Major Considerations and Outcomes of Clinical Studies on Vitamin D Deficiency in Patients with Crohn’s

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Introduction: The literature shows a bimodal incidence of Crohn’s disease in relation to age, with peaks from 15-40 and from 50-80 years and more women have Crohn’s disease than men. Clinical studies have shown a direct correlation of vitamin D deficiency with Crohn’s disease.

Objective: Using a systematic review, the objective of this study was to identify the main correlations and outcomes of clinical studies about vitamin D in Crohn’s disease.

Methods: Following the rules for systematic reviews (PRISMA), the key search terms used were Crohn’s disease, vitamin D, clinical studies, immunotherapy and quality of life. After applying exclusion criteria, 117 articles were included and discussed in this study.

Conclusion: The prevalence of low serum vitamin D levels has been demonstrated in patients suffering from Crohn’s disease. However, further studies that are more comprehensive are still needed, in particular investigations that aim to evaluate the effects of serum vitamin D levels on clinical treatment and the effects of vitamin D supplementation on disease activity and mucosal healing. Thus, it may be possible to optimize the treatment of Crohn’s disease patients thereby improving their quality of life.

Keywords: Crohn’s disease; Vitamin D; Clinical trials; Immunotherapy; Quality of life

As vitamin D plays a significant role in modulating the immune system in the intestine, it is possible that its deficiency could impair the function of the intestinal barrier favoring the translocation of endotoxins such as lipopolysaccharides (LPSs) into blood circulation. LPSs are known to promote low-grade inflammation, which predisposes the patient to insulin resistance [19,21]. Numerous circulating biomarkers have been used to assess clinical inflammation and for research purposes [22,23].

Certain compositions of the intestinal microbiota have been associated with systemic inflammation and metabolic disorders. Particularly, gram-negative bacteria, which contain LPS in their outer layer, have been shown to stimulate immune response and to provoke metabolic endotoxemia, while other genera, such as bifidobacteria, reduce endotoxemia [18]. Despite being gram-negative, Akkermansia was found to improve the intestinal barrier function and to induce beneficial metabolic effects [24].
Vitamin D deficiency and the lack of VDR have been associated with intestinal dysbiosis and increased susceptibility to intestinal diseases [25-27]. Few studies have investigated whether vitamin D status contributes to disorders of the glucose metabolism by modulating the composition of the intestinal microbiota [28-30]. A better understanding of the underlying mechanisms of cardiometabolic diseases is important in respect to their impact on population mortality rates.

The Nutritionist Health Study (NutriHS) was designed to evaluate new biomarkers and predictors of Crohn’s disease outcomes with this study collecting a variety of retrospective and prospective data [31]. Because of the importance of the response of the intestinal immune system to microbial stimulation and the immune modulatory role of vitamin D, it has been hypothesized that the vitamin D status is associated with the intestinal microbiota due to low-grade inflammation. In the NutriHS, the associations between vitamin D intake and 25-hydroxyvitamin D \([25(OH)D]\) concentrations were examined in relation to fecal microbiota composition, inflammatory markers and the biochemical profile of young adults [30-32].

Therefore, using a systematic review, the present study aimed to investigate the main correlations and outcomes of clinical studies about vitamin D and Crohn’s disease.

**Strategy of Search and Design**

Following the rules of the PRISMA methodology (Preferred Reporting Items for Systematic Reviews and Meta-Analyses - http://www.prisma-statement.org/), the key search terms were Crohn’s disease, vitamin D, clinical studies, immunotherapy and quality of life. The literature research was conducted using the PubMed, Periodicos.com and Google Scholar online databases.

**Article Eligibility**

One hundred and sixty-two articles were found related to Crohn’s disease and vitamin D. Initially, duplicate articles were excluded and the titles of articles were read to confirm their importance to this study. Subsequently, the abstracts were evaluated and more articles were excluded. One hundred and twenty-two articles were read with 117 that fulfilled the inclusion criteria being included and discussed in this study, according to Figure 1.

**Literature Review and Discussion**

The effect of vitamin D on the immune system translates into increased innate immunity associated with multifaceted regulation of acquired immunity [33]. A relationship between vitamin D deficiency and the prevalence of some autoimmune diseases such as Crohn’s disease has been demonstrated. The literature shows a bimodal incidence of Crohn’s disease in respect to age with two peaks corresponding to 15-40 years and from 50-80 years [34-37]. There is also agreement about gender involvement with a higher percentage of affected women [38,39].

The findings of the vast majority of published studies corroborated the prevalence of vitamin D deficiency in Crohn’s disease; the mean serum vitamin D level among patients with Crohn’s disease varied from 13.1-27 ng/mL whereas the Control Group had adequate serum vitamin D levels [40-42].

The primary source of vitamin D depends on exposure of the skin to sunlight with up to 20.0 % coming from ingestion. It is still controversial as to whether the consumption of foods containing vitamin D has a direct impact on circulating levels [43-48]. Vitamin D2 (ergocalciferol) is found in yeast, mushrooms and some vegetables and vitamin D3 (cholecalciferol), synthesized in the skin by ultraviolet radiation, is found in foods of animal origin [49].

To be biologically active, vitamin D undergoes hydroxylation in the liver mediated by 25-hydroxylase and in the kidney by 1α-hydroxylase. 1,25-dihydroxyvitamin D is recognized by its specific receptors (VDR) in different cells, primarily in the gut to increase calcium uptake and in the bone to regulate skeletal homeostasis [50,51]. Altered metabolic patterns result in metabolic disorders of calcium and phosphorus with vitamin D disorders having been implicated in some diseases [52].

Vitamin D plays important roles in innate and adaptive immune responses, in the cell cycle and in metabolic processes, evidenced by the reported relationship between its deficiency and the prevalence of...
immune-mediated disorders, cancer and cardiometabolic diseases [47,49-52]. An inverse correlation between vitamin D concentrations has been described in respect to the prevalence of obesity and type 2 diabetes mellitus [53,54].

VDR play a part in the production of β cells, endothelium, cardiac myocytes and renin suggesting a role for vitamin D in immune-mediated disorders, cancer and cardiometabolic diseases [55-57]. In addition, there is evidence that vitamin D deficiency increases inflammatory cytokines and reduces insulin sensitivity with both these conditions having been described as pathophysiological links in cardiometabolic diseases [58,59]. Metabolism-induced intestinal microbiota endotoxemia has been associated with increased cardiometabolic risk [60].

Vitamin D deficiency could increase the competitive advantage of Haemophilus and Veillonella, as these pathogens are found to be relatively more abundant in subjects with low compared to high intake with Crohn's disease with no evidence of in the control group [89].

In a study published in the Indian Journal of Medical Research in 2009, researchers at the Christian Medical College in Vellore, India compared serum vitamin D levels in 34 patients with Crohn's disease and 34 matched controls [93]. They found that not only were patients with Crohn's disease significantly more likely to have a poor vitamin D status than healthy patients, but lower levels of vitamin D were also significantly and independently correlated with increased disease severity [93].

Another study was conducted by researchers at the McGille University Health Center by the Universite de Montreal and published in the Journal of Biological Chemistry in 2010 [94,95]. In this study, the researchers found that vitamin D acts directly on the beta-defensin-2 and NOD2 genes, both of which have been associated with Crohn's disease. Beta-defensin-2 is known to encode an antimicrobial protein, while NOD2 helps to alert cells about the presence of invading microbes. Failure of NOD2 is known to prevent the immune system from reacting adequately to intestinal infections [96,97].

A study conducted by researchers at the University of Sheffield, England and published in the BMJ Case Reports in December 2012 suggests that vitamin D supplementation may help reduce the severity of inflammatory bowel syndrome (IBS) or even completely prevent it [98,99]. The research was motivated by a case study of a woman who suffered from IBS for 25 years and who had been unable to obtain consistent relief from all traditional or alternative therapies. After hearing that some people used mega-doses of vitamin D to treat IBS, the woman started a supplementation program that restored her digestive health to virtually normal [100-102].

The mechanism by which vitamin D deficiency occurs most frequently in IBD appears to be due to a combination of effects, such as low intake, vitamin D malabsorption and decreased exposure to the sun [103-110]. In an experiment of IBD using inactivated knockout mice, vitamin D deficiency accelerated the disease with earlier onset of diarrhea and cachexia and higher mortality [111-113]. On the other hand, treatment with 1-alpha, 25-Dihydroxyvitamin D3 [1-alpha, 25(OH)(2)D3] prevented the onset of symptoms and reduced progression and severity [114-116].

A study by Jahnssen et al. [117] found vitamin D deficiency in 27.0 % of patients with Crohn's disease and 15.0 % of those with ulcerative colitis. In this context, the researchers looked at Internet forums where IBS patients discussed vitamin D supplementation. They found that among the 37 patients with IBS who reported having used the therapy, 70 percent had significant improvements in their symptoms [103].

Conclusion
A high prevalence of patients suffering from Crohn's disease has low serum vitamin D levels. However, further studies are still needed, especially in respect to evaluating serum vitamin D levels in clinical treatment and also to investigate the effects of vitamin D supplementation on disease activity and mucosal healing. Thus, it will be possible to evaluate the true effects of vitamin D supplementation in the remission of Crohn's disease and to optimize the treatment of patients and improve their quality of life.
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8. Raftery T, O'Morain CA, O'Sullivan M (2012) Vitamin D: new roles and scientific advancements. I also thank ABRAN - Brazilian Association of Nutrology for all learning and optimization of knowledge.


