albumin and the vitamin D-binding protein. *J Clin Endocrinol Metab* 1986;**63**:954–9.
34. Malmstroem S, Rejnmark L, Imboden JB, Shoback DM, Bikle DD. Current assays to determine free 25-hydroxyvitamin D in serum. *J AOAC Int* 2017;**100**:1323–7.

35. Recant L, Riggs DS. Thyroid function in nephrosis. *J Clin Invest* 1952;**31**:789–97.
36. Powe CE, Ricciardi C, Berg AH, *et al.* Vitamin D-binding protein modifies the vitamin D-bone mineral density relationship. *J Bone Miner Res* 2011;**26**:1609–16.
37. Abreu MT, Kantorovich V, Vasiliauskas EA, *et al.* 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**:1129–36.
38. Augustine MV, Leonard MB, Thayu M, *et al.* Changes in vitamin D-related mineral metabolism after induction with anti-tumor necrosis factor-α therapy in Crohn's disease. *J Clin Endocrinol Metab* 2014;**99**:E991–8.
39. Pike JW, Meyer MB. The vitamin D receptor: new paradigms for the regulation of gene expression by 1,25-dihydroxyvitamin D[3]. *Endocrinol Metab Clin North Am* 2010;**39**:255–69, table of contents.
40. Leyssens C, Verlinden L, De Hertogh G, *et al.* Impact on experimental colitis of vitamin D receptor deletion in intestinal epithelial or myeloid cells. *Endocrinology* 2017;**158**:2354–66.
41. Peterson LW, Artis D. Intestinal epithelial cells: regulators of barrier function and immune homeostasis. *Nat Rev Immunol* 2014;**14**:141–53.
42. Seidelin JB, Coskun M, Nielsen OH. Mucosal healing in ulcerative colitis: pathophysiology and pharmacology. *Adv Clin Chem* 2013;**59**:101–23.
43. Hooper LV. Epithelial cell contributions to intestinal immunity. *Adv Immunol* 2015;**126**:129–72.
44. Luettig J, Rosenthal R, Barmeyer C, Schulzke JD. Claudin-2 as a mediator of leaky gut barrier during intestinal inflammation. *Tissue Barriers* 2015;**3**:e977176.
45. Stio M, Retico L, Annese V, Bonanomi AG. Vitamin D regulates the tight-junction protein expression in active ulcerative colitis. *Scand J Gastroenterol* 2016;**51**:1193–9.
46. Barbáchano A, Fernández-Barral A, Ferrer-Mayorga G, Costales-Carrera A, Larriba MJ, Muñoz A. The endocrine vitamin D system in the gut. *Mol Cell Endocrinol* 2017;**453**:79–87.
47. Gombart AF, Borregaard N, Koeffler HP. Human cathelicidin antimicrobial peptide [CAMP] gene is a direct target of the vitamin D receptor and is strongly upregulated in myeloid cells by 1,25-dihydroxyvitamin D3. *FASEB J* 2005;**19**:1067–77.
48. Liu PT, Stenger S, Li H, *et al.* Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006;**311**:1770–3.
49. Raftery T, O'Sullivan M. Optimal vitamin D levels in Crohn's disease: a review. *Proc Nutr Soc* 2015;**74**:56–66.
50. Vandamme D, Landuyt B, Luyten W, Schoofs L. A comprehensive summary of LL-37, the factotum human cathelicidin peptide. *Cell Immunol* 2012;**280**:22–35.
51. Sharifi A, Hosseinzadeh-Attar MJ, Vahedi H, Nedjat S. A randomized controlled trial on the effect of vitamin D3 on inflammation and cathelicidin gene expression in ulcerative colitis patients. *Saudi J Gastroenterol* 2016;**22**:316–23.
52. Salem M, Seidelin JB, Rogler G, Nielsen OH. Muramyl dipeptide responsive pathways in Crohn's disease: from NOD2 and beyond. *Cell Mol Life Sci* 2013;**70**:3391–404.
53. Strober W, Asano N, Fuss I, Kitani A, Watanabe T. Cellular and molecular mechanisms underlying NOD2 risk-associated polymorphisms in Crohn's disease. *Immunol Rev* 2014;**260**:249–60.
54. Philpott DJ, Sorbara MT, Robertson SJ, Croitoru K, Girardin SE. NOD proteins: regulators of inflammation in health and disease. *Nat Rev Immunol* 2014;**14**:9–23.
55. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med* 2009;**361**:2066–78.
56. Wang TT, Dabbas B, Laperriere D, *et al.* Direct and indirect induction by 1,25-dihydroxyvitamin D3 of the NOD2/CARD15-defensin beta2 innate immune pathway defective in Crohn disease. *J Biol Chem* 2010;**285**:2227–31.
57. Salem M, Ammitzboell M, Nys K, Seidelin JB, Nielsen OH. ATG16L1: a multifunctional susceptibility factor in Crohn disease. *Autophagy* 2015;**11**:585–94.
58. Shaw SY, Tran K, Castoreno AB, *et al.* Selective modulation of autophagy, innate immunity, and adaptive immunity by small molecules. *ACS Chem Biol* 2013;**8**:2724–33.
59. Sun J. VDR/vitamin D receptor regulates autophagic activity through ATG16L1. *Autophagy* 2016;**12**:1057–8.
60. Wu S, Zhang YG, Lu R, *et al.* Intestinal epithelial vitamin D receptor deletion leads to defective autophagy in colitis. *Gut* 2015;**64**:1082–94.
61. Konya V, Czarnewski P, Forkel M, *et al.* Vitamin D downregulates the IL-23 receptor pathway in human mucosal group 3 innate lymphoid cells. *J Allergy Clin Immunol* 2018;**141**:279–92.
62. Dimitrov V, White JH. Vitamin D signaling in intestinal innate immunity and homeostasis. *Mol Cell Endocrinol* 2017;**453**:68–78.
63. Waldschmitt N, Chamaillard M. Time for epithelial sensing of vitamin D to step into the limelight. *Gut* 2015;**64**:1013–4.
64. Ng SC, Kamm MA, Stagg AJ, Knight SC. Intestinal dendritic cells: their role in bacterial recognition, lymphocyte homing, and intestinal inflammation. *Inflamm Bowel Dis* 2010;**16**:1787–807.
65. Bartels LE, Jørgensen SP, Bendix M, *et al.* 25-Hydroxy vitamin D3 modulates dendritic cell phenotype and function in Crohn's disease. *Inflammopharmacology* 2013;**21**:177–86.
66. Bartels LE, Bendix M, Hvas CL, *et al.* Oral vitamin D3 supplementation reduces monocyte-derived dendritic cell maturation and cytokine production in Crohn's disease patients. *Inflammopharmacology* 2014;**22**:95–103.
67. Heine G, Niesner U, Chang HD, *et al.* 1,25-dihydroxyvitamin D[3] promotes IL-10 production in human B cells. *Eur J Immunol* 2008;**38**:2210–8.
68. Bartels LE, Jørgensen SP, Agnholt J, Kelsen J, Hvas CL, Dahlerup JF. 1,25-dihydroxyvitamin D3 and dexamethasone increase interleukin-10 production in CD4+ T cells from patients with Crohn's disease. *Int Immunopharmacol* 2007;**7**:1755–64.
69. Pedersen J, LaCasse EC, Seidelin JB, Coskun M, Nielsen OH. Inhibitors of apoptosis [IAPs] regulate intestinal immunity and inflammatory bowel disease [IBD] inflammation. *Trends Mol Med* 2014;**20**:652–65.
70. Reich KM, Fedorak RN, Madsen K, Kroeker KI. Vitamin D improves inflammatory bowel disease outcomes: basic science and clinical review. *World J Gastroenterol* 2014;**20**:4934–47.
71. Martinesi M, Treves C, d'Albasio G, Bagnoli S, Bonanomi AG, Stio M. Vitamin D derivatives induce apoptosis and downregulate ICAM-1 levels in peripheral blood mononuclear cells of inflammatory bowel disease patients. *Inflamm Bowel Dis* 2008;**14**:597–604.
72. Raman M, Milestone AN, Walters JR, Hart AL, Ghosh S. Vitamin D and gastrointestinal diseases: inflammatory bowel disease and colorectal cancer. *Therap Adv Gastroenterol* 2011;**4**:49–62.
73. Gubatan J, Mitsuhashi S, Longhi MS, *et al.* Higher serum vitamin D levels are associated with protective serum cytokine profiles in patients with ulcerative colitis. *Cytokine* 2018;**103**:38–45.
74. Manson JE, Brannon PM, Rosen CJ, Taylor CL. Vitamin D deficiency is there really a pandemic? *N Engl J Med* 2016;**375**:1817–20.
75. Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Ross AC, Taylor CL, Yaktine AL, Del Valle HB (editors). *Review Dietary Reference Intakes for Vitamin D and Calcium*. Washington [DC]: National Academies Press; 2011.
76. Rooney MR, Harnack L, Michos ED, Ogilvie RP, Sempos CT, Lutsey PL. Trends in use of high-dose vitamin D supplements exceeding 1000 or 4000 International units daily, 1999–2014. *JAMA* 2017;**317**:2448–50.
77. Ross AC, Manson JE, Abrams SA, *et al.* 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**:53–8.
78. Bischoff-Ferrari HA. Optimal serum 25-hydroxyvitamin D levels for multiple health outcomes. *Adv Exp Med Biol* 2008;**624**:55–71.
79. Saliba W, Barnett O, Rennert HS, Lavi I, Rennert G. The relationship between serum 25[OH]D and parathyroid hormone levels. *Am J Med* 2011;**124**:1165–70.
80. Garg M. Serum vitamin D and risk of clinical relapse in patients with ulcerative colitis. *Clin Gastroenterol Hepatol* 2017;**15**:1136.
81. Chen Y, Du J, Zhang Z, *et al.* MicroRNA-346 mediates tumor necrosis factor α-induced downregulation of gut epithelial vitamin D receptor in inflammatory bowel diseases. *Inflamm Bowel Dis* 2014;**20**:1910–8.
82. Du J, Chen Y, Shi Y, *et al.* 1,25-Dihydroxyvitamin D protects intestinal epithelial barrier by regulating the myosin light chain kinase signaling pathway. *Inflamm Bowel Dis* 2015;**21**:2495–506.

83. Liu W, Chen Y, Golan MA, *et al.* Intestinal epithelial vitamin D receptor signaling inhibits experimental colitis. *J Clin Invest* 2013;**123**:3983–96.
84. Meckel K, Li YC, Lim J, *et al.* Serum 25-hydroxyvitamin D concentration is inversely associated with mucosal inflammation in patients with ulcerative colitis. *Am J Clin Nutr* 2016;**104**:113–20.
85. Sanders KM, Stuart AL, Williamson EJ, *et al.* Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA* 2010;**303**:1815–22.
86. Wallace RB, Wactawski-Wende J, O'Sullivan MJ, *et al.* Urinary tract stone occurrence in the Women's Health Initiative [WHI] randomized clinical trial of calcium and vitamin D supplements. *Am J Clin Nutr* 2011;**94**:270–7.
87. Del Pinto R, Pietropaoli D, Chandar AK, Ferri C, Cominelli F. Association between inflammatory bowel disease and vitamin D deficiency: a systematic review and meta-analysis. *Inflamm Bowel Dis* 2015;**21**:2708–17.
88. Torki M, Gholamrezaei A, Mirbagher L, Danesh M, Kheiri S, Emami MH. Vitamin D deficiency associated with disease activity in patients with inflammatory bowel diseases. *Dig Dis Sci* 2015;**60**:3085–91.
89. Sadeghian M, Saneei P, Siassi F, Esmaillzadeh A. Vitamin D status in relation to Crohn's disease: meta-analysis of observational studies. *Nutrition* 2016;**32**:505–14.
90. Ulitsky A, Ananthakrishnan AN, Naik A, *et al.* Vitamin D deficiency in patients with inflammatory bowel disease: association with disease activity and quality of life. *JPEN J Parenter Enteral Nutr* 2011;**35**:308–16.
91. 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**:182–8.
92. Hassan V, Hassan S, Seyed-Javad P, *et al.* Association between serum 25[OH]vitamin D concentrations and Inflammatory Bowel Diseases [IBDs] activity. *Med J Malaysia* 2013;**68**:34–8.
93. Raftery T, Merrick M, Healy M, *et al.* Vitamin D status is associated with intestinal inflammation as measured by fecal calprotectin in Crohn's disease in clinical remission. *Dig Dis Sci* 2015;**60**:2427–35.
94. 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**:e407–13.
95. Ham M, Longhi MS, Lahiff C, Cheifetz A, Robson S, Moss AC. Vitamin D levels in adults with Crohn's disease are responsive to disease activity and treatment. *Inflamm Bowel Dis* 2014;**20**:856–60.
96. Hlavaty T, Krajcovicova A, Koller T, *et al.* Higher vitamin D serum concentration increases health related quality of life in patients with inflammatory bowel diseases. *World J Gastroenterol* 2014;**20**:15787–96.
97. Dolatshahi S, Pishgar E, Jamali R. Does serum 25 hydroxy vitamin D level predict disease activity in ulcerative colitis patients? *Acta Clin Belg* 2016;**71**:46–50.
98. Gubatan J, Mitsuhashi S, Zenlea T, Rosenberg L, Robson S, Moss AC. Low serum vitamin D during remission increases risk of clinical relapse in patients with ulcerative colitis. *Clin Gastroenterol Hepatol* 2017;**15**:240–6.e1.
99. Ananthakrishnan AN, Cagan A, Gainer VS, *et al.* Higher plasma vitamin D is associated with reduced risk of Clostridium difficile infection in patients with inflammatory bowel diseases. *Aliment Pharmacol Ther* 2014;**39**:1136–42.
100. Winter RW, Collins E, Cao B, Carrellas M, Crowell AM, Korzenik JR. Higher 25-hydroxyvitamin D levels are associated with greater odds of remission with anti-tumour necrosis factor-α medications among patients with inflammatory bowel diseases. *Aliment Pharmacol Ther* 2017;**45**:653–9.
101. Zator ZA, Cantu SM, Konijeti GG, *et al.* Pretreatment 25-hydroxyvitamin D levels and durability of anti-tumor necrosis factor-α therapy in inflammatory bowel diseases. *JPEN J Parenter Enteral Nutr* 2014;**38**:385–91.
102. Cantorna MT, Munsick C, Bemiss C, Mahon BD. 1,25-Dihydroxycholecalciferol prevents and ameliorates symptoms of experimental murine inflammatory bowel disease. *J Nutr* 2000;**130**:2648–52.
103. Daniel C, Radeke HH, Sartory NA, *et al.* The new low calcemic vitamin D analog 22-ene-25-oxa-vitamin D prominently ameliorates T helper cell type 1-mediated colitis in mice. *J Pharmacol Exp Ther* 2006;**319**:622–31.
104. Garg M, Rosella O, Lubel JS, Gibson PR. Association of circulating vitamin D concentrations with intestinal but not systemic inflammation in inflammatory bowel disease. *Inflamm Bowel Dis* 2013;**19**:2634–43.
105. Jin D, Wu S, Zhang YG, *et al.* Lack of vitamin D receptor causes dysbiosis and changes the functions of the murine intestinal microbiome. *Clin Ther* 2015;**37**:996–1009.e7.
106. Ryz NR, Lochner A, Bhullar K, *et al.* Dietary vitamin D3 deficiency alters intestinal mucosal defense and increases susceptibility to Citrobacter rodentium-induced colitis. *Am J Physiol Gastrointest Liver Physiol* 2015;**309**:G730–42.
107. Olsen KS, Aksnes L, Frøyland L, Lund E, Rylander C. Vitamin D status and PUFA ratios in a national representative cross-section of healthy, middle-aged Norwegian women—the Norwegian Women and Cancer Post-Genome Cohort. *Scand J Public Health* 2014;**42**:814–20.
108. Pappa HM, Mitchell PD, Jiang H, *et al.* Treatment of vitamin D insufficiency in children and adolescents with inflammatory bowel disease: a randomized clinical trial comparing three regimens. *J Clin Endocrinol Metab* 2012;**97**:2134–42.
109. Narula N, Cooray M, Anglin R, Muqtadir Z, Narula A, Marshall JK. Impact of high-dose vitamin D3 supplementation in patients with Crohn's disease in remission: a pilot randomized double-blind controlled study. *Dig Dis Sci* 2017;**62**:448–55.
110. 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* 2017, Jun 15. doi: 10.1016/j.clnu.2017.06.011. [Epub ahead of print.]
111. Binkley N, Dawson-Hughes B, Durazo-Arvizu R, *et al.* Vitamin D measurement standardization: the way out of the chaos. *J Steroid Biochem Mol Biol* 2017;**173**:117–21.
112. O'Sullivan M. Is vitamin D supplementation a viable treatment for Crohn's disease? *Expert Rev Gastroenterol Hepatol* 2016;**10**:1–4.