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Short Review

The Role of Vitamin D for Children with Inflammatory Bowel Disease

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Special Issue: Vitamin D Status and Its Relation to Energy Expenditure, Chronic Disease and Health Status

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Abstract

Children with inflammatory bowel disease (IBD) have a high prevalence of vitamin D insufficiency secondary to factors such as malabsorption and decreased intake. In recent years the benefits of optimal vitamin D status have been highlighted for their potential to improve the disease course and long-term outcomes in this population. Clinical benefits have been seen to bone health, the immune system, and gut health, with further improvements to disease and treatment outcomes. Recommendations for vitamin D treatment parameters to optimize these benefits have been developed, as well as the identification of risk factors for insufficiency specific to children with IBD. While various supplementation regimens are available reports of efficacy are inconsistent, as are guidelines for frequency of testing. Further research is required to elucidate whether hypovitaminosis D is a cause or consequence of IBD, and the role of vitamin D supplementation in treatment warrants significant attention.

Keywords
Vitamin D; bone health; hypovitaminosis D; immunomodulatory; supplementation; children; inflammatory bowel disease

1. Introduction

The incidence of inflammatory bowel disease (IBD) is rising globally and with up to 25% of IBD cases developing during childhood or adolescence it has become one of the most important and serious chronic diseases of childhood [1-3]. Childhood-onset IBD is typically more severe with more extensive disease and a more complex progression than IBD diagnosed as an adult [4, 5]. Consequently, IBD in childhood can have detrimental effects on growth, developmental, and cognitive trajectories.

The term IBD incorporates the clinical sub-types of Crohn's disease (CD) and ulcerative colitis (UC), both of which are complex, relapsing inflammatory conditions of the gastrointestinal tract. CD is defined as a transmural, segmental condition that may occur in any part of the gut, while UC involves continuous involvement of the mucosal and submucosal layers of the colon [6]. The pathogenesis of IBD is a result of the interplay between the mechanisms of environmental factors, immune response, intestinal barrier, and genetics. Genome-wide association studies have identified over 200 genetic risk loci associated with IBD, of which some are specific to CD, some specific to UC, but many associated with both sub-types, indicating that these diseases share common inflammatory pathways [7].

Micronutrient deficiencies are commonly observed in children with IBD, predominantly attributable to malabsorption and/or decreased intake. Although some micronutrient deficiencies are dependent on disease location, medications or surgery, overall the most common reported deficiencies are of iron, vitamin D and calcium with further deficits in essential fatty acids, and water/fat soluble vitamins [8-11]. These deficiencies are particularly problematic when IBD is diagnosed during childhood as it is a critical period of growth and development.

A focus of recent global research has been on the importance of vitamin D specifically and the role it plays in the disease course of individuals with IBD. This mini-review aims to highlight the significance of optimal vitamin D status (as measured by the serum concentration of 25-hydroxyvitamin D (25(OH)D) for children with IBD, as well as the efficacy of various treatment options in managing sub-optimal 25(OH)D concentrations. Literature was identified from comprehensive topic-specific searches of health databases (Medline, Embase) alongside reference list reviews of relevant studies.

2. Vitamin D

2.1 Overview

Vitamin D is a liposoluble nutrient with two major physiologically relevant forms; ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3), both of which are provided from the diet, and also can be fortified in some food products [12, 13]. Vitamin D3 is also cutaneously synthesized under the influence of ultraviolet (UV) light [14]. Vitamin D insufficiency or deficiency may occur secondary

to reduced synthesis during winter months when there are fewer sunshine hours [15], and due to western diets being a poor source of vitamin D [16]. Subsequently, sub-optimal 25(OH)D concentrations are seen in populations around the world [15]. The physiological effects of optimal vitamin D status for children with IBD are multifactorial and have garnered interest for their potential to ameliorate the effects of the disease. Benefits have been seen in parameters relating to bone health, the immune system, the gut, treatment efficacy, and clinical outcomes.

Vitamin D status is assessed by measuring serum or plasma concentrations of the metabolite 25-hydroxyvitamin D (25-OH-D), a reliable marker of dietary intake and cutaneous synthesis [17, 18]. The consensus of an optimal serum concentration of 25(OH)D has varied over time. However, it is currently considered that a concentration of ≥75 nmol/l (≥30 ng/ml) may be required for children with IBD in order to achieve benefits to the immune system, bone health, and clinical outcomes [19-21]. A commonly used term for vitamin insufficiency or deficiency is 'hypovitaminosis', and will be referred to herein.

2.2 Clinical Benefits

2.2.1 Bone Health

Vitamin D is essential to bone health throughout the life-span. Adequate serum concentrations are needed to optimize intestinal absorption of calcium, and for maintenance of the serum calcium/phosphate balance required for calcification of the growth plate and mineralization of osteoid in cortical and trabecular bone [18, 22]. The importance of this process is highlighted in previous work that demonstrated prolonged vitamin D deficiency resulted in delayed growth and rickets in healthy children as well as osteoporosis and osteopenia in adults [23].

The prevalence of poor bone health, manifesting as low bone mineral density (BMD), is high among children with IBD and comes during a period in their lives when bone mass acquisition should be most rapid [24, 25]. Subsequent failure to attain peak bone mass by adulthood is disadvantageous and has been linked with increased risk of fractures during childhood and in later life [24, 26, 27]. The pathogenesis of low BMD among children with IBD is complex and suboptimal vitamin D is just one contributing factor. Other risk factors include medications, chronic inflammation, delayed puberty, decreased growth factors, decreased physical activity, low BMI, and malnutrition [24, 25].

A number of studies have reported BMD and the association with 25(OH)D concentrations in children with IBD. In all cohorts studied, children with IBD had subnormal BMD, or levels significantly lower than controls [28-32], however, the role of vitamin D in this process was less clear. Conflicting results were seen, with some studies reporting a positive association between BMD and vitamin D [28, 30], while others showed no correlation [29, 31]. Vitamin D supplementation was shown to accelerate accrual of BMD in two studies [28, 32], with contrasting results found in another [33]. The disparity in these results may be due to the fact that bone mineral accretion is normally cumulative and, therefore, measuring vitamin D at a single time point may not correlate well with a single measurement of BMD [34]. In addition, children with IBD can be shown to have low BMD and vitamin D at the time of diagnosis and this does not necessarily improve longitudinally following treatment, thereby limiting the assumptions that can be made regarding normal bone mass acquisition [9, 31, 35]. A meta-analysis of studies among healthy children aiming to assess efficacy of vitamin D supplementation on BMD showed no significant effect with BMD measured at a

number of sites (total hip, forearm, lumbar-spine) [36]. When sub-group analyses were carried out on studies including participants with low baseline 25(OH)D concentrations the only effect seen was of borderline significance in one study for improvements to bone mineral content [36]. Consequently, while disease variables for children with IBD may negatively affect their BMD the possibility of improvement with the use of vitamin D supplementation is by no means guaranteed, especially in combination with other contributing factors.

2.2.2 Immunomodulatory Effect

In addition to its association with bone health, vitamin D plays a diverse and dynamic role upon the gut microbiota, as well as regulating adaptive and innate immunity. Optimal serum concentrations may play a protective role in the onset and clinical course of IBD [12, 20, 37]. It has been shown that vitamin D3 induces nucleotide-binding oligomerization domain protein (NOD2) gene expression, and exerts different effects on the expression of toll-like receptor (TLR) and NOD2 induced cytokines in CD [38]. The intestinal microbiota and its metabolites act on both NOD1 and NOD2 receptors, and their defective signaling may contribute to the onset of IBD [38, 39]. In relation to the clinical course of IBD, one mechanism by which vitamin D plays a role is through altering the immune response. T lymphocytes contain vitamin D receptors that are both direct and indirect targets of the micronutrient [40]. Vitamin D is crucial to activation of T cells, but also indirectly alters inflammation by affecting antigen-presenting cells. Dendritic cells and macrophages that are treated with vitamin D3 decrease their secretion of pro-inflammatory cytokines following activation; the resultant modulation of differentiation and maturation promotes the induction of T cells with regulatory phenotypes [12, 38, 40].

2.2.3 Gut Health

Children with IBD commonly have increased permeability of the intestinal barrier, which has been associated with inflammation and dysbiosis due to increased exposure of the immune system to the intestinal microbiota [13, 40]. Vitamin D benefits gut health by targeting three major components of the gastrointestinal tract: the intestinal epithelial barrier, gut immunity, and gut microbiota [12]. Vitamin D signaling is imperative in maintaining the integrity of the epithelial barrier by protecting against infectious and inflammatory insults in a number of ways: by increasing its resistance to irritants in the intestinal mucosa, suppressing epithelial cell apoptosis, enhancing repair, and increasing the expression of specific tight junction proteins [12, 40]. In addition, vitamin D promotes a rich and diverse gut microbiome, with high dose supplementation shown to lead to increased bacterial richness in the gastrointestinal tract [12, 41]. Consequently, sub-optimal concentrations of 25(OH)D may negatively affect the gut barrier and immune function and lead to increased dysbiosis and potential translocation of gut bacteria, thus affecting IBD onset and progression [13, 42]. Much of the research relating to gut integrity is *in vitro*, but low concentrations of 25(OH)D have been shown to inversely correlate with surrogate markers of gut inflammation such as fecal calprotectin [43-46], as well as tumor necrosis factor (TNF) and other pro-inflammatory cytokines [43].

2.2.4 Disease Outcomes

Vitamin D sufficiency has been linked to a number of clinical benefits for children with IBD, in particular the role vitamin D plays in moderating disease activity. While a small number of studies have observed lower disease activity among children with sufficient, or higher, vitamin D levels [47-50], the few studies available on vitamin D supplementation that reported on disease activity also suggest a beneficial effect on these specific clinical indices. A double blind, placebo controlled RCT to treat hypovitaminosis D showed that supplementation significantly reduced disease activity indices, relapse frequency, disease severity score, and a number of inflammatory markers: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fecal calprotectin, TNF-α, and the inter-leukins (IL) IL-17, 10, 12, and 23 [43]. In addition, this study reported benefits to quality of life, along with reduced hospitalizations and emergency department visits [43]. Retrospective reviews have also reported benefit to disease activity indices, [51, 52], CRP [51, 53], ESR [51, 53], and IL-6 [53], although all at different dosing regimens.

A number of meta-analyses on vitamin D supplementation have been performed, however, most comprise either predominantly adults with IBD, or included the pediatric studies cited above. Overall, the relapse rate and/or disease activity scores were significantly reduced using vitamin D supplementation in four analyses [54-57], but not in one [58]. A significant reduction of CRP was seen in two analyses [56, 58] but no change in ESR [55, 58] or CRP [55] in others. All analyses reported significant bias in many of their included studies, and the vitamin D dosing regimens were not consistent.

2.2.5 Treatment Outcomes

In addition to the benefits previously highlighted, vitamin D may play a beneficial role in the response of children with IBD to anti-TNF medications, which are an effective treatment for CD and UC. Anti-TNF primary nonresponse, or loss of response, poses a significant problem but vitamin D sufficiency may ameliorate this. Studies have reported that children and adults with IBD on anti-TNF therapy with vitamin D insufficiency had significantly higher levels of early treatment termination due to loss of response [19, 41, 59]. Another report indicated decreased odds of being in remission following induction in subjects with insufficiency compared to those that were vitamin D sufficient [60]. In addition, when those treated with an anti-TNF therapy were given vitamin D supplementation remission rates were higher for those with greater 25(OH)D concentrations [44]. It is hypothesized that the way in which vitamin D affects disease severity is via the TNF pathway, with genome-wide analysis revealing that 25(OH)D concentrations influence a large number of genes [37, 60]. These data suggest anti-TNF medications and vitamin D may be synergistic in decreasing TNF levels, thereby suggesting an adjunctive role of vitamin D in IBD treatment regimens.

2.3 Vitamin D Concentrations in the Setting of IBD in Children

Vitamin D deficiency among the general pediatric population has been defined in a number of ways in the literature. In guidelines from Central Europe, Australasia, and the Americas moderate and severe deficiency is defined as serum 25(OH)D concentrations less than 50 nmol/L and 30 nmol/L respectively, and insufficiency as between 51 and 75 nmol/L [14, 61-63]. Other work in Europe defines the cutoff for deficiency as 50 nmol/L [14, 61, 64]. When studies specific to children

with IBD are examined there is considerable variation in terminology, units of measurement, and concentration cut-offs, even within geographic areas (Table 1). Inferences on the proportion of children with IBD and hypovitaminosis D is, therefore, complex with prevalence up to 81% of individuals being below the recommended range by definition (Table 1).

Table 1 Vitamin D cut-off definitions and prevalence of deficiencies among individual studies.

Author	Country	Cohort	Definition	Vitamin D levels	Proportion of vitamin D deficiencies	Difference between diagnoses
Alkhouri [65]	US (New York)	All: 61 CD 46 UC 12 IC 3	Deficient: <30 nmol/L Severe deficient: <10 nmol/L	Mean (SD) ng/dL **All**: 27.8 (15.3) **CD**: 29.9 (12.7) **UC**: 32 (25.8) **IC:** 21.7 (7.5)	Deficient: 62% Severe deficient: 3%	-
Badalyan [30]	US (Virginia)	215	Normal: >30 ng/mL Insufficient: 20-30 ng/mL Deficient: <20 ng/mL	Mean 26 (SD 10.7) ng/mL	Normal: 29% Insufficient: 45% Deficient: 26%	-
Ehrlich [9]	Israel (Petach Tovka)	All: 359 CD 240 UC 119	Normal: 50-250 nmol/L	Mean (SD) nmol/L At diagnosis **CD**: 55 (22) **UC**: 52 (19.8) After 1 year **CD**: 60 (23) **UC**: 55 (19.3)	Deficient at diagnosis **CD**: 39% **UC**: 49% Deficient after 1 year **CD**: 39% **UC**: 44%	NS
Hradsky [32]	Czech Republic (Prague)	All: 55 CD 38 UC 17	Normal: >50 nmol/L Insufficient: 30-50 nmol/L Deficient: <30 nmol/L	Median 57.63 (IQR 42.79 to 78.5) nmol/L	Normal: 67% Insufficient: 16% Deficient: 17%	-

Jin [66]	Korea (Seoul)	All: 127 CD 117 UC 10	Deficient: <20 ng/mL	Mean (SD) ng/mL **All**: 4.5 (7.0) **CD**: 14.55 (7.04) **UC**: 13.69 (5.85)	Deficient: **All**: 81.7% **CD**: 82% **UC**: 78%	-
Kim [50]	Korea (Seoul)	All: 96 CD 72 UC 24	Sufficient: >30 ng/mL Insufficient: 21–29 ng/mL Deficient: <20 ng/mL	Median (IQR) ng/mL: **CD remission**: 17.5 (12.7–20.4) **CD active**: 12.4 (8.8–15.3) **UC remission**: 19.4 (11–23.8) **UC active**: 12.5 (7.4–19.7)	Deficient: 80.2%	NS
Levin [67]	Australia (Sydney)	All: 78 CD 70 UC 5 IBDU 3	Insufficient: 51-75 nmol/L Moderate deficient: <51 nmol/L Severe deficient: <30 nmol/L	Mean 71.2 (SD 26.5) nmol/L	Insufficient: 38% Moderate deficient: 20% Severe deficient: 4%	-
Pappa [48]	US (Massachusetts)	All: 130 CD 94 UC 36	Deficient: <15 ng/mL	Mean 20.9 (SD 10.7) ng/mL	Deficiency: 34.6% Severe deficiency: 10.8%	NS
Pappa [68]	US (Boston)	All: 448 CD 288 UC 143 IC 17	Optimal: >32ng/mL Suboptimal: ≤32ng/mL Insufficient: ≤20 ng/mL Deficient: ≤15ng/mL	Mean (SD) ng/mL **All:** 31 (12) **CD**: 33 (12) **UC**: 29 (11)	**All** Suboptimal: 58.5% Insufficient: 14.3% Deficient: 5.8% **CD** Suboptimal: 55.6% Insufficient: 10.8% Deficient: 4.2%	UC significantly lower vitamin D levels then CD, and significantly greater% insufficient than CD

					UC Suboptimal: 63.6% Insufficient: 19.6% Deficient: 8.4%	
Prosnitz [69]	US (Philadelphia)	CD: 78	Deficient: 20 ng/mL	Mean (SD) ng/mL **Non-black participants**: 23.5 (9.2) **Black participants**: 10.5 (4.6)	Deficient: 42%	-
Rempel [10]	Canada (Winnipeg)	All: 165 CD 87 UC 78	Normal: 50–250 nmol/L	Mean (SD) nmol/L <u>At diagnosis</u> **CD**: 65.8 (29) **UC**: 57.2 (27.1) <u>After 1 year</u> **CD**: 81.6 (34.5) **UC**: 73.1 (29.2)	<u>Deficient at diagnosis</u> **All**: 22% **CD**: 16% **UC**: 28% <u>Deficient after 1 year</u> **All**: 13% **CD**: 6% **UC**: 21%	-
Safdi [49]	US (Georgia)	184	Deficient: ≤15 ng/mL	-	Deficiency: 21%	-
Salehi [28]	US (New York)	110	-	-	Deficient: 63.6%	-
Sentongo [18]	US (Philadelphia)	CD 112	Hypovitaminosis D: <38 nmol/L	Mean 26.75 (SD 7.98) nmol/L	Hypovitaminosis D: 16%	-
Tran [70]	Canada (Quebec)	All: 240 CD 193 UC 47	Low: <75 nmol/L	Median 55 (IQR 26) nmol/L	Low: 80.7% overall <u>Normal</u> **CD**: 31.5% **UC**: 40.6%	
Veit [71]	US (Massachusetts)	All: 58 CD 40	Sufficient: 75 nmol/ L	Mean (SD) nmol/L **CD**: 61.69 (24.43)	**CD** Sufficient: 72.5%	NS

	UC 18	Insufficient: 50–74.5 nmol/L Deficient: 50 nmol/L	**UC:** 53.26 (25.51)	Insufficient: 40% Deficient: 15% **UC** Sufficient: 83.3% Insufficient: 50% Deficient: 27.8%

CD = Crohn's disease, UC = ulcerative colitis, IBDU = IBD unclassified, IC = indeterminate colitis, SD = standard deviation, IQR = inter-quartile range, NS = non-significant, - = not reported

All values and units as stated in original article.

A number of systematic reviews that included children with IBD, and additional pediatric studies, report that overall the serum concentrations of 25(OH)D in children with IBD are lower than controls [42, 47, 54, 69]. However, this was not evident in two individual studies [65, 71]. Evidence to determine whether there is a difference in concentrations between the IBD clinical sub-types is lacking, with one study reporting children with UC having significantly lower vitamin D than children with CD some reporting no difference, and many not comparing the groups (Table 1).

2.3.1 Risk Factors for Hypovitaminosis D

A number of disease-related risk factors for hypovitaminosis D have been identified for children with IBD, with additional factors that are also relevant to the general population. The magnitude of exposure to corticosteroids has been shown to negatively affect 25(OH)D concentrations [18, 67], as well as factors relating to a reduced intake and absorption of vitamin D such as reduced appetite, malnutrition, and gastrointestinal (GI) losses [8, 24]. Disease activity, whether classified by increased inflammatory markers or clinical indices, may be associated with sub-optimal vitamin D [47, 49, 50]. Furthermore, a number of studies have reported increased risk of low 25(OH)D concentrations in children with upper gastrointestinal CD [18, 20, 24, 48, 72]. Poor growth as represented by a low body mass index (BMI) score was shown to be a risk factor in one study [48], with the opposite found in other research with a high BMI being a risk factor [68, 71] likely due to a greater proportion of the body's vitamin D being stored in adipose tissue [17].

Risk factors common to children with IBD as well as the general population are well reported. Low exposure to UV light is a significant cause of hypovitaminosis D that could be consequent to reduced outdoor activities as a consequence of IBD symptomatology [42]. Other factors such as darker skin pigmentation, age, and use of sunscreen may reduce the effective exposure to UV light of the vitamin D precursor [15, 18, 68, 73]. Seasonal variations in 25(OH)D concentrations during winter months are well reported as there is insufficient UV light exposure to allow cutaneous synthesis [18, 68]. In addition, the latitude at which people reside exerts an influence as the skin synthesizes lower levels of vitamin D from sun exposure at latitudes 37° north or south of the equator [15, 40]. Further evidence of this link is seen in the emerging global gradient of IBD with higher incidence rates in more northern or southern countries, as well as within-country gradients [74-79].

While work has been carried out confirming that genetic polymorphisms and alterations are related to vitamin D status, the underlying genetic determinants remain poorly understood [80]. Additional research is needed in order to clarify these genetic determinants, and to examine the mechanisms of action responsible for the association with vitamin D status that may identify susceptible individuals who may benefit from supplementation [80].

The main prevention strategy for vitamin D insufficiency within the population of children with IBD should be to identify those at risk according to the criteria outlined above, and to correct and optimize their 25(OH)D concentrations, as below.

2.4 Correction of Hypovitaminosis D

In order to correct and optimize 25(OH)D concentrations for children with IBD a number of strategies may be applied relating to environmental factors, dietary intake, and clinical treatment. Vitamin D may be obtained from two sources: UV mediated synthesis and oral intake. UV exposure

accounts for 80% to 90% of vitamin D in the human body [15], but if there is inadequate exposure to sunlight then support from diet and/or supplements is fundamental to achieve optimal concentrations [13, 17, 24]. Education on the importance of including vitamin D rich foods in the diet is beneficial, with recommendations from the European Food Safety Authority being for a daily intake of 1000 IU/day for infants 0 to 12 months, 2000 IU/day for children ages 1 to 10 years, and 4000 IU/day for children ages 11 to 17 years of vitamin D [64]. While few foods contain substantial amounts, sources with high levels include: oily fish, eggs, beef liver, as well as fortified products such as milk, juices, breads, and cereals [13, 24]. However, with only 20% of daily vitamin D needs being met through diet, and children with IBD experiencing risk factors that may contribute to further reduced intake or absorption, oral supplementation may provide a method for restoring optimal concentrations.

2.4.1 Supplementation

Ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) are the most frequently used forms of oral supplement, with evidence recommending preferential use of cholecalciferol due to superior efficacy [8, 24, 81]. A number of regimens for supplementation of vitamin D2/D3 may be used, such as daily, weekly, or one-off high dose vitamin D3 (Stoss therapy). Varying levels of efficacy were reported in a recent systematic review [82]. When studies looking specifically at restoration of hypovitaminosis D were examined it was seen that while many regimens are effective at increasing serum concentrations, few report on longitudinal benefit or comment on the proportion who sustain sufficient levels (Table 2). No definitive dosing recommendations for daily, weekly, or Stoss therapy can be extrapolated from these studies (Table 2), or identified in reviews [14, 61]. Attention should be paid to the research presented comparing different supplements and doses as are available in individual centers, and to evaluate which are effective for restoration and maintenance [24, 53]. Patient preference should also be considered, with Stoss therapy reported as the patient's preferred method [83], with this one-off dose reducing associated problems of ongoing treatment adherence and increased medication burden [52].

Table 2 Overview of studies reporting vitamin D supplementation for treatment of hypovitaminosis D in children with IBD.

Author	Study design	Population	Baseline 25(OH)D concentration–inclusion criteria	Vitamin D dose	25(OH)D concentration
El Amrousy [43]	Double blind, placebo controlled RCT to treat hypovitaminosis D	All 98: CD 53 UC 45	<20 ng/mL	<u>All for 6 months:</u> Daily oral vit D3 2000 IU *versus* placebo	Mean serum concentration significantly increased from baseline to above 50 ng/mL in vitamin D group (Mean 13 ng/mL to 53 ng/mL), but not placebo controls (Mean 14.5 ng/mL to 13 ng/mL)
Lee [83]	RCT of two dosing regimens	All: 44 CD 28 UC 16	<30 ng/mL	Weekly oral vit D3 50,000 IU for 6 weeks *versus* single oral vit D3 Stoss dose of 300,000 IU	Mean serum concentration significantly improved from baseline to 1 month for weekly vit D3 (23 to 54.6 ng/mL and Stoss group (20.4 to 53.6 ng/mL) with no difference between the interventions. After 3 months the mean concentration had dropped in both groups but was significantly higher in the weekly vit D3 group (40.4 ng/mL) than the Stoss group (29.8 ng/mL).
Martin [51]	Retrospective chart review	All: 23 CD 19 UC 2 IBDU 2	<50 nmol/L	Single oral Stoss dose vit D3 <3 y = 200,000 IU 3-12y = 400,000 IU >12y = 800,000 IU	Serum concentration significantly increased from baseline (Mean 39 nmol/L) to 1-2 months post-Stoss dose (189 nmol/L), with all children achieving a level >75 nmol/L
Pappa [81]	RCT of three dosing regimens to treat deficiency	All: 71 CD 41 UC 27 IC 3	<20 ng/mL	<u>All for 6 weeks:</u> Daily oral vit D2 2000 IU *versus* daily oral vitamin D3	Mean change (Δ) of serum concentration was significantly greater in the daily oral vit D3 2000IU group (Δ 16.4 ng/mL) and the weekly oral vit D2

				2000IU *versus* weekly oral vit D2 50,000 IU	50,000 IU (Δ 25.4 ng/mL) than the daily D2 2000 IU (Δ 9.3 ng/mL). Daily vit D3 and weekly D2 were 95% successful in raising serum concentration above 20 ng/ml; however, only 38% of subjects in daily vit D3 group and 75% in weekly vit D group had serum 25OHD concentration rasied above 32 ng/ml
Shepherd [52]	Retrospective chart review	All: 76 CD 53 UC 11 IBDU 12	<50 nmol/L	Single oral Stoss dose vit D3 <3 y = 200,000 IU 3-12y = 400,000 IU >12y = 800,000 IU	Mean serum concentration significantly increased from baseline (41 nmol/L) to above 75 nmol/L at 1 month (146 nmol/L) and 3 months (87 nmol/L) but had dropped below by 6 months (69 nmol/L)
Simek [84]	RCT of two dosing regimens	All: 34 CD 28 UC 4	<30 ng/mL (75 nmol/L)	<u>All for 6 weeks</u> Weekly oral vit D3 5000 IU vitamin D3 per 10 kg body weight *versus* weekly oral vit D3 10,000 IU per 10 kg body weight	Mean serum concentration increased significantly from baseline to 8 weeks but not 12 weeks in the 5000 IU/10 kg group (24 to 41.5 to 30.8 ng/mL) and increased significantly from baseline to 8 weeks and 12 weeks in the 10,000 IU/10 kg group (23.7 to 49.2 to 35.1 ng/mL). There was no significant difference between the increase in both dosing regimens at 8 or 12 weeks.

RCT = randomized controlled trial, CD = Crohn's disease, UC = ulcerative colitis, IBDU = IBD unclassified, IC = indeterminate colitis,

All values and units as stated in original article.

Vitamin D supplementation may result in hypervitaminosis D, leading on to adverse effects related to high concentrations of calcium, phosphate, and paraththyroid hormone, and consequent complications such as renal calculi. However, these adverse effects were not seen in the identified literature among children with IBD using a range of supplementation regimens [43, 51-53, 81, 83].

2.4.2 Testing Frequency

Screening for hypovitaminosis D should be carried out on children with CD or UC as both are at risk of deficiency [68]. While concentrations are lower at the time of diagnosis, many children remain deficient following treatment and follow up, and should be monitored accordingly [9]. Few papers provide recommendations relating to testing frequency, but screening is endorsed at diagnosis and then at least yearly, with particular attention to seasonality, as well as during active and asymptomatic periods [13].

2.4.3 Formal Guidelines

Scientific societies relating to Pediatric gastroenterology, hepatology and nutrition (PGHAN) are evident in all areas of the world, and bring together expertise to develop evidence based clinical practice guidelines. A small number of these organizations have published recommendations for the testing and treatment regimens relating to hypovitaminosis D for children with IBD. The North American Society (NASPGHAN) recommend measuring serum concentrations if there is significant bone mineral deficit, as well as checking yearly, however do not provide guidance on which specific concentrations should be used as cut-off for supplementation [85]. This review does provide comprehensive information on the types of vitamin D supplement available, nutritional sources, as well as dosing regimens for the treatment of rickets [85]. The European Society (ESPGHAN) have published guidance for children with UC, stating that there is insufficient evidence for supplementing all children on steroid therapy, but those with 25(OH)D concentrations less than 50 nmol/l should be provided with single high dose Stoss therapy (vitamin D3 300,000 to 500,000 IU) or regular supplementation (50,000 IU of vitamin D3 orally once weekly for 2 to 3 months, or 3 times weekly for 1 month), but they do not provide guidelines for testing frequency [86]. ESPGHAN have not provided recommendations in either of their consensus statements for the management of vitamin D in children with CD [87, 88]. The British PGHAN (BSPGHAN) have comprehensive recommendations available to their members relating to monitoring, concentration cut-offs, and supplementation, but these are not published, nor intended to be used as a guideline [89].

3. Discussion

This review reports that vitamin D deficiency is prevalent among children with IBD and may be associated with worse disease activity and subsequent increased symptomatology that reduces oral intake and increases GI losses. The reported benefits of optimal vitamin D to bone health, the immune system, the gut, and clinical outcomes suggest that vitamin D may play a substantial role in ameliorating the effect of CD and UC among children. Consistent guidelines in relation to diagnostic testing frequency, optimal concentrations, and treatment of sub-optimal vitamin D, are lacking but this may reflect the dynamic changes and emerging evidence within this field in recent years.

The evaluation of vitamin D status should be established as standard-of-care for all children with IBD, regardless of any existing disease related or environmental factors, as many will satisfy at least one risk factor for insufficiency. Children with IBD undergo frequent testing as part of their disease monitoring so the additional assessment of vitamin D status should not pose a significant burden to them

While reducing disease activity, ensuring optimal dietary intake, and maximizing UV exposure, will contribute to maintaining vitamin D, many children with IBD will require restoration and maintenance using supplementation. Review of the current literature suggests that clearer guidance and strategies are needed for correcting hypovitaminosis D among children with IBD. However, the recent work highlighting the serum concentrations required for clinical benefit could be utilized as a therapeutic target for all children as opposed to supplementing on an individual basis as required.

The role of vitamin D as an inexpensive concomitant treatment warrants extensive investigation as there is still much to be learned about the vitamin D pathway and its capacity to affect the progression of CD and UC among children. The direction of future research may include investigation in to vitamin D metabolites as biomarkers, as well as measuring vitamin D absorption in order to optimize dosing and therapy, and further defining optimal concentrations for clinical benefit [12]. Work on the vitamin D axis, incorporating the vitamin D receptor and binding protein, may elucidate the importance of measuring these variables to determine their role in the pathogenesis of hypovitaminosis D and the clinical course of IBD, as well as being a target for treatment [39, 47, 90].

4. Conclusion

This review has added to the literature regarding this topic by providing an overview of the substantial research available, and highlighting that many aspects need further work to confirm relevance or determine importance. Due to the complex association between vitamin D and IBD, it remains unclear whether insufficiency in this population is causative of poor outcomes, or a consequence of the disease process. Large scale studies with well-established control groups are needed in order to elucidate this matter as the path of future research within this field will elicit heterogeneous outcomes until directionality is determined.

Author Contributions

All named authors made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. All named authors revised the work critically for important intellectual content and gave approval for the final draft to be published. All named authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing Interests

The authors have declared that no competing interests exist.

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