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Optimal vitamin D levels in Crohn's disease: a review

Tara Raftery and Maria O'Sullivan*

Department of Medicine, Trinity Centre for Health Science, St. James's Hospital, Dublin 8, Ireland

Vitamin D deficiency is common among patients with Crohn's disease. Serum 25-hydroxyvitamin D (25(OH)D) is the best measure of an individual's vitamin D status and current cut-off ranges for sufficiency are debatable. Several factors contribute to vitamin D deficiency in Crohn's disease. These include inadequate exposure to sunlight, inadequate dietary intake, impaired conversion of vitamin D to its active metabolite, increased catabolism, increased excretion and genetic variants in vitamin D hydroxylation and transport. The effects of low 25(OH)D on outcomes other than bone health are understudied in Crohn's disease. The aim of the present review is to discuss the potential roles of vitamin D and the possible levels required to achieve them. Emerging evidence suggests that vitamin D may have roles in innate and adaptive immunity, in the immune-pathogenesis of Crohn's disease, prevention of Crohn's disease-related hospitalisations and surgery, in reducing disease severity and in colon cancer prevention. The present literature appears to suggest that 25(OH)D concentrations of ≥75 nmol/l may be required for non-skeletal effects; however, further research on optimal levels is required.

Crohn's disease: 25-hydroxyvitamin D: Vitamin D levels: Inflammation

Crohn's disease and ulcerative colitis are immune-mediated idiopathic diseases of the gastrointestinal tract. Crohn's disease can involve the entire gastrointestinal tract, while ulcerative colitis is isolated to the colon and rectum, both conditions are collectively referred to as inflammatory bowel disease (IBD)[1]. The key pathological mechanism in both cases is thought to be a dysregulated host immune response to commensal intestinal flora in genetically susceptible individuals[2,3]. Almost 100 genetic loci are currently associated with IBD, yet they incompletely explain the variance in disease incidence, suggesting a strong role for environmental factors, as supported by epidemiological data[3–5].

Vitamin D has long been recognised as a major regulator of calcium and phosphorus metabolism and thus has key roles in bone formation and resorption[6–8]. Low bone mineral density is a common manifestation in Crohn's disease[9,10] and guidelines regarding supplementation are well established[11]. Despite this vitamin D insufficiency remains common. With the discovery of the vitamin D receptor (VDR) in numerous tissues throughout the body beyond bone, including immune cells, a strong interest in understanding the role of vitamin D in disease pathogenesis and as a possible therapy in Crohn's disease has emerged[12–15]. The aim of the present review is to discuss vitamin D insufficiency in Crohn's disease, the potential benefits of supplementation and possible serum levels required to achieve the same.

Vitamin D physiology

Vitamin D metabolism

Vitamin D is a precursor of the active hormone calcitrol ($1,25(OH)_2D$) and is present in two forms; vitamin D_3 (cholecalciferol), which is the physiological form, and the synthetic analogue of vitamin D_2 (ergocalciferol). In human subjects, vitamin D can be obtained from two sources; diet and UVB exposure. Dietary sources of vitamin D_2 include irradiated yeast, plants and fungi, whereas vitamin D_3 is found in fish liver oils,

Abbreviations: CDAI, Crohn's disease activity index; IBD, inflammatory bowel disease; $1,25(OH)_2D$, calcitriol; 25(OH)D, 25-hydroxyvitamin D; QoL, quality of life; VDR, vitamin D receptor.

***Corresponding author:** Professor M. O'Sullivan, fax +353 1 896 2988, email maria.osullivan@tcd.ie

oily fish, meat, eggs and some fortified produce. Sunlight is the major source of vitamin D_3 for human subjects. In the skin, UVB rays promote cleavage of 7-dehydrocholesterol (provitamin D_3) into previtamin D_3, which, in turn, is converted by a thermal process to vitamin D_3. Regardless of the source, vitamin D is hydroxylated twice, first in the liver, followed by the kidney. The latter hydroxylation generates $1,25(OH)_2D$ that exerts its actions by binding to a VDR[16]. VDR are present on at least thirty different tissues throughout the body, including the intestinal and colonic tissues, circulating immune cells (such as activated lymphocyte T and B cells), monocytes, macrophages and muscle cells[7]. Importantly, many of these non-skeletal tissues also express vitamin D-activating enzymes, thereby permitting local production of $1,25(OH)_2D$. Investigations into the role of the VDR and $1,25(OH)_2D$ in these extra-skeletal tissues has uncovered novel anti-proliferative, anti-inflammatory and immune-modulating effects, which may be relevant to Crohn's disease.

Optimal vitamin D status

The best measure of an individual's vitamin D status is serum 25-hydroxyvitamin D (25(OH)D)[6,8] which reflects both sunlight exposure and dietary vitamin D intake. The definition of vitamin D deficiency remains controversial. At present there is no target level set for people with Crohn's disease beyond recommendations for the general, healthy population. The US Institute of Medicine define deficiency as <30 nmol/l, and use 40 and 50 nmol/l to define the estimated average requirement and recommended daily allowance respectively with intakes of 15μg (600 IU) vitamin D_3/d recommended for adults and children, a tolerable upper intake level of 100μg (4000 IU)/d and a no observed adverse effect level of 250μg (10 000 IU) vitamin D_3/d[17]. The US Endocrine Society's Clinical Practice Guideline suggests 75 nmol/l as a cut-off for adequacy and intakes of 37·5–50μg (1500–2000 IU) vitamin D_3/d to achieve this concentration. Irrespective of the cut-off applied (30, 50 or 75 nmol/l), several studies have reported a high prevalence of vitamin D insufficiency and deficiency in established IBD cases (Table 1) and in 80 % of new Crohn's disease diagnoses[9]. In paediatric cases, 25 % of patients have severe deficient levels[18] (Table 1).

Vitamin D toxicity

Vitamin D toxicity is a rare clinical syndrome of both hypervitaminosis D and hypercalcaemia. Clinical symptoms of vitamin D toxicity include nausea, vomiting, dehydration, muscle weakness, lethargy and confusion[19]. An upper toxic level of 250 nmol/l is frequently cited in the literature;[20,21] however, toxicity may not occur until 25(OH)D levels exceed 500 nmol/l[22] or even 750 nmol/l[23]. Data on vitamin D toxicity derives mainly from studies involving healthy cohorts. A study in 340 healthy school children[24] showed that administration of 350μg (14 000 IU) vitamin D_3/week for 1 year was safe and brought the mean 25(OH)D concentrations to 90 (SD 55) nmol/l. Measurements conducted in adults with a constant sun exposure (Puerto-Rican farmers) revealed serum 25(OH)D levels which were often between 100 and 200 nmol/l, while their calcium status was normal[25]. In Crohn's disease, Jorgensen *et al.*[15] supplemented forty-six patients with 30μg (1200 IU) vitamin D_3/d and levels increased to 96 (SD 27) nmol/l without any side-effects such as hypercalcaemia after 12 months of treatment. In a smaller study (*n* 18), 125μg (5000 IU) vitamin D_3/d increased 25(OH)D concentrations to 112·5 (SD 47·5) nmol/l without safety concerns[26]. Currently 50μg (2000 IU) vitamin D_3/d is regarded as acceptable and can be taken without medical supervision[27], although most clinical trials in Crohn's disease do monitor patients tolerance to supplementation regardless of the dose used as part of the study protocol.

Factors influencing vitamin D levels in Crohn's disease

Several factors predict vitamin D deficiency in Crohn's disease including; longer disease duration, higher Crohn's disease activity index (CDAI) scores, C-reactive protein levels, poor nutrition status, smoking[28–31], small bowel involvement[31] and resection[32], non-Caucasian ethnicity[33], sunlight exposure, impaired conversion of vitamin D to its active metabolite, increased catabolism and increased excretion due to steatorrhoea.

In Crohn's disease dietary intakes and supplemental intakes appear inadequate for achieving sufficient 25 (OH)D status. Less than half (43 %) of the patients are consumers of a vitamin D supplement, with multivitamin preparations being the most common form reported providing on average 5.6μg (5–10μg); 225 IU (200–400 IU) vitamin D daily. Moreover, for bone health, present guidelines suggest intakes of 20μg (800 IU)/d[11] which may or may not result in 25(OH)D concentrations ≥75 nmol/l. Studies have indicated intakes of 30, 50 or 125μg (1200, 2000 or 5000 IU)/d may be required to achieve levels ≥75 nmol/l, depending on baseline levels[15,26,34].

Diet in Crohn's disease provides approximately 1·0 μg/d (95 % CI 0·6, 1·9)[35,36] with the main food sources being oily fish (38 %), followed by eggs (27 %)[35]. Despite being low, dietary intakes in Crohn's disease are comparable with population intakes[29,37,38]. Poor dietary intakes may also be hindered by reduced absorption. Vitamin D is absorbed in the proximal small intestine, particularly in the jejunum[39]. The effect on vitamin D status due to small bowel involvement is uncertain. In a small study of twelve Crohn's disease patients with a terminal ileum resection a decline in vitamin D absorption correlating with the length of the resection was observed[40]. Conversely Ulitsky *et al.*[41] reported no difference in vitamin D levels between those with a resection *v.* no resection.

Whereas most of the predictors of low serum 25(OH)D in Crohn's disease are consistent throughout the literature, the effect of Crohn's disease activity on the vitamin D status is not confirmed. Some studies have reported no difference in 25(OH)D-based disease activity,[31,42]

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Table 1. Prevalence of suboptimal vitamin D status in inflammatory bowel disease in patients with active and quiescent disease

Author	Year	Cohort	Disease status (remission/active)	Country	% with 25(OH)D levels
					<25 nmol/l
Siffledeen *et al.*[28]	2003	242 CD	Not reported	Canada	8
Tajika *et al.*[128]	2004	33 CD	Active and remission	Japan	27
Ulitsky *et al.*[41]	2011	403 CD	Active and remission	Wisconsin, USA	11
Alkhouri *et al.*[18]*	2013	61 IBD	Active	Buffalo, USA	25
					<30 nmol/l
Jahnsen *et al.*[129]	2002	60 CD, 60 UC	Active and remission	Oslo, Norway	27 in CD, 15 in UC
Yang *et al.*[26]	2013	18 CD	Active	Pennsylvania	52
Wingate *et al.*[130]*	2014	83 CD	Remission	Canada	16
					<40 nmol/l
Sentongo *et al.*[131]*	2002	112 CD	Not reported	USA	16
Siffledeen *et al.*[28]	2003	242 CD	Not reported	Alberta, Canada	22
Pappa *et al.*[132]	2006	94 CD, 36 UC	Not reported	Boston, USA	35
Laakso *et al.*[10]*	2012	49 UC, 28 CD	65 % – remission	Helsinki, Finland	30
Wingate *et al.*[130]	2014	83 CD	Remission	Canada	33
					<50 nmol/l
McCarthy *et al.*[29]	2005	44 CD	Not reported	Cork, Ireland	50
Gilman *et al.*[31]	2006	58 CD	48 % – remission	Cork, Ireland	50
Vagianos *et al.*[133]	2007	84 CD	62 % – remission	Canada	46
Fu *et al.*[134]	2012	40 CD	46 % – remission	Canada	37
Ananthakrishnan *et al.*[135]	2013	1763 CD, 1454 UC	Remission and active disease	USA	32
Nic Suibhne *et al.*[35]	2012	81 CD	Remission	Ireland	63
Garg *et al.*[136]	2013	40 CD	55 % – remission	Melbourne, Australia	23
Grunbaum *et al.*[137]	2013	34 CD	Remission/mild activity	Canada	29
Abraham *et al.*[138]	2014	105 CD, 61UC	Not reported	Texas	23
Wingate *et al.*[130]	2014	83 CD	Remission	Canada	33
					<75 nmol/l
Vagianas *et al.*[133]	2007	84 CD	62 % – remission	Mantioba, Canada	70
Ulitsky *et al.*[41]	2011	403 CD, 101 UC	Active and remission	Milwaukee, Wisconsin	50
Garg *et al.*[136]	2013	40 CD	55 % – remission	Melbourne, Australia	58
Hassan *et al.*[42]	2013	26 CD, 34 UC	59 % – remission	Iran	95
Grunbaum *et al.*[137]	2013	34 CD	Remission/mild activity	Montreal, Canada	50
Abraham *et al.*[138]	2014	105 CD, 61UC	Not reported	Texas	60
Wingate *et al.*[130]	2014	83 CD	Remission	Canada	79
de Bruyn *et al.*[33]	2014	101 CD	Not reported	The Netherlands	81
Dumitrescu *et al.*[139]	2014	14 CD	Active and remission	Romania	79

CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis; 25(OH)D, 25-hydroxyvitamin D.
* Paediatric studies.

whereas Jorgensen *et al.* reported low levels were associated with active disease[43]. A clear trend of decreasing 25(OH)D from remission (64 nmol/l) to mild disease (49 nmol/l) and moderately active disease (21 nmol/l) ($P < 0{\cdot}01$) was reported[43]. A recent study confirmed these findings insofar as patients with active Crohn's disease had lower 25(OH)D levels than those in clinical remission; this measurement was independent of season or reported supplement use[44]. There also appears to be wide variation in the absorption of vitamin D in Crohn's disease; for example, Farraye *et al.*[45] reported that even in quiescent disease ability to absorb vitamin D is reduced by an average of 30 % in comparison with normal subjects after supplementation with 1250μg (50 000 IU) vitamin D_2. Whether or not the outcome would have been similar had vitamin D_3 been used remains to be seen.

In symptomatic/active disease cholestryamine may also be prescribed to reduce post-resectional diarrhoea. It also reduces bile acids, which are required for vitamin D absorption and may induce vitamin D malabsorption. Protein loosing enteropathy is a condition which can arise in severe disease and can result in the loss of vitamin D-binding protein along with the vitamin D bound to it[46]. Moreover, genetic variants in vitamin D hydroxylation and transport may also contribute substantially to both the development of vitamin D insufficiency and poor response to supplementation[47].

Beyond diet, sunlight and casual UVB exposure is the main source of vitamin D for most of the population. However, in Crohn's disease immunosuppressive therapy, such as azathioprine and adalimumab, can increase the risk of skin cancer. For this reason patients prescribed such medications are counselled regarding the careful use of sunscreen, which also prevents UVB synthesis of vitamin D. Sun exposure may also have a link to Crohn's disease pre-diagnosis. UVB exposure is often reduced at higher latitudes and coincides with a higher prevalence of autoimmune diseases and colorectal cancer in these regions compared with those more southerly[48,49] suggesting a possible relationship between latitude and Crohn's disease.

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Epidemiological evidence: low vitamin D status and Crohn's disease

Environmental triggers for IBD have been difficult to identify[50]. A German twin cohort study confirmed the strong genetic element to IBD, yet concordance rates between monozygotic twins are nonetheless low (35 % for Crohn's disease and 16 % for ulcerative colitis). This suggests important environmental interactions with disease-inducing genes[51]. One potential environmental risk factor is the UVB exposure. Recently a link between latitude and incidence rates of Crohn's disease has been identified in a large prospective study[52]. By tracking the location and lifestyle information of approximately 175 000 female American nurses biennially over 20 years, the authors detected a greater increase in the incidence rates of Crohn's disease and ulcerative colitis the farther subjects lived from the equator. At age 30 years, living in southern latitudes was associated with a roughly halved risk of developing Crohn's disease and approximately a 40 % reduced risk of developing ulcerative colitis. Similarly Ananthakrishnan *et al.*[12] found that women with a higher serum vitamin D level had a significantly reduced risk of Crohn's disease (hazard ratio: 0·38) suggesting a protective effect of vitamin D sufficiency.

In Europe an evident north–south gradient of incidence and prevalence also exists[53–55]. For example, low sunlight exposure was associated with an increased incidence of Crohn's disease in France and no association with ulcerative colitis[56]. Migration of populations who live near the equator to countries of greater latitude also increases the rate of Crohn's disease[57,58]. More recently, Limketkai *et al.*[59] reported that lower UV exposure is associated with greater rates of hospitalisation, prolonged hospitalisation and the need for bowel surgery in IBD. Further studies are needed to determine if this association is causal and also the role of other environmental factors that might explain these findings such as pollutants, diet and commensal or pathogenic microorganisms.

Vitamin D and immune function in Crohn's disease: experimental data

Vitamin D appears to have an important role in innate immunity[14,60]. For example, human cathelicidin antimicrobial peptide and beta defensins are antimicrobial peptides of the innate immune system, which are expressed by the gastrointestinal epithelium[61]. Antimicrobial peptides protect against bacterial invasion[62] and human cathelicidin antimicrobial peptide is important in maintaining and re-establishing intestinal barrier integrity[63] and in the healing of human intestinal epithelial cells[63]. Moreover *in vitro* studies have shown that $1,25(OH)_2D$ can induce the expression of the gene encoding human cathelicidin antimicrobial peptide[64]. However, the largest body of experimental evidence for an immunoregulatory role for vitamin D in IBD concerns the adaptive T-cell response. Several types of T-cells are important for the regulation of homeostasis in the gastrointestinal tract and either induce or suppress IBD. The VDR and $1,25(OH)_2D$ inhibit Th1 and Th17 functions by suppressing the production of particular cytokines[13,65,66] which restores gastrointestinal homeostasis post infection or chemical injury. In addition, $1,25(OH)_2D$ stimulates dendritic cell production of IL-10, and T-cell levels of CTLA-4 (an inhibitory co-stimulatory signal), which further enhances its anti-inflammatory effect[67].

Vitamin D and intestinal permeability in Crohn's disease: experimental data

Animal studies have shown that vitamin D may be linked to Crohn's disease severity and the function of the epithelial barrier. Vitamin D deficiency increased symptoms of several experimental models of IBD[68] and VDR deficiency increased susceptibility of mice to colitis[69,70]. Conversely treatment with $1,25(OH)_2D$ improves IBD symptoms and blocks the progression of colitis in mice[65,70,71]

Vitamin D may also function on the epithelial barrier. Epithelial cells are connected by intercellular junctions, comprising tight junctions and adherens junctions[72]. Patients with Crohn's disease have increased small intestine permeability[73] resulting in part from defects in these junctions. Compromised barrier function in Crohn's disease has been associated with inflammation, dysbiosis[74], disease pathogenesis and as a predictor of clinical relapse[75,76]. Evidence suggests that vitamin D increases tight junction proteins and enhances gut mucosal healing post-injury[77]. For example, following exposure to dextran sulphate sodium, a chemical which induces colitis, the VDR knock out mice were unable to maintain the integrity of the epithelial barrier[69,78] and had lower expression of tight junction proteins than in wild-type mice[77–79]. As a result of reduced tight junction proteins, vitamin D-deficient and VDR knock out mice had increased gut permeability compared with vitamin D-sufficient wild-type mice[78]. Whilst the basic science supports a role for vitamin D in Crohn's disease as reviewed elsewhere[80], further work is required to establish if this translates to human studies.

Observational studies: association between vitamin D levels, disease activity and surgery in Crohn's disease

Whilst epidemiological, animal and experimental data are promising the full possible range of effects of vitamin D in Crohn's disease are unknown, as are the optimal level(s) for inducing them. Observational studies which have focused on vitamin D and its effect on clinical markers such as CDAI (a research tool used to quantify the symptoms of patients with Crohn's disease) and inflammatory markers have been inconclusive. In cross-sectional IBD cohort studies El-Matary *et al.*[81] and Hassan *et al.*[42] reported no association between 25(OH)D and CDAI. CDAI levels <150 are indicative

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of remission, whereas levels above that suggest active disease. The mean 25(OH)D in these two studies were 66·7 (SD 27·3) nmol/l and 32·7 (SD 28·3) nmol/l, respectively. The cohorts included both Crohn's disease and ulcerative colitis patients and the sample sizes were small. Another cross-sectional study exclusive to Crohn's disease (*n* 34) reported a significant inverse association between 25 (OH)D and CDAI with mean concentrations of 53·5 (SD 27) nmol/l[82]. Similar findings were reported by Ulitsky *et al.*[41] who observed greater disease activity in those with lower 25(OH)D levels (Table 2).

Almost two-thirds of patients with Crohn's disease will eventually require surgery as part of their clinical course. Ananthakrishnan *et al.*[83] reported that 25(OH)D levels >50 nmol/l in Crohn's disease were associated with fewer surgeries and hospitalisations compared with those with levels below this threshold. A more aggressive disease course and need for surgery among those with vitamin D deficiency was also seen in a South Asian cohort[84]. Overall, despite limitations inherent in cross-sectional studies, such as mixed cohorts of ulcerative colitis and Crohn's disease, a reduced spread of vitamin D levels, different methods of data analysis, role of causality and various primary outcome measures, most of these studies suggest positive correlations between vitamin D and Crohn's disease-related outcomes (Table 2).

Clinical studies; association between 25-hyroxyvitamin D levels, disease activity and relapse in Crohn's disease

Only a small number of intervention studies have examined the effects of vitamin D supplementation in a clinical trial setting in IBD (Table 3). Two studies have reported positive associations with disease activity. The first, a prospective open label study compared supplementation with active vitamin D (alfacalcidiol) to 25μg (1000 IU) vitamin D_3 (cholecalciferol) in Crohn's disease[85]. After 6 weeks alfacalcidiol treatment resulted in a significant decrease in CDAI scores and C-reactive protein levels, as well as improvement in quality of life (QoL) scores. In spite of this at 12 months there were no significant differences between the groups with respect to these variables[85]. The primary aim of the present study was to examine the effects on bone metabolism and not disease activity; moreover, the paper did not report the 25(OH)D levels obtained by the groups, which may have not been in the therapeutic range at 12 months. Yang *et al.*[26] titrated vitamin D_3 intake until such a point serum levels were ≥100 nmol/l (commonly requiring 125μg (5000 IU)/d) and reported significant improvements in CDAI with a mean reduction in CDAI from 230 (SD 74) to 118 (SD 66; $P < 0·0001$). This may suggest a minimum level of 100 nmol/l is required to exert a significant effect on disease severity but further research is warranted. Whilst promising these studies were open label trials and therefore have their inherent limitations. A double-blind randomised placebo-controlled study assessed the effectiveness of vitamin D_3 supplementation in preventing clinical relapse. In comparison with the placebo group, oral vitamin D_3 supplementation of 30μg (1200 IU)/d for 12 months reduced the risk of relapse from 29 to 13 % at 1 year ($P = 0·056$)[15]. This difference in relapse was not statistically significant and merits further work (Table 3).

The current authors previously examined the effects of vitamin D supplementation on intestinal permeability as measured by the lactulose : mannitol ratio and sucrose excretion which indicates small bowel permeability[86]. In a double-blind placebo-controlled study 27 Crohn's disease patients were randomised to 50μg (2000 IU)/d vitamin D_3 or placebo. At follow-up (3 months) mean (95 % CI) 25 (OH)D levels were as expected significantly higher in the vitamin D group 91·6 (75·5–107·6) nmol/l than in the placebo group 40·4 (30·4–50·4) nmol/l ($P < 0·001$). At 3 months, there was a significant increase in lactulose : mannitol ratio ($P = 0·010$) and sucrose excretion ($P = 0·030$) in the controls, but these parameters were unchanged in the vitamin D group, suggesting that 25(OH) D levels ≥75 nmol/l may preserve intestinal integrity.

Clinical studies; association between 25-hyroxyvitamin D levels and muscle function

Compared with healthy controls in Crohn's disease skeletal muscle mass and strength are reduced[87–89] and muscle fatigue is increased[90]. Fatigue is a major concern in Crohn's disease[91–94] with two of five patients reporting that it negatively impacts their QoL, even in remission[95]. Reasons for this may include elevated pro-inflammatory factors such as TNFα and IL-6[96,97] which are associated with lower muscle mass and strength in elderly populations[98,99], poor nutrition, physical inactivity and prolonged corticosteroid therapy[89]. The underlying mechanisms of how vitamin D might improve muscle are poorly understood; however, several lines of evidence support a role of vitamin D in muscle health. First, proximal muscle weakness is a prominent feature of vitamin D deficiency[100] in addition to diffuse muscle pain and gait impairments such as a waddling way of walking[101]. Secondly, skeletal muscle is a major reservoir of 25(OH) D[102]; however, whilst it was previously thought that VDR were abundantly expressed in muscle cells with roles myogenesis and contractility this is currently under debate[103]. Although vitamin D supplementation increases muscle strength and balance in some populations for example in the elderly[104] data in Crohn's disease are not as widely available. In a cross-sectional study, van Landenberg *et al.*[105] reported that high 25(OH)D and physical activity may protect against reduced muscle mass[90]. Conversely Salacinski *et al.*[106] were unable to show a relationship between 25(OH)D levels and muscle strength in Crohn's disease. Although they did show that those with higher 25(OH)D levels (≥100 nmol/l) exhibited greater muscle strength (normalised to body weight) than those with lower levels (≤80 nmol/l) suggesting perhaps optimal effects on muscle function with levels ≥100 nmol/l; however, this is tentative data.

The current authors previously reported the results of a 3-month randomised, double-blind intervention study in quiescent Crohn's disease (*n* 27)[34]. Patients were

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Table 2. Observational studies of the association between 25-hyroxyvitamin D (25(OH)D) status and disease related outcomes in inflammatory bowel disease (IBD)

Author	Study design, *n*	Location	Outcome	Result	25(OH)D (nmol/l)	Association
Joseph *et al*.[82]	Cross-sectional 34 CD	India	Disease activity (HBI)	Disease activity negatively correlated with 25(OH)D	Mean level: 53·5 (SD 27) nmol/l (correlation coefficient: 0·484)	Positive
Hassan *et al*.[42]	Cross-sectional - 26 CD - 34 UC	Iran	Disease activity (CDAI)	25(OH)D had no association with disease activity	Mean level: 32·8 (SD 28·3) nmol/l	Nil
El-Matary *et al*. [81]	Cross-sectional - 39 CD - 21 UC	UK	Disease activity (Paediatric CDAI/ Paediatric UCAI)	25(OH)D had no association with disease activity	Mean level: 66·7 (SD 27·3) nmol/l	Nil
Ulitsky *et al*.[41]	Retrospective - 403 CD - 101 UC	USA	Disease activity – (HBI)	25(OH)D >75 nmol/l was associated with less disease activity in CD but not UC	Levels >75 nmol/l *v*. >50 nmol/l were associated less disease activity (−2·2, 95 % CI −4·1, −0·3) in CD	Positive
Ananthakrishnan *et al*.[12]	Prospective - 1763 CD - 1454 UC	USA	IBD related surgeries and hospitalisations	25(OH)D >50 nmol/l was associated with less risk of surgery and hospitalisations in CD	25(OH)D >50 nmol/l was associated with less surgery (OR 1·8, 95 % CI 1·2, 2·5) and hospitalisations (OR 2·1, 95 % CI 1·6, 2·7) in CD	Positive
Garg *et al*.[136]	Prospective - 40 CD - 31 UD - 23 controls	Australia	Fecal calprotectin (μg/g) CRP (mg/g)	25(OH)D negatively correlated with calprotectin in CD	Mean in CD: 70(95% CI 61, 78) nmol/l Mean in UC :70(95% CI 58, 81) nmol/l	Positive
Ananthakrishnan *et al*.[140]	3188 IBD patients	USA	CDI	25(OH)D >50 nmol/l were less likely to develop CDI (OR 2·27, 95 % CI 1·16, 4·44) *v.* individuals with vitamin D <50 nmol/l	Mean 25(OH)D in those who developed CDI; 51 nmol/l and in those who did not develop CDI; 67·8 nmol/l	Positive

CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; HBI, Harvey Bradshaw index; CDAI, Crohn's disease activity index; CDI, *Clostridium difficile* infection; CRP, C-reactive protein; UCAI, ulcerative colitis activity index.

Table 3. Intervention studies; relationship between 25-hyroxyvitamin D (25(OH)D) and outcomes in Crohn's disease

Author	Design	Intervention and duration	Outcome	Result	25(OH)D	Association
Miheller *et al*.[85]	Open label study *n* 37 Inactive Crohn's disease	0·5 μg alfacalcidiol/d or 50μg (1000 IU) vitamin D_3/d for 12 months	CDAI	Mean CDAI decreased from 69 to 57. Mean CRP (mg/l) decreased from 15·8 to 7·8 nmol/l ($P < 0·05$) in patients treated with alfacalcidiol	Not reported	Positive
Yang *et al*.[26]	Open label study Prospective *n* 18 Mild–moderate CD	125μg (5000 IU) vitamin D_3/d for 24 weeks	CDAI QoL	Vitamin D supplementation reduced CDAI scores from 230 (74) to 118 (66) ($P < 0·0001$) QoL improved from 156 (24) to 178 (22) ($P < 0·0006$)	112·5 (SD 47·5) nmol/l	Positive
Jorgensen *et al*.[15]	Randomised double-blind placebo-controlled study, *n* 94	30μg (1200 IU) vitamin D_3/d 12 months	Relapse in a 12 month period	No significant difference in relapse between groups ($P = 0·056$)	96 (SD 27) nmol/l in the treated group	Negative

CD, Crohn's disease, CDAI, Crohn's disease activity index; QoL, quality of life.

randomised to either 50μg (2000 IU)/d vitamin D_3 or placebo and the primary outcome measures included changes in hand-grip strength, a proxy measure for muscle strength. Post-intervention, both dominant and non-dominant hand-grip strength were significantly higher in the vitamin D-treated group compared with the controls. In the same study group, we also assessed changes in fatigue and QoL[34]. At 3 months, patients who achieved 25(OH)D levels ≥75 nmol/l had significantly higher QoL compared with patients below this cut-off ($P = <0·0001$)]. In line with this, significantly less fatigue was experienced in those with 25(OH)D levels ≥75 nmol/l compared with those below this cut-off, as assessed by question 2 of the IBD questionnaire.

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In a cross-sectional study of 504 IBD patients (403 Crohn's disease patients and 101 ulcerative colitis patients) vitamin D deficiency (<50 nmol/l) was associated with lower QoL in Crohn's disease but not ulcerative colitis;[41] however, muscle function and fatigue were not measured in the present study. Another intervention study[26] also showed improved QoL scores following vitamin D supplementation ($P < 0{\cdot}0004$), particularly when serum concentrations were ≥100 nmol/l[26]. This was paralleled with significant improvements in CDAI scores; however, muscle strength was not measured in this study.

Vitamin D and cancer in Crohn's disease

More recently, associations between vitamin D status and cancer have been examined. Epidemiological studies suggest an increased risk of and mortality from cancer in northern latitudes with reduced UVB exposure, an association possibly mediated by vitamin D[107]. Furthermore, prospective cohorts have demonstrated an inverse association between 25(OH)D and cancers of the colon, breast and prostate[108–111] with one intervention study reporting a reduced risk of cancer by 60 %[112] with levels >80 nmol/l. Ananthakrishnan *et al.*[12] looked at data from 2809 patients with IBD and a median plasma 25(OH)D level of 65 nmol/l. During a median follow-up period of 11 years, 196 patients (7 %) developed cancer, excluding nonmelanoma skin cancer (forty-one cases of colorectal cancer). Patients with vitamin D deficiency had an increased risk of cancer (adjusted OR, 1·82; 95 % CI 1·25, 2·65) compared with those with sufficient levels. Each 1–2·5 nmol/l increase in plasma 25(OH)D was associated with an 8 % reduction in risk of colorectal cancer (OR, 0·92; 95 % CI 0·88, 0·96). The mean plasma 25(OH)D in patients who subsequently developed cancer was 12·5 nmol/l lower than in those who did not develop cancer (57 *v.* 69 nmol/l; $P < 0{\cdot}0001$). They also reported a statistically significant inverse association for lung cancer (OR, 0·95; 95 % CI 0·90, 0·99). However, the study has its limitations; for example, the confounding impact of inflammation and low BMI on low 25(OH)D status was not reported and there was a lack of information on screening practices and on smoking.

Conclusion

Vitamin D insufficiency in IBD remains common. Consensus expert opinion has suggested 25(OH)D levels of 75–100 nmol/l may provide optimal benefits for musculoskeletal and cancer outcomes[20] and levels of 100–175 nmol/l for optimal immune effects[113]. The data reviewed here show evidence of positive associations with levels ≥75 nmol/l in Crohn's disease, and further possible associations with levels ≥100 nmol/l but such associations need validation with well-designed randomised controlled trials. These include associations with CDAI, muscle function, fatigue, QoL, maintenance of epithelial barrier function, decreased hospitalisations, reduced risk of surgery and cancer. In terms of dosage required to achieve these levels 20–25μg (800–1000 IU)/d vitamin D_3 appears sufficient to achieve a serum level of 50 nmol/l, and between 25 and 100μg (1000 and 4000 IU)/d to bring levels beyond 75 nmol/l (on average 50μg (2000 IU)/d is required for this purpose[114–123]). In the present study of Crohn's disease patients, we found that 50μg (2000 IU)/d increased mean 25(OH)D levels to 91·6 (95% CI 75·5, 107·6) nmol/l over winter months, which was significantly higher than levels in the placebo group 40·4 (95% CI 30·4, 50·4) nmol/l ($P < 0{\cdot}001$)[34]. To obtain 25(OH)D status ≥100 nmol/l in Crohn's disease, 125μg (5000 IU)/d may be required[26]. This is the lower end of what is considered the 'physiological' zone of 75–200 nmol/l, the range which corresponds to the serum levels observed in outdoor workers[25,124,125] as well as in traditionally living populations in East Africa[126]. This zone is far below the toxic zone, which appears to be located above the 400 nmol/l serum level[127]. To conclude there are many unanswered clinical questions regarding the role of vitamin D in Crohn's disease such as: (1) what is the optimal role of vitamin D supplementation as a therapeutic modality in Crohn's disease; (2) what is the effect of disease activity and resection on circulating 25(OH)D concentrations; (3) what is the level with which a plateau effect is observed in terms of relapse prevention/immune augmentation, if any. Additional well-designed and executed randomised double-blind placebo-controlled trials which investigate 25(OH)D levels are required to address these questions.

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Conflict of Interest

None.

Authorship

T. R. and M. O'S. wrote the manuscript and approved the final draft of the submitted manuscript.

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