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Is vitamin D supplementation a viable treatment for Crohn's disease?

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Summary

Vitamin D, important for maintaining bone health in CD, may have potential as a treatment for the core inflammatory disease process. There is plausible evidence in favour of vitamin D as an anti-inflammatory from animal models, epidemiological and cross sectional studies of CD. Few clinical trials, however, have been published and therefore the translation of this promise into clinical benefit for people with CD remains unclear. The purpose of this piece is to consider the viability of vitamin D as a treatment for CD based on the current available evidence.

Keywords: Vitamin D, 25-hydroxyvitamin D (25OHD); Crohn's disease (CD); randomised controlled trial (RCT); dietary supplements.

Vitamin D Deficiency is Prevalent in CD

Vitamin D deficiency is common in CD, affecting an estimated 35-100% of patients across different populations and studies [1]. This is not surprising considering the high background prevalence of vitamin D deficiency among healthy populations combined with an increased risk of deficiency conferred by a chronic inflammatory intestinal disease. A high rate of deficiency is a concern for bone health, and a likely consequence of disease-related (low dietary intake, malabsorption) and generic factors (low sun exposure habits, northern latitudes) [1]. Nevertheless, deficiency alone does not imply therapeutic potential for vitamin D.

Vitamin D Deficiency May be a Risk Factor for Developing CD

Epidemiological studies [2, see 3-4 for review] show a higher incidence of CD in countries of more northern latitudes, mirroring sunlight patterns and likely vitamin D status. This finding is paralleled in other autoimmune diseases and cancer [5].

Although geographic location can reflect factors other than serum vitamin D levels, considered with more recent findings employing measured 25OHD [6], suggest that low vitamin D status may be associated with increased risk of developing CD. While this is an interesting hypothesis in terms of disease initiation and pathogenesis, risk factors are not necessarily viable therapeutic targets.

Vitamin D Deficiency is Associated with Disease Activity in CD

Several cross-sectional studies report an association between circulating vitamin D [25-hydroxyvitamin D, (25OHD)] concentrations and more severe and/or more active CD, but the data are inconsistent [3,4]. Studies differ considerably in terms of design, patient cohorts and the variables used to capture disease activity, and a consistent core outcomes set is lacking across studies. For example, results vary depending on whether the Crohn's disease activity index (CDAI), Harvey Bradshaw Index, C-Reactive Protein (CRP) or other severity markers were applied, although the association between 25OHD and intestinal inflammation as measured by faecal calprotectin [7,8] may be more consistent. Collectively, observational studies appear to indicate a co-existence of lower vitamin D concentrations and more active/ severe disease, but cannot distinguish 'cause and effect'. The important question remains, that is, whether or not interventions to raise 25OHD levels would modify disease activity or relapse rates in these cohorts.

Can Vitamin D Supplementation Reduce the Risk of Relapse in CD?

Few randomised controlled trials (RCTs) have been published on the effects of vitamin D supplementation in preventing relapse or inducing remission in CD. The largest trial, conducted by Jorgensen et al [9], showed a non-significant reduction in relapse rates in CD patients treated with 1200 IU vitamin D_3 daily for 12 months. Patients were in clinical remission at enrolment and the relapse rates were 12% and

29% in the vitamin D and placebo groups respectively (p=0.06). This study was of good size (n, 98), but showed fewer relapses than anticipated by the authors at 12 months, of note also was the relatively high 25OHD levels at enrolment, as discussed later; and while clinical relapse is an important endpoint, endoscopic score or faecal calprotectin would be of interest in future studies. A recent pilot RCT, [9] (n, 28) showed that 3 months administration of 2000 IU oral vitamin D_3 daily appeared to prevent deterioration in intestinal permeability in the treated group, however, longer follow-up would be required to determine effects on clinical relapse.

While most studies use the traditional approach of a fixed daily dose of vitamin D supplement, Yang et al [11] focussed on achieving a target circulating 25OHD level of 100 nmol/L using an escalated dose of vitamin D_3 up to 5000 IU daily. This study, comprising patients (n 18) with mild to moderately active CD, showed a significant reduction in CDAI scores at 6 months [11] but was limited by the absence of a control group. A further open-label study [12] (n, 37) reported a significant short term reduction in disease activity (CDAI and CRP) in response to either 1000 IU oral D_3 daily or the active form of vitamin D, although the primary focus of the study was on bone markers. Currently there is insufficient RCT evidence to recommend vitamin D therapy, judging from studies in progress (clinicaltrials.gov), however, new data should be emerging to address this gap.

Vitamin D as Therapy: Baseline 25OHD Levels and Clinical Outcomes

Nutrient treatments pose several challenges compared with pharmaceutical trials where, for example, the placebo group is typically unexposed to the therapy of

interest [13]. A therapeutic response to vitamin D supplements is likely to depend on the individual's basal vitamin D status.

Published RCTs to date were amongst patients with reasonable baseline 25OHD concentration at study enrolment (69 nmol/L for both Jorgensen et al [9] and Raftery et al [10], where ≤50 is considered suboptimal [14]). It is plausible that supplementation in a vitamin D deficient CD group would show greater benefit compared to a replete group. This concept is supported by evidence from RCTs in other diseases. For example Martineau et al [15] showed that vitamin D_3 treatment in chronic obstructive pulmonary disease protected against mild/moderate exacerbation only in patients with low baseline vitamin D (25OHD ≤ 50nmol/L). The response to supplementation targeted at vitamin D deficient patients needs to be tested in CD.

Vitamin D as Therapy: Post-treatment 25OHD Levels and Clinical Outcomes

While circulating 25OHD of 50 nmol/L is considered adequate for bone health [14], it is argued that immunomodulatory and other non-skeletal effects require concentrations above 75 nmol/L or higher [16, 17]. In current RCTs [9,10], mean post-treatment 25OHD was between 90-100 nmol/L, with baseline levels reasonable on enrolment in these studies. Targeting the level of 25OHD rather than focussing on a fixed uniform dose, similar to Yang et al [11], in a randomised controlled manner would be informative. Taken together, intervention studies have on average achieved 25OHD levels within what is postulated as a 'therapeutic zone'. Although vitamin D toxicity is rare, at the extremes of circulating 25OHD concentrations, outcomes tend to be unfavourable, and may show a U-shaped distribution, but this itself remains an issue of debate [13]. It seems logical that levels at baseline, post-

treatment and the magnitude of change in 25OHD concentrations are important considerations in understanding the therapeutic response to vitamin D.

Other Factors that may Predict Response to Vitamin D Therapy

Vitamin D supplementation as a treatment for CD has primarily been administered as an adjunct to standard medical therapy; whether the nature of the concomitant drug therapy influences the outcomes is not known. Recently, an association between vitamin D levels and response to biologics [18] has been suggested. Furthermore, host factors such as phenotype or genotype may predict response, (for example NOD-2 or genetic variants associated with low 25OHD) suggesting scope for a personalised or tailored treatment approach. Consistent with this, an RCT in tuberculosis reported that adjunctive vitamin D therapy was more effective in participants with the tt genotype of the TaqI vitamin D receptor polymorphism [19].

Vitamin D as Therapy – Possible Biological Mechanisms in CD

There is plausible evidence from animal models that vitamin D reduces intestinal inflammation [20, 21], supresses tumour necrosis factor-alpha (TNF-α) and interferon gamma (IFNγ) and induces IL10 [20]. Consistent with this, increased IL-10 and reduced IFNγ [for review see 3-4] has been documented in human CD, however, others [11] failed to detect changes in cytokine profiles in response to vitamin D treatment. Recently, direct effects of vitamin D action on the intestinal barrier and junctional proteins have been reported primarily in animal models [22] although preliminary work in human CD [10] may support this hypothesis. Newer directions include the effect of vitamin D as a regulator of late immune responses [21], in autophagy [23] on the gut microbiome [20] as well as non-vitamin effects of sunlight (UV-A). Clinical studies, tend to focus on circulating 25OHD, however, there remains

a major gap in the current knowledge regarding the relationship between circulating vitamin D concentrations and the regulation of vitamin D pathways at a tissue and cellular level in Crohn's, and other diseases.

Research Agenda and Future Directions

If proven effective, clinical application for vitamin D treatment might focus more on vitamin D levels rather than on standard doses; or on preventing deficiency as part of lifestyle advice rather than 'treatment'. Vitamin D supplementation is not an entirely new departure in CD management, as current guidance recommends 800 IU vitamin D_3 daily for bone health [24] for patients prescribed corticosteroids. Therefore, relapse prevention this may fit within an extension of current recommendations. In the meantime, for people with CD, it is sensible to recommend, as a minimum, the prevention of vitamin D deficiency.

Currently, there are insufficient clinical studies (RCTs) to judge if vitamin D supplementation translates into a viable treatment for CD; observational studies, though interesting, may simply reflect that low vitamin D is a biomarker of more severe/ active CD. And if active disease is treated, then vitamin D levels may increase [25]. There is an ongoing need for data from high quality well-designed clinical trials that allow analysis by basal 25OHD levels, changes in vitamin D status and that use core outcome sets, along with the publication of negative findings and small trials to allow meta-analysis. This should assist decision making as to whether or not anti-inflammatory effects attributed to vitamin D translate into clinical benefits for patients with CD.

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* = of interest; ** = of considerable interest

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