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Review Article

Vitamin D and Inflammatory Bowel Diseases

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Abstract and Introduction

Abstract

Background Vitamin D is traditionally associated with bone metabolism. The immunological effects of vitamin D have increasingly come into focus.

Aim To review the evidence supporting a role of vitamin D in inflammatory bowel diseases.

Methods A comprehensive search was performed on PubMed using the terms 'crohn's disease' 'ulcerative colitis' and 'vitamin D'.

Results Vitamin D deficiency is common in patients with inflammatory bowel diseases (IBD) (16–95%) including those with recently diagnosed disease. Evidence supports immunological role of vitamin D in IBD. In animal models, deficiency of vitamin D increases susceptibility to dextran sodium sulphate colitis, while 1,25(OH) $_2$D $_3$ ameliorates such colitis. One prospective cohort study found low predicted vitamin D levels to be associated with an increased risk of Crohn's disease (CD). Limited data also suggest an association between low vitamin D levels and increased disease activity, particularly in CD. In a large cohort, vitamin D deficiency (<20 ng/mL) was associated with increased risk of surgery (OR 1.8, 95% CI 1.2–2.5) in CD and hospitalisations in both CD (OR 2.1, 95% CI 1.6–2.7) and UC (OR 2.3, 95% CI 1.7–3.1). A single randomised controlled trial demonstrated that vitamin D supplementation may be associated with reduced frequency of relapses in patients with CD compared with placebo (13% vs. 29%, P = 0.06).

Conclusions There is growing epidemiological evidence to suggest a role for vitamin D deficiency in the development of IBD and also its influence on disease severity. The possible therapeutic role of vitamin D in patients with IBD merits continued investigation.

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) constitute chronic idiopathic inflammatory bowel diseases (IBD). The key underlying pathogenic mechanisms for both diseases is a dysregulated host immune response to commensal intestinal flora in genetically susceptible individuals. [1,2] Known genetic variants incompletely explain the variance in disease incidence, suggesting a strong role for environmental factors, supported by epidemiological evidence. [3,4]

Vitamin D has long been recognised as a major regulator of calcium and phosphorus metabolism and key in maintaining bone health. [5–7] However, several recent studies have yielded new insights into the role of vitamin D in various other physiological processes. In particular, vitamin D appears to play important roles in immune regulation, particularly involving the innate immune system, cardiovascular and renal physiology, and development of cancer. [6] Importantly, an increasing body of literature supports an important role of vitamin D in the pathogenesis as well as potential therapy of IBD. [8–13] The current review examines the evidence linking vitamin D to IBD, both through its effect on bone health and association with pathogenesis and natural history of these diseases.

Methods

A comprehensive literature search on Pubmed was conducted using the following search terms: 'Crohn's disease' 'ulcerative colitis' and 'vitamin D' to identify relevant English language articles published between 1966 and 2013. In addition, bibliographies of the retrieved articles were searched to identify additional relevant articles.

Results

Vitamin D Synthesis

The main source of vitamin D is endogenous production in the skin where ultraviolet B energy in the sunlight converts 7-dehydrocholestrol to cholecalciferol (vitamin D3) (Figure 1). [5,14] Dietary contribution to vitamin D status includes foods such as egg yolk, beef liver, cod liver oil, fatty fish, fortified milk and milk products. [5] Vitamin D from the endogenous production on exposure to sunlight as well as that absorbed from diet is metabolised within the liver to 25-hydroxyvitamin D (25(OH)D) by the enzyme vitamin D 25-hydroxylase. 25(OH)D is the major circulating form of vitamin D and is also used to determine the status of vitamin D in clinical practice. 25(OH)D is biologically inactive and is activated within the proximal tubules of nephrons in the kidneys by the enzyme 25-hydroxyvitamin D-1alpha-hydroxylase (also known as CYP27B1) to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). The renal synthesis of the active biological product of vitamin D ($1,25(OH)_2D$) is regulated by various factors including serum calcium and phosphorus levels, parathormone and fibroblast growth factor 23. [15]

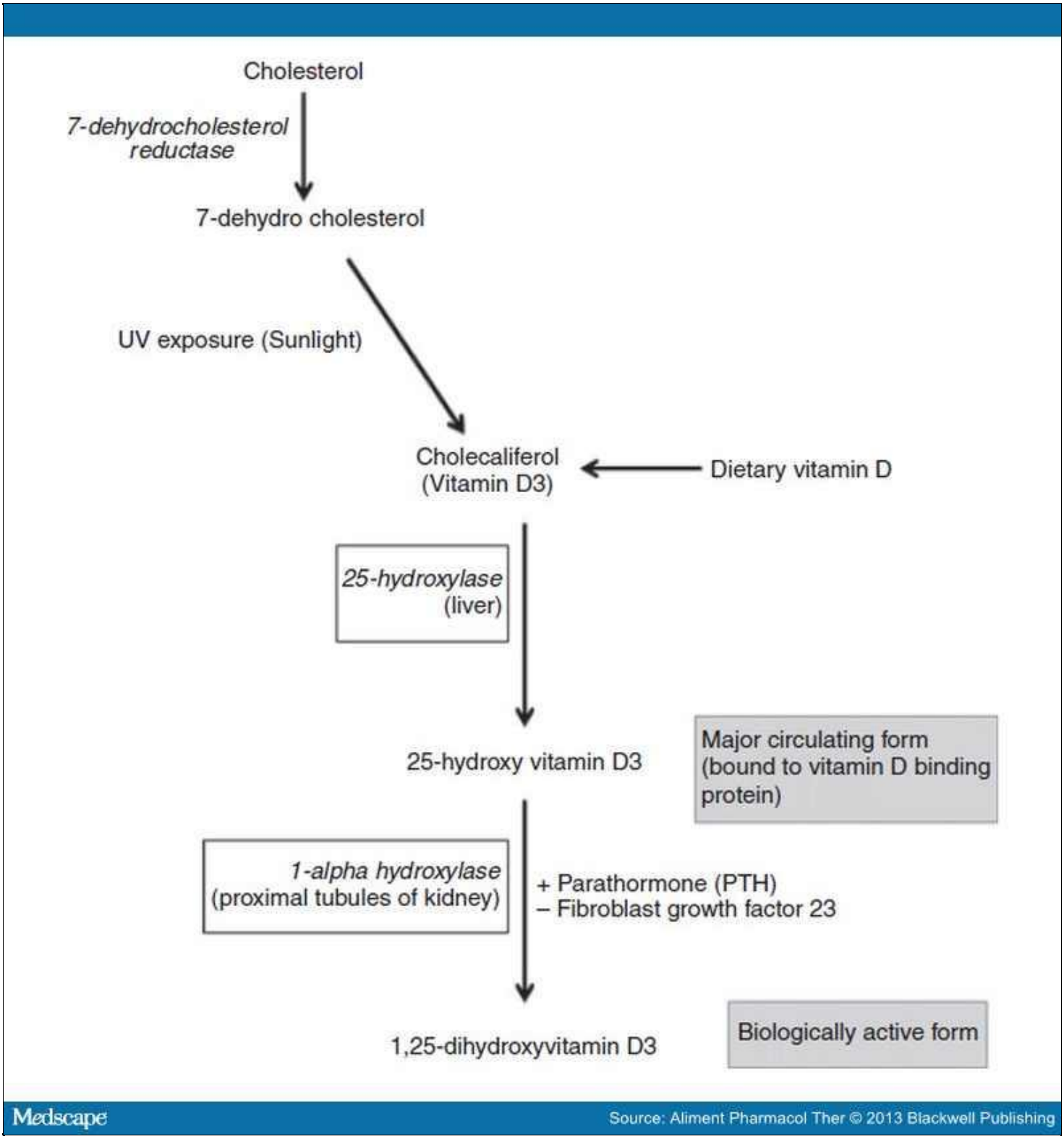

Figure 1.

Metabolism of vitamin D.

Prevalence of Vitamin D Deficiency in IBD

While it is relatively easy to ascertain macronutrient deficiency clinically, micronutrient deficiency may not always be clinically evident and usually requires laboratory testing. The best measure of an individual's vitamin D status is serum 25(OH)D. [5,7,16] Serum 25(OH)D levels of less than 20 ng/mL (50 nmol/L) indicate vitamin D deficiency. Serum 25(OH)D levels between 21 and

29 ng/mL (52.5 and 72.5 nmol/L) represent vitamin D insufficiency, while levels between 30 and 100 ng/mL (75 and 250 nmol/L) represent normal values. [5,7,16] Several studies have reported a high prevalence of vitamin D deficiency in patients with IBD, although it has not been universally established that this rate is higher than in other chronic illnesses, inflammatory diseases, or even health individuals in that region (). Levin *et al.* reported vitamin D deficiency in 19% and insufficiency in 38% of children with IBD in a cohort predominantly consisting of patients with CD. [17] In contrast, Alkhouri *et al.* reported that the prevalence of vitamin D deficiency in children with IBD (62%) was lower than the rate in their controls (75%). [18] In a large, retrospective study of adult patients with IBD from Wisconsin (101 UC, 403 CD), nearly 50% of the patients had vitamin D deficiency and about 11% of patients had severe vitamin D deficiency, [19] a frequency estimate that is consistent with other published IBD cohorts. [13] While most studies have examined prevalence in patients with well established IBD, deficiency of vitamin D does not appear to be consequent to long-standing disease alone. In a cohort of newly diagnosed IBD patients from Manitoba providence in Canada, only 22% were found to have sufficient levels of vitamin D. [20]

Table 1. Prevalence of vitamin D deficiency in unselected cohorts of patients with inflammatory bowel diseases

Author	Year	Cohort size	Vitamin D status
Driscoll [84]	1982	82 CD	65% of patients had low serum 25(OH)D 25% had levels below 10 ng/mL
Jahnsen [44]	2002	60 CD 60 UC	27% of CD patients had 25(OH)D levels <30 nmol/L 15% of UC patients had 25(OH)D levels <30 nmol/L
Lamb [85]	2002	23 UC 11 CD 18 IBS controls	Mean 25(OH)D was lower in IBD patients (18.7 mcg/L) compared with controls (28.5 mcg/L) (*P* < 0.05)
Sentongo [27]	2002	112 CD*	16% of CD patients had vitamin D < 38 nmol/L
Siffledeen [86]	2003	242 CD	22% had 25(OH)D levels <40 nmol/L 8% had 25(OH)D levels <25 nmol/L
Tajika [25]	2004	33 CD 15 controls	27% of CD patients were deficient (25(OH)D < 10 ng/mL) compared to 7% of controls
McCarthy [22]	2005	44 CD	During late-summer, 5% of controls and 18% of CD patients were deficient (<50 nmol/L) During late-winter, 25% of controls and 50% of CD patients were deficient
Gilman [21]	2006	58 CD	50% were vitamin D deficient during winter (<50 nmol/L) and 19% were deficient during summer
Pappa [87]	2006	94 CD* 36 UC*	Prevalence of vitamin D deficiency (25(OH)D < 15 ng/mL) was 35%
Leslie [20]	2008	56 CD 45 UC	88% had serum 25(OH)D levels below 75 nmol/L
Kuwabara [88]	2009	29 CD 41 UC	Mean 25(OH) levels were lower in CD patients (11 ng/mL) compared with those with UC (20 ng/mL) (*P* < 0.001)
Joseph [89]	2009	34 CD 34 controls	25(OH)D levels were lower in CD patients (16 ng/mL) compared with controls (23 ng/mL)
Ulitsky [19]	2011	403 CD101 UC	50% of patients had 25(OH)D < 30 ng/dL, 11% had levels below 10 ng/dL
Pappa [90]	2011	288 CD* 143 UC* 17 IC*	Vitamin D insufficiency (<20 ng/mL) was seen in 31% of patients with CD and 28% of UC patients
Levin [17]	2011	70 CD 5 UC 3 IBDU	19% of patients were deficient in vitamin D (<51 nmol/L)
Atia [91]	2011	125 IBD	37% had vitamin D deficiency
Suibhne [92]	2012	81 CD	63% of patients with CD were deficient (<50 nmol/L)
Fu [93]	2012	60 UC 40 CD	39% of the entire cohort had low vitamin D (<50 nmol/L); this was more frequent in 43% of CD and 37% of UC patients

Laakso [94]	2012	49 UC 28 CD	30% of patients with CD had levels below 37.5 nmol/L compared to 37% of controls
Hassan [95]	2013	60 IBD	95% of patients had deficient vitamin D levels (25(OH)D < 30 ng/mL)
Ananthakrishnan [13]	2013	1763 CD 1454 UC	28% had insufficient (20–30 ng/mL) and 32% had deficient (<20 ng/mL) levels
Alkhouri [18]	2013	61 IBD*	62% of patients had low vitamin D levels compared to 75% of controls

IBD, inflammatory bowel diseases; CD, Crohn's disease; UC, ulcerative colitis, IC, indeterminate colitis.
*Paediatric cohorts.

Causes of Vitamin D Deficiency in Patients With IBD

There are several factors contributing to vitamin D deficiency in patients with IBD, some causes specifically related to the underlying bowel disease, while others are in common with the non-IBD population. These include inadequate exposure to sunlight either related to lifestyle or persistent symptoms of active disease restricting physical activity, inadequate dietary intake due to symptoms of bowel disease, impaired absorption, impaired conversion of vitamin D to its active products, increased catabolism and increased excretion. [5,7] That inadequate exposure to sunlight is an important cause of vitamin D deficiency in patients with IBD is supported by evidence. Several studies, particularly from northern climates, have consistently demonstrated an association between vitamin D deficiency and winter season, a period of likely low sunlight and UVB exposure. [13,21,22] Insufficient dietary consumption also contributes to low vitamin D in some patients with IBD. In a detailed nutritional survey of 126 IBD patients, inadequate vitamin D consumption was found in 36% of patients and suboptimal serum vitamin D levels were found in 18% of patients. [23] Oral intake correlated significantly with serum levels in CD and with all IBD in remission. [23] While other small studies suggested no correlation between dietary vitamin D intake and serum 25(OH)D in CD patients, they may have been limited by lack of statistical power. [24]

Fats and fat-soluble vitamins are absorbed after emulsification by bile acids. The bile acid pool is maintained by an enterohepatic circulation occurring from the terminal ileum. Interruption of the enterohepatic circulation (e.g., by terminal ileal resection) could theoretically contribute to vitamin D deficiency. However, clinical data in support of this are conflicting. Terminal ileal resection was associated with vitamin D deficiency in some studies. [25,26] In a study of 12 CD patients who underwent terminal ileal resection, absorption of vitamin D was reduced with the decline in absorption correlating with the length of the resected segment. However, other studies failed to identify an effect of ileal resection or active disease. [19] Malabsorption may theoretically contribute to low vitamin D in CD patients as vitamin D is absorbed in the proximal part of small intestine. The prevalence of vitamin D deficiency is higher in CD patients with upper gastrointestinal tract involvement. [27] However, when absorption of vitamin D was specifically tested, only 10% of patients with CD had decreased absorption of vitamin D compared to 50% of patients with pancreatic insufficiency. [28] There also appears to be a wide variation in absorption of vitamin D in patients with CD even in those with quiescent disease. [29] Protein-losing enteropathy occurs in some patients with IBD. As vitamin D and its metabolites circulate predominantly as bound forms to plasma vitamin D binding protein (DBP), the loss of DBP along with the bound vitamin D could be an additional plausible mechanism of vitamin D deficiency, particularly in those with severe disease. Finally, recent studies have suggested that genetic variants contribute both to development of vitamin D insufficiency and response to supplementation. In a genome-wide association study of nearly 30 000 individuals of European descent, variants at three loci near the genes involved in cholesterol synthesis, vitamin D hydroxylation and vitamin D transport were associated with vitamin D insufficiency. [30] The contribution of such genetic variants to vitamin D status in patients with IBD has not yet been studied.

Role of Vitamin D in Bone Turnover and Mineral Metabolism

Vitamin D helps to maintain calcium homoeostasis by acting on the small intestine epithelium and osteoblasts. 1,25(OH) $_2$D acts mainly through the nuclear vitamin D receptor (VDR), which forms a heterodimer with a retinoid X receptor, binds to the vitamin D response element and recruits co-activators and enzymes with histone acetylation activity, thereby regulating gene expression. [10,31–33] 25(OH)D interacts with the VDR in the small intestinal epithelium and augments the absorption of calcium and phosphorus from the small intestine. [34] 1,25(OH) $_2$D also interacts with the VDR on osteoblasts and increases the surface expression of Receptor Activator for Nuclear Factor κB ligand (RANKL), which, after binding with RANK on pre-osteoclasts, converts them into osteoclasts. [35,36] Osteoclasts function in dissolution of bone matrix and mobilise calcium stores into circulation, thus helping in the maintenance of calcium homoeostasis. Dissolution of bone matrix by osteoclasts is an essential part of bone remodelling.

Vitamin D deficiency leads to reduction in serum levels of ionised calcium leading to secondary hyperparathyroidism, resulting in osteoclastogenesis, a disproportionate increase in bone resorption, osteopenia and osteoporosis. [37] In children, vitamin D deficiency results in poor mineralisation of the epiphyseal growth plates leading to bone deformities and stunted longitudinal growth, which are the typical features of rickets. In adults with vitamin D deficiency, there is defective mineralisation of the newly formed bone collagen matrix resulting in osteomalacia which manifests as bone pain, fractures and proximal muscle weakness. [5,7,16]

There is a high prevalence of metabolic bone disease in patients with IBD. The prevalence of osteopenia ranges from 23% to 67% and osteoporosis from 7% to 35% among patients with CD or UC. [38–40] Active inflammatory disease is a strong risk factor for low bone mineral density (BMD) in patients with IBD, with BMD improving with increasing duration of remission. [41] This is supported by the known effect of TNF-α and other pro-inflammatory cytokines like IL-1, IL-6, IL-17 in activating osteoclasts. [42,43] In addition, glucocorticoids use is an important risk factor for bone loss in patients with IBD. [39] However, the data linking vitamin D deficiency and impaired BMD in patients with IBD have been conflicting, with some studies supporting such an association and others finding no effect. [20,39,44]

Vitamin D and Innate Immunity

Vitamin D receptor is ubiquitously expressed in several human tissues including immune cells, keratinocytes, pancreatic beta-cells, cardiac myocytes, central nervous system, renal tubules and the intestine. Many of these tissues also contain the enzymes for conversion of vitamin D to its active metabolites, supporting a widespread extraskeletal role of vitamin D. [45] Vitamin D appears to have an important role in innate immunity as well as adaptive immunity. [10,33] It acts as a key link between toll-like receptor (TLR) activation and antibacterial responses in innate immunity. Activation of TLRs on macrophages by a *Mycobacterium tuberculosis* derived lipopeptide leads to upregulation of conversion of 25(OH)D to the active 1,25(OH) $_2$D, upregulation of VDR expression and induction of downstream targets of VDR including cathelicidin, an antimicrobial peptide. [46] 1,25(OH) $_2$D also acts synergistically with activated NF- κB to induce expression of β-defensin 4 gene. [47]

Supplementation with vitamin D in individuals with insufficient serum levels of 25(OH)D leads to induction of cathelicidin, thus enhancing the innate immune defences against microbial agents. [48]

Autophagy plays an important role in the pathogenesis of CD, and several lines of evidence support the hypothesis that the effect of vitamin D on IBD pathogenesis may be through this pathway. 1,25 (OH) $_2$D helps in autophagy in macrophages by enhancing the co-localisation of pathogen harbouring phagosomes with autophagosomes in a cathelicidin-dependent manner. [49] Similar induction of autophagy by vitamin D has also been demonstrated in several models of cancer cell lines. Vitamin D3 has been hypothesised to regulate autophagy at several steps. [50] Increased calcium absorption mediated by the effect of vitamin D3 on the VDR can activate autophagy through various calcium-dependent kinases and phosphates, while vitamin D3 can itself downregulate the expression of mTOR, a negative regulator of autophagy. [50,51] Vitamin D3 can also induce autophagy through increasing beclin-1 expression, a regulatory of autophagy, and activating the PI $_3$K signalling pathway. [50–52] Vitamin D has been long used to treat mycobacterial infections [46,53,54] and vitamin D supplementation may reduce likelihood of tuberculin conversion. [55,56] In a randomised controlled trial, vitamin D supplementation was associated with a reduced rate of development of a positive tuberculin reaction, suggesting a protective effect against tuberculosis infection in an endemic population. [56] Low serum vitamin D is also associated with reduced immunoreactivity to an anergy panel, and supplementation with vitamin D in anergic individuals with deficient levels restored delayed hypersensitivity response. [57]

Vitamin D also plays a role in preventing over-activation of pro-inflammatory responses. 1,25(OH) $_2$D within the monocytes dose-dependently inhibits lipopolysaccharide (LPS)-induced p38 phosphorylation and production of IL-6 and TNF-α in LPS-stimulated monocytes. [58] Antigen-presenting cells, including dendritic cells, express VDR. [59] The action of 1,25(OH) $_2$D on dendritic cells leads to a tolerogenic phenotype, thus protecting against autoimmune type 1 diabetes in adult non-obese diabetic mice. [60] Maturation of dendritic cells is prevented by the interaction of 1,25(OH) $_2$D with VDR on the dendritic cells. [61]

Vitamin D and Adaptive Immunity

Vitamin D receptor is expressed in mitotically active T and B lymphocytes. [62] 1,25(OH) $_2$D acts on helper T cells (T_H cells), inhibits production of IL-2 and immunoglobulin synthesis by T_H cell regulated B lymphocytes. [63] Regulatory T cells (T_{reg}), which are responsible for maintenance of tolerance to self-antigens, are also modulated by 1,25(OH) $_2$D. [10,33] Although the

effect of vitamin D on B cells is predominantly through modulation of T-cell function, recent evidence suggests that 1,25(OH) $_2$D may also act directly on the B cells, affecting the proliferation of activated B cells and inhibiting the generation of plasma cells and post-switch memory B cells. [64]

Role of Vitamin D in the Immunopathogenesis of IBD

Several lines of epidemiological and laboratory evidence support a role for vitamin D in the pathogenesis of IBD. First, there is a north–south gradient in IBD incidence, a gradient that parallels UV exposure and consequently vitamin D levels. In a study by Khalili *et al.*, residence in Southern latitudes of the United States, particularly at age 30 was associated with a significantly lower risk of CD [Hazard ratio (HR) 0.48, 95% CI 0.30–0.77] and UC (HR 0.62, 95% CI 0.42–0.90). [65] This has been supported by other studies that have modelled residential UV exposure and shown an inverse correlation between UV exposure and IBD incidence. [66] Mice lacking VDR are more susceptible to dextran sodium sulphate (DSS)-induced mucosal injury compared with the wild type mice. [67] The disruption in the epithelial junctions was severe in mice lacking VDR and 1,25(OH) $_2$D preserved the integrity of the tight junctions in Caco-2 cells monolayers. [67] Genetic epidemiological studies have suggested a link between polymorphisms in the VDR gene region on chromosome 12 to development of IBD, [10,68–70] although not all cohorts have yielded positive results. Variations in the DBP were also found to be associated with IBD. [71]

Few studies have been able to examine the association between vitamin D status and incident IBD directly. One such study was using the Nurses' Health Study, a cohort of female registered nurses in the United States, followed prospectively using biennial questionnaires, and comprehensive assessment of diet and supplement intake and physical activity during the cohort follow-up timeline. [8] The vitamin D status of the participants was defined using a validated regression model incorporating race, diet, physical activity and region of residence. Over a 22-year follow-up, higher predicted plasma 25(OH)D leves was associated with a significant reduction in the risk of incident CD, but not UC. [8] Compared to women with the lowest quartile of plasma vitamin D, those in highest quartile had a reduced risk of CD (HR 0.54, 95% CI 0.30–0.99). [8] For each 1 ng/mL increase in the plasma level of 25(OH)D, there was a 6% relative risk reduction for CD. There was also an inverse association between vitamin D intake from dietary sources and supplement and the risk for incident UC; each 100 IU/day increase in total vitamin D intake was associated with a 10% relative reduction in the risk of UC. [8]

Relationship of Vitamin D Levels and IBD Disease Severity

In tune with its immune-modulating effects, vitamin D may also influence severity of inflammation in IBD. Vitamin D deficiency causes more severe growth retardation and weight loss and also led to higher mortality in IL-10 KO mice colitis. [72] Disease severity correlated with vitamin D status in mice with DSS-induced colitis; both local as well as endocrine effects of 1,25 (OH) $_2$D affect the disease severity. [73] TNF-α plays a central role in inflammation. 1,25(OH) $_2$D reduces the severity of colitis in IL-10 KO mice by downregulating several genes associated with TNF-α. [74] When mice with tri-nitro-benzene sulphonic (TNBS) acid-induced colitis were treated with a combination of corticosteroids and 1,25 (OH) $_2$D, the improvement in disease activity paralleled downregulation of T $_{H1}$ inflammatory cytokines profile as well as T $_{H17}$ effector functions along with the promotion of T $_{H2}$ and regulatory T-cell profiles. [75]

Data supporting a clinical association between vitamin D deficiency and disease activity in IBD are conflicting (). Neither El-Matary *et al.* nor Levin *et al.* found a correlation between vitamin D levels and disease activity in cross-sectional studies of IBD cohorts. [17,76] In contrast, a retrospective study by Ulitsky *et al.* concluded that vitamin D deficiency was associated with lower health-related quality of life and increased disease activity in patients with CD, but not with UC. [19] Overcoming some of the limitations engendered by cross-sectional assessment of vitamin D and disease severity, we examined prospectively the association between vitamin D deficiency and need for IBD-related surgery or hospitalisations in a large cohort of 3217 patients with at least one measurement of plasma 25(OH)D. [13] We found that plasma 25(OH)D < 20 ng/mL was associated with an increased risk of surgery [Odds ratio (OR) 1.76; 95% CI 1.24–2.51] and hospitalisation (OR 2.07; 95% CI 1.59–2.68) compared with those with sufficient levels. [13] Furthermore, CD patients who normalised their plasma 25(OH)D had a reduced likelihood of IBD-related surgery (OR 0.56; 95% CI 0.32–0.98) compared with those who remained deficient. [13]

Table 2. Observational studies of the association between vitamin D levels and outcomes in Crohn's disease and ulcerative colitis

Author	Year	Study design	Number of patients	Predictor variable	Outcome	Result
						Serum 25(OH)D negatively correlated

Joseph [89]	2009	Cross-sectional	34 CD	Serum 25(OH)D	HBI	with disease activity (correlation co-efficient −0.484)
El-Matary [76]	2011	Cross-sectional	60 IBD (39 CD, 21 UC)	Serum 25(OH)D	PCDAI or PUCAI	Vitamin D levels were not associated with disease activity
Ulitsky [19]	2011	Retrospective	504 IBD (403 CD, 101 UC)	Serum 25(OH)D	HBI or SCCAI Health-related quality of life	Vitamin D deficiency was associated with lower HRQoL (−2.2, 95% CI −4.1 to −0.3) and increased disease activity (1.1, 95% CI 0.4–1.7) in CD, but not in UC
Ananthakrishnan [13]	2013	Prospective	3217 IBD (1763 CD, 1454 UC)	Serum 25(OH)D	IBD-related surgery IBD-related hospitalisations	Vitamin D deficiency (<20 ng/mL) was associated with increased risk of surgery (OR 1.8, 95% CI 1.2–2.5) in CD and hospitalisations in both CD (OR 2.1, 95% CI 1.6–2.7) and UC (OR 2.3, 95% CI 1.7–3.1)
Zator [79]	2013	Retrospective	101 IBD (74 CD, 27 UC) patients initiating anti-TNF therapy	Serum 25(OH)D within 3 months of anti-TNF initiation	Cessation of anti-TNF therapy	Patients with low vitamin D had an increased risk of early cessation of anti-TNF therapy (HR 2.1, 95% CI 1.0–4.4)

CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; HBI, Harvey Bradshaw index; PCDAI, Paediatric Crohn's disease activity index; PUCAI, paediatric ulcerative colitis activity index; SCCAI, simple clinical colitis activity index.

Does Vitamin D Have a Role in the Treatment of IBD

There have been several studies examining the role of vitamin D as a therapeutic agent for IBD in animal models. [77] Vitamin D-deficient IL-10 KO mice spontaneously develop an accelerated and severe form of IBD. However, when such mice were fed high-calcium diet and 1,25(OH) $_2$D, they developed only mild disease. [72] Both in TNBS- and DSS-induced colitis models, administration of 1,25(OH) $_2$D led to an improvement in disease activity and addition of 1,25(OH) $_2$D to a steroid regimen had a synergistic effect and this combination most effectively reduced the disease severity. [78] A novel vitamin D analogue with anti-proliferative effects and limited calcemic activity was also found to alleviate disease activity in mice with DSS-induced colitis. [78]

There have been few human studies (). Jorgensen *et al*. conducted a multicentre, randomised, double-blind, placebo-controlled trial in Denmark evaluating the efficacy of 1,25(OH) $_2$D as a maintenance therapy in CD patients in remission. [12] One hundred and eight patients were randomised to receive either 1200 IU of 1,25(OH) $_2$D with 1200 mg of calcium or 1200 mg of calcium alone daily over 1 year. Nearly one-third of the study population had vitamin D deficiency defined as serum 25(OH)D levels <50 nmol/L. Only 13% of patients in the vitamin D group relapsed during the 1-year study period compared to 29% in the placebo group (P = 0.06). [12] A second study by Zator *et al*. examined the influence of vitamin D status on response to anti-TNF therapy. In a single centre cohort of patients with CD and UC, plasma 25(OH)D levels measured within 3 months of initiation of anti-TNF therapy demonstrated a significant inverse association with durability of anti-TNF treatment, with a more pronounced effect on patients with CD. [79] Miheller *et al*. compared the therapeutic effects of 1,25(OH) $_2$D and 25(OH) D in patients with CD with respect to disease activity and bone health. [80] There was a significant improvement in disease activity as well as bone metabolism in the short-term at 6 weeks with 1,25(OH) $_2$D but not 25(OH)D. [80]

Table 3. Interventional studies examining the effect of vitamin D supplementation on disease activity in Crohn's disease and ulcerative colitis

Author	Year	Study design	Number of patients	Intervention	Outcome	Result

Miheller [80]	2009	Open label	37 patients with inactive CD	Daily 0.5 mcg of alfacalcidiol or 1000 IU of cholecalciferol	CDAI	Mean CDAI decreased from 69 to 57 in patients treated with alfacalcidiol
Jorgensen [12]	2010	Randomised placebo-controlled trial	104 CD patients in clinical remission	Oral vitamin D3 1200 IU daily or placebo	Relapse	Relapse rate was lower in patients treated with vitamin D3 (13%) compared to placebo (29%) (*P* = 0.06)
Yang [81]	2013	Open label	18 patients with mild-to-moderate CD	Vitamin D3 at 1000 IU daily; dose increase after 2 weeks to achieved serum 25(OH)D of 40 ng/mL	CDAI Quality of life	Vitamin D supplementation reduced CDAI scores from 230 to 118 (*P* < 0.0001), and improved health-related quality of life

CD, Crohn's disease; CDAI, Crohn's disease activity index.

Discussion

Limitations

Despite emerging promising data, there exist several limitations in the literature regarding the role of vitamin D in IBD pathogenesis. First, while consistently supported by experimental animal models, the association between low pre-diagnosis vitamin D and increased risk of CD has been examined in a single prospective cohort study that used a regression model to predict an individual's vitamin D status. Ongoing analysis of pre-diagnosis banked specimens from ongoing prospective cohorts as well as additional high-risk IBD cohorts will provide a more definitive answer to this hypothesis as randomised controlled trials of vitamin D in prevention of IBD are unlikely to be feasible, given relatively low incidence of disease in the general population, and need for large numbers of participants and long follow-up. The association between low vitamin D and increased disease activity, particularly in CD, is also supported primarily by observational data. While initial studies were cross-sectional and unable to differentiate effect of vitamin D on disease activity from that of disease course on vitamin D levels, more recent analyses of large cohorts have been able to prospectively demonstrate an association between low vitamin D levels and increased risk for surgery and hospitalisations, particularly in CD. [13] However, only one randomised controlled trial has examined the role of vitamin D in preventing relapse, but was also limited by small numbers. [12] Effect of vitamin D supplementation in ameliorating disease activity in CD has been examined only in two open-label pilot studies, and no studies have evaluated this in UC. Consequently, there is an urgent need for high-quality randomised intervention trials of vitamin D supplementation in both CD and UC with disease activity as a treatment end point. [80,81]

Clinical Practice

Patients with IBD are at risk of developing vitamin D deficiency. The Endocrine Clinical Practice Guidelines Committee recommends screening of patients with IBD as well as patients who are on corticosteroids for vitamin D status. [16] While there is lack of professional guidelines regarding subsequent assessments of vitamin D status, we adopt the following in our practice. If the baseline vitamin D status is normal, it may be logical to consider rechecking the status annually or biennially if there is active disease, if there is documented metabolic bone disease or if there is continued use of systemic corticosteroids. The Institute of Medicine and the Endocrine Practice Guidelines Committee recommend a dietary intake of 400 IU of vitamin D per day for infants, 600 IU of vitamin D per day for children beyond 1 year of age and adults and 800 IU of vitamin D per day for the elderly aged above 70 years. [82] However, to consistently raise the level of 25(OH)D to more than 30 ng/mL, especially in patients who are at risk for vitamin D deficiency, the Endocrine Practice Guidelines Committee recommended that a maintenance dose of at least 1000 IU per day would be required. [16] To treat documented vitamin D deficiency, it is recommended to use either vitamin D2 or vitamin D3 in a dosage of 2000 IU per day for 6 weeks, or 50 000 IU once a week for 6 weeks in case of children and vitamin D2 or vitamin D3 6000 IU per day for 8 weeks, or 50 000 IU once a week for 8 weeks for adults to achieve serum 25(OH)D levels of more than 30 ng/mL. The optimal therapeutic regimen in IBD patients was examined in a single clinical trial by Pappa *et al*. in which 71 patients with IBD aged 5–21 years with vitamin D deficiency were randomised to one of the following three regimens for 6 weeks: 2000 IU daily of vitamin D2; 2000 IU daily of vitamin D3; or 50 000 IU weekly of vitamin D2. [83] It was found that the 6-week regimens of 50 000 IU of vitamin D2 per week and 2000 IU of vitamin D3 daily were superior to vitamin D2 2000 IU daily. Whereas the regimen of 50 000 IU per week of vitamin D2 improved the serum 25(OH)D levels to more than 32 ng/mL in 75% of patients, only 38% of patients who received 2000 IU of vitamin D3

daily and 25% of patients who received 2000 IU of vitamin D2 daily achieved serum 25(OH)D levels of more 32 ng/mL after 6 weeks of therapy. All the three regimens were found to be safe and well tolerated.

Future Directions

Several unanswered question remain regarding the role of vitamin D in IBD (). Further investigation is needed to understand the effects of dietary intake of vitamin D and vitamin D supplementation in relation to polymorphisms of DBP or VDR to identify if there are subgroups who may derive greater benefit from prophylaxis or who would require greater doses for treatment. With recent evidence pointing towards vitamin D deficiency as associated with IBD risk, confirmation of such findings in other cohorts would establish the vitamin D as one of the links in the gene-environment-gut microbiome-immune system interactions necessary for the development of IBD. It also merits investigation whether vitamin D deficiency leads causally to increased disease severity or is merely a consequence of severe disease. Furthermore, it needs to be identified if there are high-risk groups of patients who may need to be screened for vitamin D deficiency and preemptively treated to prevent the onset of IBD. Further high-quality studies are needed to evaluate if correction of vitamin D deficiency or if vitamin D supplementation can prevent disease relapses, whether it can be used to induce remission in active disease, and whether it has a role in prevention of long-term disease-related complications like colorectal cancer as has been identified in non-IBD patients. Continued and fertile interactions between biochemists, nutritional epidemiologists, laboratory scientists and clinical researchers will help address many of these unanswered questions, improve our understanding of the role of the complex panoply of functions of vitamin D, and its application into clinical practice.

Table 4. Unanswered clinical questions regarding the role of vitamin D in inflammatory bowel diseases

1. Does low serum vitamin D cause Crohn's disease or ulcerative colitis, or is it a marker for other risk factors?
2. Can supplementation with vitamin D in high-risk individuals prevent or delay the onset of Crohn's disease or ulcerative colitis?
3. Does vitamin D deficiency cause a more severe phenotype or increased inflammatory activity in Crohn's disease, or is it merely a consequence of severity of disease? Is vitamin D status predictive of recurrence of Crohn's disease post-operatively?
4. What is the optimal role of vitamin D supplementation as a therapeutic modality in patients with IBD? • Induction of remission? • Maintenance of remission and prevention of relapse? • Prevention of post-operative recurrence?
5. What is the optimal serum 25(OH)D level for its effect on inflammation in patients with IBD?
6. What is the optimal dose and modality for treatment of vitamin D deficiency in IBD patients?
7. Can vitamin D supplementation reduce risk of colorectal cancer in IBD?

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Author contributions

Mouli and Ananthakrishnan performed literature review. Mouli wrote the first draft of the manuscript. Ananthakrishnan provided supervision and both authors approved the final version of the manuscript.

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