



Major clinical outcomes of vitamin D deficiency in inflammatory bowel diseases: a systematic and integrative review

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Abstract

Introduction: Clinical studies have proven the direct correlation of vitamin D deficiency in patients suffering from inflammatory bowel diseases, such as Crohn's disease, with an average age of 41 years and more frequently in women. Vitamin D seems to interact with the immune system through its action on the regulation and differentiation of cells such as lymphocytes, macrophages, and natural killer (NK) cells, in addition to interfering with the production of cytokines. **Objective:** It was to present, through a systematic review, the main clinical outcomes of the correlation of vitamin D deficiency and inflammatory bowel diseases, highlighting Crohn's disease. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from August to October 2022 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 207 articles were found, and 142 articles were evaluated and 117 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with a high risk of bias and 28 studies that did not meet GRADE. Most studies showed homogeneity in their results, with $R^2 = 95.7\% > 50\%$. It was shown that the highest prevalence of low serum levels of vitamin D is among patients suffering from Crohn's disease and other inflammatory bowel diseases when compared to a control group. However, more comprehensive studies are still needed, especially those that aim to evaluate serum vitamin D in values related to clinical treatment and also the effects of vitamin D

supplementation on disease activity and mucosal healing. Thus, it will be possible to evaluate in a relevant way, the replacement of vitamin D in the remission of Crohn's disease, optimizing the treatment of patients and corroborating the improvement in quality of life.

Keywords: Vitamin D. Hypovitaminosis D. Inflammatory bowel diseases. Crohn's disease. Immunodeficiency.

Introduction

The literature shows the bimodal incidence of Crohn's disease (CD) concerning age, affecting individuals from 15 to 40 years and 50 to 80 years [1-4]. Still, there is a higher percentage of women [5-12]. Clinical studies have proven the direct correlation of vitamin D deficiency in patients suffering from Crohn's disease, with an average age of 41 years, and more frequently in women [13-17]. A similar epidemiological finding was demonstrated by Ananthakrishnan et al. [18] and Azzopardi et al. [19]. Characteristics between groups, patients with Crohn's disease and the control group were similar.

In this context, CD is an inflammatory bowel disease characterized by chronic intestinal inflammation of an autoimmune nature and uncertain etiology [1-7]. However, there is evidence of the importance of the interaction between genetic and environmental factors in triggering the aberrant cellular immune response through Th1 cells, Th17 cells, and their professional inflammatory cytokines [7-11]. In the context of cellular immunity, the discovery of the presence of vitamin D receptor (VDR) in macrophages and lymphocytes opened a new path for the research of autoimmune diseases [7-13].

Vitamin D appears to interact with the immune system through its action on the regulation and differentiation of cells such as lymphocytes, macrophages, and natural killer (NK) cells, in addition to interfering with the production of cytokines in vivo and in vitro [14-17]. Among the demonstrated immunomodulatory effects, the following stand out: decreased production of interleukin-2 (IL-2), interferon-gamma (INF γ), and tumor necrosis factor (TNF); inhibition of IL6 expression and inhibition of secretion and production of autoantibodies by B lymphocytes [18-20].

As vitamin D plays a significant role in modulating the immune system in the intestine, it is possible that its deficiency could deteriorate the intestinal barrier function favoring the translocation of endotoxins such as lipopolysaccharides (LPSs) in circulation. LPSs are known to promote low-grade inflammation, which predisposes to insulin resistance [19,20]. Numerous circulating biomarkers have been used to assess clinical inflammation and for research purposes [21-23].

Certain gut microbiota compositions have been associated with systemic inflammation and metabolic disturbances. In particular, gram-negative bacteria, containing LPS in their outer layer, have been shown to stimulate the immune response and provoke metabolic endotoxemia, while other genera, such as Bifidobacteria, have been shown to reduce endotoxemia [18]. Despite being gram-negative, Akkermansia has been found to improve intestinal barrier function and induce beneficial metabolic effects [24].

Vitamin D deficiency and 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 disturbances of glucose metabolism by modulating gut microbiota composition [28-30]. A deepening understanding of the underlying mechanisms of cardiometabolic diseases is desirable considering their impact on population mortality rates.

The Nutritionist Health Study (NutriHS) was designed to evaluate novel biomarkers and predictors of Crohn's disease outcomes [31]. Collected a variety of retrospective and prospective data. Facing the importance of the intestinal immune system to respond to microbial stimuli, and the immune-modulatory role of vitamin D, it was hypothesized that vitamin D status is associated with the intestinal microbiota through low-grade inflammation. We examined the association between vitamin D intake and 25-hydroxyvitamin D concentration with fecal microbiota composition, inflammatory markers, and biochemical profile in young adult NutriHS participants [30-32].

In this sense, the present study presented, through a systematic review, the main clinical outcomes of the correlation between vitamin D deficiency and inflammatory bowel diseases, highlighting Crohn's disease.

Methods

Study Design

The present study followed a concise systematic review model, following the systematic review rules – PRISMA. Available at: www.prisma-statement.org/. Accessed on: 03/20/2023.

Search Strategy and Search Sources

The literary search process was carried out from September to October 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, addressing scientific articles from various eras to the present day. The descriptors (MeSH Terms) were used: "Vitamin D. Hypovitaminosis D. Inflammatory bowel diseases. Crohn's disease. Immunodeficiency", and using the Boolean "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

Quality was rated as high, moderate, low, or very low for risk of bias, clarity of comparisons, accuracy, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through the analysis of the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Results and Discussion

Summary of Findings

As a corollary of the literary search system, a total of 207 articles were found that were submitted to the eligibility analysis and, then, 117 of the 142 final studies were selected to compose the results of this systematic review. The listed studies showed medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies in types of study such as meta-analysis, consensus, randomized clinical trial, prospective and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with $R^2=95.7\%>50\%$. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with a high risk of bias and 28 studies that did not meet GRADE.

Figure 1. Flowchart showing the article selection process.

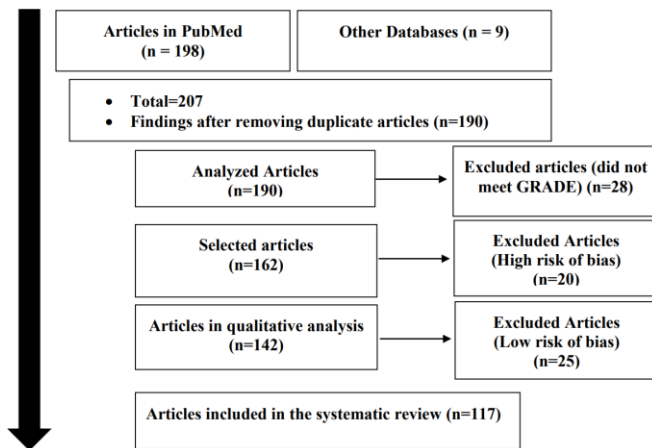
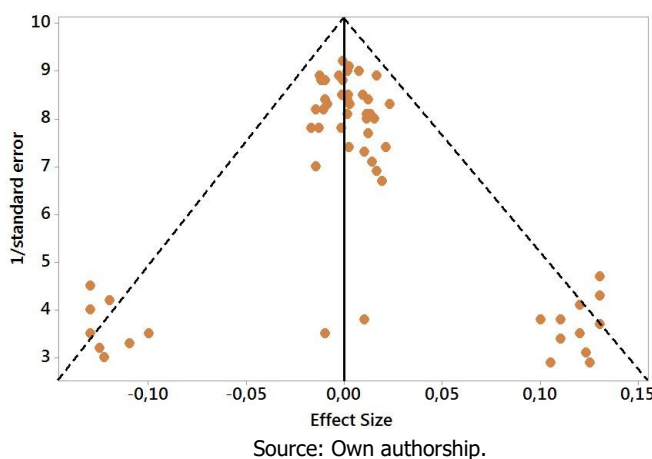


Figure 2 presents the results of the risk of bias of the studies through the Funnel Plot, showing the calculation of the Effect Size using the Cohen Test (d). Sample size was indirectly determined by the inverse of the standard error. This chart had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with small sample sizes (lower precision) that are shown at the bottom of the chart and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (n=117 studies).



Clinical Outcomes

The effect of vitamin D on the immune system translates into increased innate immunity associated with the multifaceted regulation of acquired immunity [22]. A relationship has been demonstrated between vitamin D deficiency and the prevalence of some autoimmune diseases such as Crohn's Disease. The

disease corroborated the findings of the vast majority of studies already published, demonstrating the prevalence of hypovitaminosis D. The average serum vitamin S among patients with Crohn's disease varied, in the literature, from 13.1 to 27 ng/mL [2,4-6,8,14,17]. However, the control group had serum levels of vitamin D considered adequate [33-39].

The primary source of vitamin D depends on the skin's exposure to sunlight and up to 20.0% comes from ingestion. It is still controversial whether the consumption of foods containing vitamin D has a direct impact on its circulating levels [40-48]. Vitamin D2 (ergocalciferol) is found in yeast, mushrooms, and some vegetables, and Vitamin D3 (cholecalciferol) in animal foods. The latter is synthesized in the skin employing ultraviolet radiation [49].

To be biologically active, vitamin D undergoes hydroxylation in the liver mediated by 25hydroxylase, and in the kidney by 1 α -hydroxylase. 1,25(OH)2D is recognized by its specific receptors (VDR) in various cells, mainly in the intestine to enhance calcium absorption, and the bone to regulate skeletal homeostasis [50,51]. Altered metabolic patterns result in calcium and phosphorus metabolic disturbances, but, as is well known, vitamin D disturbances have been involved in some other diseases [52].

Also, vitamin D plays important roles in innate and adaptive immune responses, cell cycle, and 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 their concentrations and the prevalence of obesity and type 2 diabetes mellitus has been described [53,54].

Besides, VDR results on β cells, endothelium, cardiac myocytes, and renin production suggest a role for vitamin D in these diseases [55-57]. Furthermore, there is evidence that vitamin D deficiency increases inflammatory cytokines and reduces insulin sensitivity, which has been described as pathophysiological links between cardiometabolic diseases [58,59].

Furthermore, metabolism induced by gut microbiota Endotoxemia has been associated with an increased cardiometabolic risk [60]. Given that vitamin D plays a role in modulating the immune system in the intestine, it is possible that its deficiency could deteriorate the intestinal barrier function favoring the translocation of endotoxins such as lipopolysaccharides (LPSs) into the circulation. LPS is a known low-grade inflammation that predisposes to insulin resistance [61,62]. Numerous circulating biomarkers have been used to assess clinical inflammation and research [63-65].

Added to this, a deficiency could increase the competitive advantage of *Haemophilus* and *Veillonella*, found to be relatively more abundant in the subset of individuals with low compared to the highest intake and concentration of vitamin D [1-4]. These gram-negative bacteria could explain the higher levels of LPS detected in this subset. On the other hand, a relatively small proportion of bacteria with a beneficial effect - such as the *Coprococcus* and *Bifidobacterium* genera - could activate the intestinal immune response and induce local inflammation, requiring compensatory anti-inflammatory pathways as dependent on the 25(OH)D [5-7, 66-73].

An inverse association of inflammatory markers and 25(OH)D was detected. The results support the role of vitamin D in maintaining immune system homeostasis, and we speculate that this occurs in part through interaction with the gut microbiota, although the study design precludes establishing cause-effect relationships [8, 65-68].

It was previously reported that vitamin D-deficient rats exposed to a bacterial pathogen exhibited increased translocation of endotoxins and production of inflammatory cytokines [41]. However, a recent Perspective study did not support a protective effect of vitamin D supplementation [42]. There is a significant inverse correlation of 25(OH)D with E-selectin and CRP concentrations, suggesting that even among healthy individuals, vitamin D status may warrant an anti-inflammatory condition. Several studies have reported that 25(OH)D plays a significant role in the immune system, linking higher serum levels as well as higher consumption with lower low-grade inflammation [43-46].

Furthermore, previous studies show that *Akkermansia muciniphila* is associated with effects on metabolic and inflammatory profiles [24,49]. In animal models, *A. muciniphila* benefits intestinal permeability, mucus layer thickness, and metabolism in obesity and type 2 diabetes [50]. Previously, *Haemophilus* was associated with inflammatory bowel disease and with LPS levels, and *Veillonella* with increased cytokine inflammation [51,52]. These gram-negative bacteria with a. The outer layer of LPS was less prominent in our subsets with the highest vitamin D intake and with the highest 25(OH)D; also the lowest concentration of LPS was found among the best vitamin D states [74-105].

Hypovitaminosis D and Inflammatory Bowel Disease (IBD)

IBD are immune-mediated diseases, whose pathophysiology also involves the participation of Th1 cells, producing IL-2, TNF- α , and IFN- γ . Decreased

serum levels of 25(OH)D have been described in IBD [106-116]. A study carried out by Jahnsen et al. [117] found vitamin D deficiency in 27.0% of patients with Crohn's disease and 15.0% of those with ulcerative colitis.

The mechanism by which vitamin D deficiency occurs more frequently in IBD appears to be due to a combination of effects such as low vitamin D intake and malabsorption, and less sun exposure [8, 81-84, 114-117]. In experimental IBD, using rats with inactivated IL-10 (knockout), vitamin D deficiency has been shown to accelerate the disease, with earlier onset of diarrhea and cachexia, in addition to higher mortality [85-88]. On the other hand, treatment with 1,25(OH)₂D₃ prevented the onset of symptoms, in addition to reducing their progression and severity [89-92].

In a study published in the Indian Journal of Medical Research in 2009, researchers from Christian Medical College, Vellore-India compared blood levels of vitamin D 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 poor vitamin D status than healthy patients, but lower vitamin D levels were also significantly and independently correlated with increased disease severity [93].

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

A study by researchers at the University of Sheffield, England, and published in the journal BMJ Case Reports in December 2012 suggests that vitamin D supplementation may help reduce the severity of IBS flare-ups or even prevent them altogether [98,99]. The research was prompted by a case study of a woman who had suffered from IBS for 25 years and who had been unable to get consistent relief from all traditional or alternative therapies. After hearing that some people used mega-doses of vitamin D to treat IBS, the woman began a supplementation program that restored her digestive health to nearly normal [100-102].

In this context, researchers searched Internet forums where IBS patients discussed vitamin D supplementation. They found that, among the 37 patients who reported using the therapy, 70 percent

showed significant improvements in their IBS symptoms [103]. Also, a prospective study, with statistical analysis of serum vitamin D values measured between April 2014 and April 2015 in patients with Crohn's disease. Individuals with mild anal complaints, without any colorectal involvement, made up the control group. A total of 104 patients were evaluated, whose mean age was 40.6 years, 56 (53.8%) women and 48 (46.2%) men. The average serum vitamin D level was 21.6 ng/mL, with a standard deviation of 13.85. The control group consisted of 66 individuals, whose mean age was 48.9 years, with 38 (57.6%) women and 28 (42.4%) men. In this group, the mean serum level of vitamin D was 40.9 ng/mL. Statistical significance was demonstrated with $p < 0.0001$. There was a high prevalence of hypovitaminosis D in patients with Crohn's disease when compared to the control group. Hypovitaminosis D was not observed among patients in the latter group [1].

Conclusion

It was concluded that the highest prevalence of low serum levels of vitamin D is among patients suffering from Crohn's disease and other inflammatory bowel diseases when compared to a control group. However, more comprehensive studies are still needed, especially those that aim to evaluate serum vitamin D in values related to clinical treatment and also the effects of vitamin D supplementation on disease activity and mucosal healing. Thus, it will be possible to evaluate in a relevant way, the replacement of vitamin D in the remission of Crohn's disease, optimizing the treatment of patients and corroborating the improvement in quality of life.

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Ethical Approval

Not applicable.

Informed consent

Not applicable.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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