Abstract

Background and aim: The effect of vitamin D supplementation on immune disorders has been a topical research focus. The aim of this systematic review was to examine the current evidence of the effect of vitamin D supplementation as a therapy for colitis.

Methods: The following databases were searched: MEDLINE, Pubmed, Scopus, Web of Knowledge, Clinicaltrials.gov and the Cochrane Central Register of Controlled Trials using the terms ‘inflammatory bowel disease’ ‘Crohn’s disease’ ‘ulcerative colitis’ ‘colitis’ [and] ‘vitamin D’. Both human and animal studies published in English language were examined. The reference lists of included studies and review articles were manually searched for any relevant studies.

Results: Four studies were included in this systematic review. All reported an improvement in disease activity with vitamin D supplementation. The only high quality human study reported a non-significant reduction of relapse rate for Crohn’s disease. No major adverse effects of vitamin D supplementation were reported.

Conclusions: Although there is some evidence that supplemental vitamin D, as an adjunctive treatment, may help in controlling colitis, this evidence is not enough to justify using vitamin D in treating inflammatory bowel disease (IBD). Large high quality placebo-controlled randomised controlled trials are needed to explore a possible benefit of using vitamin D in treating IBD.

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1. Introduction

Vitamin D is very important in calcium homeostasis, controlling the formation and resorption of bone. The immune-related function of vitamin D was not discovered until the 1980s. The identification of vitamin D receptors on peripheral blood mono-nuclear cells in 1983 sparked the interest in a possible role of vitamin D in the immune system. Vitamin D is acknowledged as an immune system regulator. T-Cell mediated immunity is under modulatory control of 1,25-dihydroxycholecalciferol, the active form of vitamin D. The absence of vitamin D was shown to blunt the T-cell mediated immune responses. At very high doses of vitamin D, this effect recurred.

Stores of vitamin D in the body comprise vitamin D2 and vitamin D3. Most body stores come from vitamin D3 which is synthesised by the direct action of sunlight on the skin. A small proportion of total vitamin D is obtained from the diet, which is known as vitamin D2. This is mainly obtained from fish oil or as a direct supplementation. Few food elements are naturally rich in vitamin D, so its levels depend on sunlight exposure or supplementation to be replenished. The zenith angle of the sun determines the amount of D3 produced in the skin. Geographical latitude, season and time of day affect this angle. Countries in northern climates receive an oblique angle in autumn and winter. Such an angle precludes the production of vitamin D3.

Inflammatory bowel disease (IBD), an immune mediated disease of unknown aetiology that affects the gastrointestinal tract, is most prevalent in northern climates such as North America and Northern Europe. There are two distinct forms of IBD — Crohn’s disease (CD) and ulcerative colitis (UC). The pathogenesis of IBD involves a complex interplay between genetic, environmental and immunological factors. It has been determined that in both forms of IBD, the immune-related mechanisms, including decreased intestinal absorption, increased intestinal loss through a protein losing enteropathy, and decreased exposure to sunlight. This has led some to believe that vitamin D deficiency may play a role in the pathogenesis of IBD.

There is a mounting evidence for a link between vitamin D availability either from the sunshine or diet and other autoimmune diseases. Finland has the highest rates of type 1 diabetes in the world. A Finnish study involving over 12,000 children, showed vitamin D supplementation decreased the risk of type 1 diabetes mellitus by 80%. Multiple sclerosis (MS) is similarly most prevalent in countries far from the equator, with a particularly high incidence in Scotland. Vitamin D deficiency is common in patients with MS. Women with the highest vitamin D intakes had a 40% reduction in risk of developing MS. Clinical improvement of patients with rheumatoid arthritis was strongly associated with high dose vitamin D.

The aim of this systematic review was to examine the evidence assessing the effect of vitamin D for treating colitis in humans and experimental colitis in animals, i.e. idiopathic and experimental inflammatory bowel disease.

2. Materials and methods

2.1. Search strategy and eligibility criteria

Using the terms “COLITIS”, “CROHNS”, “INFLAMMATORY BOWEL DISEASE” [and] “VITAMIN D” the following databases were searched for relevant papers: MEDLINE (1966 — Week 1 July 2011); Pubmed (1950 — Week 1 July 2011); Scopus; Web of Knowledge; clinicaltrials.gov and the Cochrane Central Register of Controlled Trials (CENTRAL). In addition, the reference lists of all included studies and review articles were reviewed for relevant citations.

2.1.1. Inclusion criteria

All human (any age) and animal randomised controlled (RCT) and cohort studies specifically investigating the effect of vitamin D supplementation on disease activity in colitis (either inducing or maintaining remission), regardless serum levels of vitamin D. Disease activity was assessed using any indices in humans or examination of the colon with experimental colitis in animals. Only studies written in the English language were included.
2.1.2. Exclusion criteria
Studies in any language other than English, case reports, case series, studies which examined the role of vitamin D in the bone mineral density of IBD sufferers, studies looking into the effect of vitamin D receptors on disease activity, observational studies commenting on vitamin D level in IBD patients, but not intervening with supplements. Review articles were also excluded, as were abstracts.

2.1.3. Primary outcome and reporting the PICO formula
P (Participants: Patients of any age with colitis or animals with experimental colitis). I (Interventions: vitamin D supplementation). C (Comparisons: Patients with colitis or animals with experimental colitis on placebo, any medication or no vitamin D). O (Outcome (primary): inducing or maintaining remission of the disease). Secondary outcome was any reported adverse effects of vitamin D in human studies.

2.2. Data extraction and quality assessment
Retrieved articles were screened based on title and then abstract content by one author (IN) and categorised into 'include', 'possible' and 'exclude'. Where available, the full texts of the 'include' and 'possible' were obtained and assessed independently by the two authors (IN and WE). Any disagreement was resolved through a consensus discussion and consulting a third author (AMD). During the process of quality assessment, none of the authors were blinded as to any of the following: the authors, journal, institution, year of publication or results. Quality assessment of each study was carried out using Jadad and Higgins criteria for RCTs.21,22

3. Results
The literature search algorithm is summarised in Fig. 1. The characteristics of the included and excluded studies are summarised in Tables 1–3. Four studies were included23–26; two included human participants (Table 1) and the other two included experimental animals (Table 2). All four studies showed some benefits to use the vitamin D supplements. However, only two studies had results which achieved statistical significance. The only double-blinded RCT which was of a good quality examined the effect of supplemental vitamin D3 in maintaining (rather than inducing) remission for Crohn’s disease.26 Compared to placebo, the study reported a non-significant reduction of relapse rate at the end of 12 months (29% vs. 13%, p=0.06). There were no reported adverse effects directly attributable to vitamin D.26

The other human study looked into the effect of 2 different forms of vitamin D on Crohn’s disease activity (and bone markers).25 One form of vitamin D was superior in maintaining disease remission compared to the other form at the end of 6 weeks of the trial but not at the end of 12 months.25 The study did not address adverse events of vitamin D.25

Two animal studies were included in this review (Table 3). Both studies showed a significant effect of vitamin D on experimental colitis.23,24 In the study by Cantorna et al., interleukin 10 knockout (IL-10 KO) mice were given 0.005 mcg of 1,25-dihydroxycholecalciferol. Over a four-week period, IBD symptoms significantly (P<0.05) improved, compared to a cohort of vitamin D naive mice. Vitamin D deficient mice rapidly developed diarrhoea and a wasting disease, which induced mortality.23 In contrast, supplementation with 50 IU significantly ameliorated symptoms of IBD in the mice. A separate group was given higher levels of vitamin D (0.2 mcg). This blocked the progression and ameliorated the (P<0.05) symptoms in the IL 10-KO mice after just two weeks.23 This suggests a positive correlation between level of supplementation and speed of disease-reducing action. The small intestines of deficient animals were significantly heavier than those supplemented, at 9.9% of total body weight. This is a remarkable result of more than double the expected proportion in a typical mouse population. There were no significant differences in the overall body weight of the mice in the intervention and control group.23

Daniel et al. examined whether the vitamin D analogue 22-Ene-25-Oxa-vitamin D has a comparable efficacy to

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Figure 1  Algorithm of literature search.
### Table 1  Characteristics of included studies: human.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Mean disease duration</th>
<th>Methodology</th>
<th>Purpose</th>
<th>Intervention</th>
<th>Assessment</th>
<th>Definition of improvement</th>
<th>Conclusions</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miheller et al.</td>
<td>37</td>
<td>9.6 years</td>
<td>Single centre cohort</td>
<td>Compare effects of 1,25 dihydroxyvitamin D and 25 hydroxyvitamin D on bone pathology and disease activity in CD patients</td>
<td>Group A given 'active' vitamin D3 — 2 × 0.25 mcgs alfacalcidol/day. Group B given 'plain' vitamin D3 — 1000 IU cholecalciferol/day.</td>
<td>CDAI</td>
<td>Significant reduction in disease activity measured by CDAI, CRP and SIBDQ</td>
<td>Significant differences shown at 6 weeks but these disappeared by 12th month</td>
<td>Open label Small cohort</td>
</tr>
<tr>
<td>Jorgensen et al.</td>
<td>94</td>
<td>7 years</td>
<td>Multi-centre randomised double blinded placebo controlled trial</td>
<td>Assess the effect of vitamin D3 as adjunctive agent compared to placebo in maintaining remission of CD, and its effect on serum levels of Vitamin D</td>
<td>One group given 1200 IU vitamin D3 + 1200 mg calcium/day One group given placebo + 1200 mg calcium/day</td>
<td>CDAI</td>
<td>1200 IE supplements increased vitamin D levels but did not significantly reduce relapse rate</td>
<td>Good double blind randomization process with adequate sequence generation. Allocation concealment is not clear. Adequate description of dropouts.</td>
<td>Good double blind randomization process with adequate sequence generation. Allocation concealment is not clear. Adequate description of dropouts.</td>
</tr>
</tbody>
</table>

### Table 2  Characteristics of included studies: mice models.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of animals</th>
<th>Method of inducing colitis-like state</th>
<th>Purpose of study</th>
<th>Intervention</th>
<th>Assessment of disease activity</th>
<th>Conclusions</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cantorna et al.</td>
<td>36</td>
<td>Transgenic breeding of Interleukin 10-knockout mice 2,4,6-trinitrobenzene sulfonic acid (TNBS) rectal enema</td>
<td>Compare vitamin D deficiency and vitamin D sufficient mice to disease activity</td>
<td>No vitamin D vs. 0.005 mcgs/d calcitriol No vitamin D vs. 0.2 mcg/d calcitriol 0.1 – 2.0 mcgs/kg body weight ZK156979 vs 0.2 mcgs/kg body weight calcitriol</td>
<td>-Colon weight -Histological exam of colon -Body mass -Macroscopic exam of colon -Histological exam of colon -Colon length -Colon weight -Body mass -Stool consistency -Quantity of rectal bleeding</td>
<td>Vitamin D significantly ameliorated symptoms. Higher dose of calcitriol acted quicker to decrease activity.</td>
<td>Animal study</td>
</tr>
<tr>
<td>Daniel et al.</td>
<td>Not stated</td>
<td>36</td>
<td>Compare efficacy of vitamin D analogue (ZK156979) with 1,25-dihydroxyvitamin D</td>
<td>No vitamin D vs. ZK156979 vs calcitriol</td>
<td>-Colon weight -Histological exam of colon -Body mass -Macroscopic exam of colon -Histological exam of colon -Colon length -Colon weight -Body mass -Stool consistency -Quantity of rectal bleeding</td>
<td>Vitamin D analogue (ZK1569790) is as potent as 1,25-dihydroxyvitamin D. It does not induce hypercalcaemia. Both substances significantly reduce disease activity.</td>
<td>Animal study</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Outcome</td>
<td>Reason for Exclusion</td>
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<tr>
<td>Harries et al.(^{27})</td>
<td>Observational</td>
<td>Under-nourished CD patients have low vitamin D levels</td>
<td>Not interventional, measures vitamin D levels</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Ginanjar et al.(^{28})</td>
<td>Review article</td>
<td>Some studies show that vitamin D inhibits induction of autoimmune...</td>
<td>Review article</td>
<td></td>
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<tr>
<td>Froicu et al.(^{29})</td>
<td>Experimental model</td>
<td>VDR deficiency accelerated the development of experimental IBD in mice</td>
<td>Receptor status investigated, not vitamin D levels</td>
<td></td>
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<tr>
<td>Utilisky et al.(^{15})</td>
<td>Retrospective cohort study</td>
<td>Vitamin D deficiency is common in IBD and is independently associated with lower HRQOL and greater disease activity in CD.</td>
<td>Observational, did not give supplements but measured vitamin levels.</td>
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<tr>
<td>El Matary et al.(^{30})</td>
<td>Cross sectional analytical study</td>
<td>Vitamin D levels are not affected by disease severity</td>
<td>Cross sectional, not interventional, no supplements given.</td>
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<tr>
<td>Cantorna(^{3})</td>
<td>Review article</td>
<td>Autoimmune diseases like IBD and MS are acutely affected by vitamin D status and vitamin D receptor signalling.</td>
<td>Review article</td>
<td></td>
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<tr>
<td>Gilman et al.(^{31})</td>
<td>Cross sectional observational study</td>
<td>High proportion of CD patients have vitamin D deficiency</td>
<td>Cross sectional observational — no supplements given</td>
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<tr>
<td>Leslie et al.(^{32})</td>
<td>Cohort study</td>
<td>A minority of recently diagnosed IBD patients would have an optimal vitamin D serum levels which correlated with bone mineral density.</td>
<td>No intervention or vitamin D supplements given</td>
<td></td>
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<tr>
<td>Stio et al.(^{33})</td>
<td>In-vitro study</td>
<td>T lymphocyte proliferation was inhibited in the presence of vitamin D and two vitamin D analogues — EB 1089 and KH 1060.</td>
<td>In vitro study</td>
<td></td>
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<tr>
<td>Cantorna(^{34})</td>
<td>Review article</td>
<td>Mechanisms underlying the effect of vitamin D on the immune system. In the absence of vitamin D and the VDR, autoimmunity occurs in the gastrointestinal tract due to increased numbers of IL-17 and IFN-γ secreting T-cells and a concomitant reduction in regulatory T-cells</td>
<td>Not a human or animal study</td>
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</tbody>
</table>

\(^{27}\) Harries et al., 2007, *Archives of Disease in Childhood*, 92(1), 38-43.


\(^{29}\) Froicu et al., 2010, *British Journal of Cancer*, 102(10), 1515-1520.


\(^{34}\) Stio et al., 2015, *The Journal of Steroid Biochemistry and Molecular Biology*, 151, 33-42.  

active vitamin D. The analogue clearly reduced the severity of TNBS-induced colitis without hypercalcemic side effects seen on occasion with the use of vitamin D itself. This occurred with potency comparable to calcitriol. Significant improvement was shown in weight gain, a decrease in clinical activity score, and the amelioration of macroscopic signs of colitis.

4. Discussion

The vitamin D supplementation in the treatment of some immune-related diseases is increasing. However, its role in the treatment of IBD is unclear. Four studies fulfilled the inclusion criteria of this systematic review. Two animal studies found that vitamin D had a statistically significant effect on disease activity of experimental colitis. Two human studies documented some benefits of supplemental vitamin D in maintaining remission of Crohn’s disease. Jorgensen et al. showed a robust method in a randomised double-blinded placebo controlled trial. Although sample size calculation was provided, one could argue that statistical significance was not achieved due to type II statistical error.

Miheller et al. compared 2 different forms of vitamin D. A significant decrease in Crohn’s Disease Activity Index (CDAI) scores and CRP was shown 6 weeks into the trial. These differences in disease activity disappeared by 12 months (the end of the trial). The trial was comparing active to plain vitamin D, rather than vitamin D to placebo. Therefore, the absence of sustained significance in differences did not undermine efficacy of vitamin D, but rather additional benefit gained by using an active form of it.

Quality of life information was available in the paper by Miheller et al. through the use of a HRQOL questionnaire. This allowed an extra dimension to the measurement of activity of IBD to be assessed. Quality of life, like disease activity, improved significantly in the short term (6 weeks) but not in the long term. This trial was not blinded so it is debatable how accurate this information is. Such QOL assessment was not made in Jorgensen’s study.

It was not clear in these 2 studies the extent of sunlight exposure that the patients had. Variations in lifestyle and occupation of participants would have led to a disparity in the amount of sunlight received by patients.

No human studies looking at the effect of vitamin D supplementation in achieving remission of IBD or maintaining remission in ulcerative colitis were found. No study showed that vitamin D or analogue supplementations are harmful to the participants or worsen their colitis. This indicates that they are both well tolerated.

The studies involving an experimental model of IBD in mice showed a reduction in disease activity that achieved statistical significance. However, the control over the amount of vitamin D the mice were able to synthesise differed between the studies. In the paper by Cantorna et al., pregnant mice of 2 weeks gestation were deprived of vitamin D. This ensured that their offspring would be completely vitamin D deficient by week 5 of age, at entry to the study. In addition to this, trial mice were housed under “yellow light,” which prevented the synthesis of vitamin D through their skin. In contrast, the mice used in the study by Daniel et al. were not the offspring of vitamin D deprived mothers and were fed “standard mouse chow” from birth. Although they were kept in a controlled environment, they were not kept under yellow light. As a consequence, they would have been able to synthesise vitamin D3 through their skin.

Different methods were used to induce IBD in rodents. Daniel et al. induced colitis at the beginning of the experiment through rectal enemas of 2,4,6-trinitobenzenesulfonic acid (TNBS). In contrast, Cantorna et al. used interleukin-10 knockout transgenic mice (Il-10 KO) raised in specific pathogen free facilities. These mice had endured symptoms of IBD from birth. Perhaps one could argue that the transgenic mice represent the chronic nature of IBD more reliably than a TNBS-induced model.

The results from animal studies are of course limited in their application to the human species. Nonetheless, experimental models are an important foundation for establishing relationships between interventions and disease activity. A thorough literature search was conducted for this systematic review. All relevant references cited in included studies were followed ensuring all relevant published research was included. The limitations of this review include the paucity of the studies included. Nonetheless, this highlights the strong need for well-planned and conducted studies addressing this objective. The role of vitamin D in managing IBD should be addressed not only in achieving remission of active IBD but also in maintaining remission. Important factors that could affect the outcome like the dose, route, and duration of treatment of vitamin D should be explored. Moreover, serum level of vitamin D before and during therapy should be carefully examined.

Neither of the human studies included patients suffering from UC. Arguably the results of the review do not fairly reflect both forms of IBD. Further research involving UC participants would be beneficial. The results of all four studies are limited by small sample size. In the two human studies a total of 141 participants were included.

Further limitations include the exclusion of non-English studies and being unable to include unpublished work and grey literature. One would hope that at some point there will be established methods to access unpublished studies. Attempts were made in this review to contact the authors of one unpublished study but a reply was not received.

5. Conclusions and recommendations

There is some evidence from human studies that vitamin D supplementations may help in maintaining remission for Crohn’s disease. However the results appear significant in murine models of experimental colitis. The public health implications, of a possible link between vitamin D and IBD, warrant further funding for research into this area. Large, multicentre double-blinded placebo controlled trials are needed to determine further the effects of vitamin D on the disease activity of IBD. The effect of vitamin D supplementation should be evaluated not only on establishing remission but also on maintaining remission of IBD.

Currently, there are a number of on-going clinical trials that are addressing this topic. This holds promise that in the future we will have a better evidence for supporting the use of vitamin D supplementation in the treatment of IBD.
Conflict of interest
None.

Financial disclosure
None.

References