

Vitamin D supplementation in inflammatory bowel disease: a narrative review

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Abstract

Abstract Inflammatory bowel disease is a chronic disorder characterized by exacerbation and remission periods, and its worldwide incidence has increased in recent decades. Vitamin D is involved in immune regulation and improves barrier functions and intestinal microbiota. Studies have observed that high vitamin D levels decrease relapses and improve the clinical course of inflammatory bowel disease. The objective of this review was to analyze the evidence on vitamin D supplementation in adult patients with inflammatory bowel disease. Among inactive patients, the studies administering less than 2000 international units per day of vitamin D did not find any beneficial effects. However, those supplementing 2000 international units of vitamin D per day increased serum levels and reduced disease activity. In patients with active disease, doses between 5000 to 10 000 international units per day reduced symptomatology. This review showed that vitamin D supplementation above 2000 international units per day among inactive patients with inflammatory bowel disease, and between 5000 to 10 000 international units per day among those in the active stage, shows potential benefits on the disease.

MAIN MESSAGES

- ◆ There is evidence to support that high serum levels of vitamin D decrease recurrence and improve the clinical course of inflammatory bowel disease.
- ◆ However, the optimal thresholds for vitamin D supplementation remain unclear.
- ◆ This narrative review analyzes the evidence on vitamin D supplementation in adult patients with inflammatory bowel disease.

INTRODUCTION

Inflammatory bowel disease is a chronic disorder characterized by exacerbation and remission periods of diarrhea, lower gastrointestinal bleeding, abdominal pain, fever, fatigue, and weight loss [1]. The two primary forms of inflammatory bowel disease are Crohn's disease and ulcerative colitis, which have increased their incidence in recent decades among developed and developing countries [2].

Vitamin D is an essential fat-soluble biomolecule since it participates in many biochemical and physiological processes, including calcium and phosphorus metabolism [3,4]. Vitamin D is ubiquitously present in tissues and is obtained through the exposure of the skin to ultraviolet light from the sun or through dietary intake of dairy products, egg yolk, red meat, and fish [4–6].

Some studies observed that vitamin D regulates the immune response [2,7,8] and improves the composition of the colonic microbiota and intestinal barrier, therefore playing a vital role in inflammatory bowel disease [6,9]. Several studies have observed that high serum levels of vitamin D decrease the recurrence of inflammatory bowel disease [10,11], and its deficiency increases the risk of clinical relapse and disease reactivation [12,13]. Consequently, the clinical benefit seen by some authors suggests vitamin D as an attractive treatment option [9], although the optimal thresholds are unclear [14,15]. This review aims to analyze the evidence on vitamin D supplementation in adult patients with Crohn's disease and ulcerative colitis.

METHODS

The present study corresponds to a narrative review. Primary studies published between 2015 to 2020, in English and Spanish, were included. The Web of Science and PubMed databases search engines were consulted. The following keywords were included in the search engine: "*vitamin d therapy*", "*vitamin d supplementation*", "*vitamin d treatment*", "*inflammatory bowel disease*", "*Crohn's disease*", and "*ulcerative colitis*". Studies were eligible according to the following inclusion criteria:

- 1) Prospective observational studies, quasi-experimental, or clinical trials.

- 2) Studies conducted in adult humans diagnosed with Crohn's disease or ulcerative colitis.
- 3) Publications reported in English or Spanish.
- 4) Studies reporting vitamin D supplementation.

RESULTS AND DISCUSSION

INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease is a chronic disorder that causes gastrointestinal tract inflammation [16,17]. Crohn's disease can alter the gastrointestinal wall from mouth to the perianal area, while ulcerative colitis generally only affects the colon and rectum [17,18]. Currently, inflammatory bowel disease onset is considered to be influenced by genetic, immunological factors, environmental interactions, smoking, and drugs, among others [19,20,20,21].

Crohn's disease and ulcerative colitis usually present with diarrhea with or without mucus and abdominal pain [22]. The severity of symptoms increases in flare-ups and may include fistulas, abscesses, and strictures in Crohn's disease; and bleeding, perforation, pseudopolyps, and toxic megacolon in ulcerative colitis [23,24]. In addition to the gastrointestinal damage, some patients may develop extraintestinal symptoms whose persistence is associated with exacerbations [25].

The assessment of disease activity for Crohn's disease is performed using the Crohn's Disease Activity Index (CDAI) and Harvey-Bradshaw index (HBI) [26]. Through the CDAI, a score lower than 50 corresponds to remission, and higher than 150 corresponds to a crisis. A crisis usually involves liquid stools, severe abdominal pain for more than seven days, and the use of antidiarrheals, extraintestinal complications, among other symptoms [26]. The HBI index evaluates daily liquid stools, abdominal pain, abdominal mass, and extraintestinal manifestations for seven days, classifying the active state with a score equal to or greater than seven [23–26]. For ulcerative colitis, the Mayo Clinic severity index is used. This score also considers blood in stool and classifies crisis into mild, moderate, and severe with scores between 3 and 4, 5 and 8, and 9 and 12 points, respectively [24].

Crohn's disease and ulcerative colitis are complex pathologies to manage during flare-ups. In this reactivation period, 20 to 40% of patients develop extraintestinal manifestations and

potentially life-threatening complications [16]. Moreover, 50% of patients with Crohn's disease and 20% to 30% of individuals with ulcerative colitis usually require surgery during activity periods [16]. In addition, patients with active inflammatory bowel disease have a 70 to 80% chance of relapse in the following year [17].

VITAMIN D

Vitamin D stands out for its multiple functions in the human body, including calcium homeostasis and exerting actions as a prohormone [27]. From a molecular perspective, vitamin D presents as ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃) [4]. The latter is the primary source of vitamin D in nature since it can be endogenously synthesized with ultraviolet light from the sun [28]. Additionally, dietary intake represents 20% of the daily requirement [4,6].

Body vitamin D is estimated by measuring the plasma concentration of 25-hydroxyvitamin D. This indicates the therapeutic window in which vitamin D can exert its phosphocalcic functions while avoiding intoxication [29]. According to most international scientific societies, blood levels lower than 20 nanograms per milliliter (less than 50 nanomol per liter) are deficient; 20 to 30 nanograms per milliliter (50 to 75 nanomol per liter) are insufficient; 30 and 50 nanograms per milliliter (75 to 125 nanomol per liter) correspond to sufficiency; 50 to 150 nanograms per milliliter (75 to 375 nanomol per liter) correlates with overdose; and greater than 150 nanograms per milliliter (greater than 375 to 500 nanomol per liter) to intoxication [29,30].

ROLE OF VITAMIN D IN INFLAMMATORY BOWEL DISEASE

Vitamin D has been shown to improve the intestinal barrier function, regulate the inflammatory process and balance the intestinal microbiota [31]. In the intestinal barrier, it reduces cell injury caused by inflammatory bowel disease by suppressing epithelial cell apoptosis, differential regulation of tight junction proteins (Occludin, Zo-1, Zo-2, Vinculin, and Claudin), and alteration of transepithelial resistance [13,32]. Additionally, vitamin D promotes mucosal regeneration, decreases inflammation, and improves intestinal function via vitamin D receptor-mediated signaling pathways [10,13]. The efficacy of vitamin D at the intestinal barrier depends on its concentration and affinity to vitamin D receptors [10,13].

The large intestine harbors a diverse array of intestinal microbiota involved in immunity, nutrient absorption, and epithelial barrier homeostasis [10,33]. Patients with inflammatory bowel disease have a reduced bacterial richness compared to healthy subjects [10]. Recent studies found that people with higher serum vitamin D levels have a developed and abundant microbiota, thereby reducing inflammation associated with the lower disease activity and relapses [10,14,34].

Regarding its anti-inflammatory role, vitamin D inhibits the synthesis of prostaglandins, decreasing intestinal permeability and hindering the proinflammatory function of immune cells [10]. Additionally, it suppresses the activity of lymphocyte subtypes, causing reduction of the inflammatory cytokines such as interleukin-2 (IL-2) and tumor necrosis factor-alpha (TNF- α) [8,13]. On the other hand, it has been shown that this vitamin modulates the activity and differentiation of monocytes and macrophages and increases anti-inflammatory cytokines such as interleukin 10 (IL-10) and 12 (IL-12) [8,35].

Vitamin D also contributes to reducing interleukin 17 (IL-17) synthesis, thereby increasing the anti-inflammatory activity of glucocorticoids [8]. Additionally, it favors an increase in interleukin 4 (IL-4), 5 (IL-5), 6 (IL-6), and 13 (IL-13), noted for exerting anti-inflammatory action by inhibiting TNF- α [8,35]. Likewise, it decreases the apoptotic activity of active B lymphocytes and plasma cells by reducing immunoglobulin E secretion [8,36].

EFFECT OF VITAMIN D SUPPLEMENTATION ON INACTIVE INFLAMMATORY BOWEL DISEASE (OUTPATIENT SETTING)

Patients with inflammatory bowel disease are more likely to have vitamin D deficiency. These patients lack a safe sunlight exposure threshold [14] due to the increased risk of melanoma [15]. Additionally, it is common that patients fail to meet the dietary intake recommendations since some foods containing vitamin D are associated with increased symptoms [15].

Studies supplementing outpatients with doses lower than 2000 international units per day of vitamin D did not find significant changes in serum levels (Table 1). The 2016 study by Kojecy and collaborators [37] observed that supplementing 1100 international units per day did not significantly reduce inflammatory bowel disease activity through the Mayo Clinic Severity Index and CDAI, possibly because it failed to reduce serum vitamin D deficiency. On the other hand, Tan et al. [38] evaluated a dose of 1667 international units per day for 12 months, which increased serum vitamin D levels but without demonstrating significant changes in the Crohn's disease and ulcerative colitis activity index.

Clinical trials by Kojecy et al. supplementing this vitamin D with 2000 international units per day found increases in serum levels [39,40]. Furthermore, Karimi and colleagues [41] detected a reduction in the Clinical Colitis Activity Index (SCCAI) score in patients with ulcerative colitis, administering the same dose of vitamin D.

EFFECT OF VITAMIN D SUPPLEMENTATION ON ACTIVE INFLAMMATORY BOWEL DISEASE

Studies that supplemented vitamin D between 5000 to 10 000 international units per day observed beneficial effects on active inflammatory bowel disease. According to Garg et al. [42],

Table 1. Characteristics of included studies regarding vitamin D supplementation in patients with inflammatory bowel disease.

Author, year	Sample	Study design	Duration of intervention	Supplementation	Results
Kojecky V, 2020	173 M and F patients, 18 to 70 years • 114 CD • 59 UC	RCT	12 weeks	- Group A: Vit D3 2000 UI/d - Group B: Vit D3 28 UI/kg/d	- Group A: ↑ serum 25 (OH) D - Non-significant AI changes
Kojecky V, 2019	108 M and F outpatients, 18 to 70 years • 71 with CD • 37 with UC	RCT	6 months	- Vit D3: 2.000 UI/d	↑ serum 25 (OH) D - Ca, P, PTH without significant changes - Non-significant AI changes
Karimi S, 2019 [41]	50 M and F patients with mild to moderate UC, ≥ 18 years	RCT	12 weeks	- Group A: Vit D3 1000 UI/d - Group B: Vit D3 2000 UI/d	- Group A: ↑ serum 25 (OH) D. ↓ IA
Tan B, 2018 [38]	124 patients > 18 years • 65 with UC • 59 with CD	RCT	12 months	- Group A: 150 000 UI Vit D3, every 3 months. 200 mg Ca 3 times per day - Group B: elemental Ca 200 mg 3 times per day - Group C: Control group	- Group A: ↑ serum 25 (OH) D - Group A: AI without significant changes Without adverse effects
Garg M, 2018	25 M and F patients, 28 to 72 years • 8 active UC • 9 inactive UC • 8 controls without IBS	QES	8 weeks	40 000 UI/week in active and inactive patients	25 (OH) D: ↑ among active and inactive patients - AI: significant ↓ among active patients CRP, Alb, FC, PC: significant improvement among active patients
Garg M, 2018	10 active patients, 24 to 67 years • 5 CD • 5 UC	QES	12 weeks	Range Vit D3: 5000 to 10 000 UI/d	↑ serum 25 (OH) D. ↓ AI - Without adverse effects
Kojecky V, 2016 [37]	167 M and F outpatients, > 18 years • 55 UC • 110 CD	CS	2 years and 3 months	1100 UI/d Vit D3	- Non-significant ↑ in serum 25 (OH) D - AI without significant changes

Symbols: >, number greater than; ≥, greater than or equal to; ↑, increase; ↓, decrease.

M: male. F: female. IBD: inflammatory bowel disease. CD: Crohn's disease. UC: ulcerative colitis. AI: disease activity index.

Vit D3: cholecalciferol. 25 (OH) D: 25-hydroxyvitamin D.

RCT: randomized clinical trial. QES: quasi-experimental study. CS: cohort study.

Ca: calcium. P: phosphorus. PTH: parathormone. CRP: C-reactive protein. FC: fecal calprotectin. Alb: albumin. PC: platelet count.

mg: milligrams. IU/d: international units per day. IU/kg/d: international unit per kilogram per day. IU/week: international units per week.

Source: adapted from Kojecy et al. [37], Tan et al. [38], Kojecy et al. [39], Kojecy et al. [40], Karimi et al. [41], Garg et al. [42], Garg et al. [43].

supplementing 5000 to 10 000 international units per day of vitamin D in subjects with active inflammatory bowel disease for 12 weeks contributed to a reduction in clinical symptomatology. Garg et al. also found that the therapy did not have serious adverse events while decreasing the activity index steadily and controlling recurrence through CDAI for Crohn's disease and HBI for ulcerative colitis [42]. Another study by Garg et al. [43] in 2018 found that 40 000 international units per

week of vitamin D in subjects with active ulcerative colitis favored a reduction in intestinal inflammation by Mayo Clinic Severity Index and Colitis Activity Index. It should be noted that vitamin D levels reported by Garg et al. [43] were above the recommendations of the Spanish Society of Endocrinology [29], so extending the period of supplementation of this dose may result contradictory. Although no serious adverse effects were observed, these could develop while maintaining high

serum vitamin D levels during prolonged supplementation periods.

CONCLUSIONS

A beneficial effect of vitamin D supplementation between 5000 and 10 000 international units per day has been found to reduce symptomatology and recurrences in active inflammatory bowel disease.

A similar effect has been identified with vitamin D supplementation above 2000 international units per day on the activity of inactive inflammatory bowel disease. However, supplementing 2000 international units per day of vitamin D in the inactive stage did not significantly affect the symptomatology or the activity indexes.

It is essential to constantly monitor serum vitamin D levels to avoid serious adverse effects. New studies incorporating immunological analyses and quantification of vitamin D intake may help understand the effect of supplementation in inflammatory bowel disease.

Notes

Contributor roles

MZ: conceptualization, research, data curation, preparation of the original article, review, and editing. JP: conceptualization, methodology, research, article review and editing, and supervision. CD: methodology, research, article review and editing, and supervision.

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Competing interest

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Suplementación con vitamina D en enfermedad inflamatoria intestinal: una revisión narrativa

Resumen

Resumen La enfermedad inflamatoria intestinal es un trastorno crónico caracterizado por presentar episodios de exacerbación y remisión, cuya incidencia mundial se ha incrementado en las últimas décadas. La vitamina D está implicada en la regulación inmunológica, mejora las funciones de la barrera y la microbiota intestinal. Estudios han observado que niveles altos de esta vitamina disminuye la incidencia de recidivas y mejora la evolución clínica de la enfermedad. El objetivo de esta revisión fue analizar la evidencia sobre la suplementación de vitamina D en pacientes adultos con enfermedad inflamatoria intestinal. Los estudios que administraron dosis menores a 2000 unidades internacionales al día de vitamina D en pacientes ambulatorios, no presentaron efectos beneficios. Por el contrario, los que suplementan niveles de 2000 unidades internacionales al día incrementaron los niveles séricos de esta vitamina y redujo la actividad de la enfermedad. En el caso de los sujetos con enfermedad activa, dosis de 5000 a 10 000 unidades internacionales al día redujeron la sintomatología clínica. Esta revisión apreció que la suplementación con vitamina D sobre 2000 unidades internacionales al día, en pacientes con enfermedad inflamatoria intestinal en etapa inactiva y entre 5000 a 10 000 unidades internacionales al día en etapa activa, muestra efectos positivos en el cuadro clínico de la patología.



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