

LOWER LEVELS OF VITAMIN D CORRELATE WITH CLINICAL DISEASE ACTIVITY AND QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE

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ABSTRACT - Background - Inflammatory bowel disease, comprising Crohn's disease and ulcerative colitis, is a group of debilitating conditions associated with deregulated mucosal immune response. Vitamin D has been implicated in immune response and gastrointestinal function. **Objectives** - To investigate the correlation between serum vitamin D levels and disease activity and quality of life in patients with inflammatory bowel disease. **Methods** - This cross-sectional study enrolled ambulatory patients with inflammatory bowel disease and assessed clinical disease activity and quality of life (Short Inflammatory Bowel Disease Questionnaire [SIBDQ]). Vitamin D levels were determined via serum 25-hydroxyvitamin D measurement; deficiency was defined as values <20 ng/mL. Statistical analysis was performed with SPSS vs 20.0. **Results** - A total of 76 patients were enrolled, 19 with ulcerative colitis (25%) and 57 with Crohn's disease (75%). Overall, mean serum 25-hydroxyvitamin D levels were low (26.0 ± 10.0 ng/mL), while those in patients with Crohn's disease were significantly lower than ulcerative colitis (24.6 ± 8.0 vs 30.0 ± 12.5 ng/mL; $P=0.032$). Vitamin D deficiency was found in 30% of patients. Patients who were in clinical remission were found to have higher levels of vitamin D than those who were not in remission (28.0 ± 10.3 vs 21.6 ± 6.0 ng/mL, $P=0.001$). Inflammatory bowel disease patients with SIBDQ scores <50 were found to have significantly lower mean vitamin D levels compared with patients who had SIBDQ scores ≥ 50 (23.4 ± 6.9 vs 27.9 ± 10.8 ng/mL, $P=0.041$). **Conclusions** - A high proportion of patients with inflammatory bowel disease were vitamin D deficient, particularly patients with Crohn's disease. Both clinical disease activity and quality of life correlated significantly with lower levels of vitamin D, illustrating a clear need for supplementation in patients with inflammatory bowel disease.

HEADINGS - Inflammatory bowel diseases. Vitamin D. Quality of life.

INTRODUCTION

Inflammatory bowel diseases (IBD) are autoimmune, chronic and relapsing diseases of unknown etiology⁽²⁶⁾. IBD comprises Crohn's disease (CD) and ulcerative colitis (UC), a group of debilitating conditions associated with deregulated mucosal immune response. These conditions affect up to 0.5% of the population in developed countries⁽²²⁾ and the incidence appears to increase as distance from the equator increases⁽³⁾.

Vitamin D has an established role in promoting bone health but is emerging as a multifunctional vitamin in IBD. It has recently being linked to a number of other functions like anti-inflammatory and anti-

carcinogenic pathways in the gastrointestinal tract⁽²⁵⁾. In humans, sun exposure is responsible for up to 95% of vitamin D production⁽⁷⁾. Vitamin D deficiency was reported in 63% of patients with CD⁽³⁰⁾ and has been proposed to play a key role in IBD pathogenesis based on geographic distribution, seasonal variation in onset and exacerbations of IBD⁽¹²⁾.

Several predictors for developing vitamin D deficiency in IBD have been identified, including longer disease duration, higher disease activity, smoking, small bowel resection, small bowel involvement, nutrition status and seasonal changes^(10, 11, 31). There is also strong evidence which supports the concept that vitamin D deficiency may be a consequence of IBD itself. Anorexia, food

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intolerance, malabsorption, reduction of outdoor activities, corticosteroid therapy, bowel resection and circulating cytokines are the consequences of gastrointestinal involvement and may lead to vitamin D deficiency⁽²⁷⁾.

The most stable measurable form of vitamin D in serum is 25-hydroxyvitamin D (25[OH]D)⁽⁷⁾. Screening for vitamin D deficiency requires a blood sample for measurement of serum 25(OH)D levels and is therefore practical and feasible in an outpatient setting⁽³⁰⁾.

Clinically, increasing 25(OH)D levels through high-dose vitamin D supplementation may have therapeutic potential and prevent relapse in CD^(17, 18), although this still warrants confirmation in controlled trials. Several studies have been conducted to demonstrate a correlation between vitamin D status and inflammatory bowel disease activity^(6, 14). However, few studies⁽³³⁾ have so far hypothesized that vitamin D deficiency is associated with a lower quality of life (QOL) in patients with IBD.

The aim of this study was to investigate the correlation between serum vitamin D levels and both disease activity and health-related QOL (HRQOL) in a cohort of patients with IBD.

METHODS

This cross-sectional study was performed in Guimarães, Northern Portugal (where the four-season climate provides a large amount of sunshine in summer) and enrolled patients with IBD in ambulatory care (CD and UC, excluding patients with ulcerative proctitis). All samples were collected during the summer months (July and August 2013). Vitamin D status was obtained thorough measurement of serum 25(OH)D by a fully automated immunoassay (ADVIA Centaur XP[®], Siemens)⁽⁵⁾, as it was considered the best measure of an individual's vitamin D status⁽²⁴⁾. Vitamin D insufficiency was defined as a level between 20 and 30 ng/mL and deficiency was defined as a level <20 ng/mL^(15, 28).

Patients were excluded if they presented with comorbid conditions that interfere with vitamin D serum values (i.e. renal failure, liver disease, pregnancy, lactation, medications such as anticonvulsants and vitamin D supplements). Patients under 18 years-old were excluded from the study.

Demographic data, disease location, duration and behavior (Montreal Classification for both CD and UC), medical history and IBD-related surgeries, were obtained from clinical records. C-reactive protein (CRP), ferritin, albumin, erythrocyte sedimentation rate (ESR) and hemoglobin levels were also measured (using routine laboratory techniques) as markers for inflammation and disease severity.

The primary outcomes were the association of vitamin D deficiency with disease activity and HRQOL. Disease activity was measured using the Harvey-Bradshaw index (HBI) for CD patients and partial Mayo score for UC patients. The HBI is a simple and validated index of CD activity based on five items (general wellbeing, abdominal pain, number of liquid stools per day, abdominal mass and complications)⁽¹³⁾. The partial Mayo Score incorporates the reported stool frequency,

presence of rectal bleeding and a physician's global assessment. This partial Mayo score in which the endoscopic component is omitted, has been shown to correlate well with the Mayo Score^(29, 32). HRQOL was quantified using the Short IBD Questionnaire (SIBDQ)⁽¹⁶⁾, a simple 10-point questionnaire that is a validated measure of HRQOL in CD and UC. The 10 questions are subdivided into bowel-related, systemic, emotional and social domains, with each question being answered on a scale ranging from 1 to 7, resulting in a total SIBDQ score between 10 (worst/low HRQOL) and 70 (best/high HRQOL).

The scores were analyzed as dichotomous outcomes with a cutoff of 50 for the SIBDQ, ≤ 3 indicating remission for HBI and ≤ 2 for partial Mayo Score, with no subscore >1.

Statistical analysis was performed using the SPSS vs 20.0 program. Continuous variables were summarized using means and standard deviations, whereas categorical variables were described using proportions. The chi-square test and the independent-samples *t* test were used for categorical and continuous variables, respectively. Binary logistic regression, for disease activity, was adjusted considering as independent variables gender, smoking status, disease location, duration and behavior and laboratory variables (serum hemoglobin, CRP, ESR, ferritin, albumin and serum 25(OH)D). Laboratory variables were used as quantitative variables. The variables measured were included if they were selected from bivariate analysis ($P < 0.05$). A *P* value <0.05 was considered statistically significant.

All patients provided written consent prior to enrollment in this study. The study was performed according to the Declaration of Helsinki and approved by the Local Ethics Board of Centro Hospitalar do Alto Ave – Guimarães, Portugal.

RESULTS

Baseline characteristics

A total of 76 patients with IBD were enrolled in this study, 72% were female, mean age was 33.8 ± 10.2 years, 19 had UC (25%) and 57 had CD (75%). The mean duration of disease was 72.0 ± 66.1 months (6–360 months). The demographic characteristics of the study population are presented in Table 1. Most of the patients with CD presented with involvement of the small bowel (93%), L1 (39%) or L3 (54%) by Montreal Classification, and only 7% had exclusive large bowel disease. More than one third of CD patients had had small bowel surgery (35%). Immunomodulators were being used by 58% of patients, while 37% were receiving anti-TNF therapy and a further 24% were receiving corticosteroids.

Vitamin D levels

Overall, 68% of all patients had insufficient levels of vitamin D (58% of UC patients and 72% of CD patients) and 30% were vitamin D deficient (<20 ng/mL). Across all patients the mean serum 25(OH)D level was 26.0 ± 10.0 ng/mL, CD patients had significantly lower levels than UC patients (24.6 ± 8.0 vs 30.0 ± 12.5 ng/mL, $P = 0.032$). However, there was no significant difference in the prevalence of vitamin D deficiency between CD and UC patients ($P = 0.313$).

TABLE 1. Patient demographics

	Ulcerative colitis (n=19)	Crohn's disease (n=57)	All patients (n=76)
Age, y, mean	35.4±11.3	33.3±9.8	
Gender, n (%)			
Male	4 (21%)	17 (30%)	
Female	15 (79%)	40 (70%)	
Disease duration, m, mean	70.7±57.0	72.4±69.4	
Disease involving colon only, n (%)	19 (100%)	4 (7%)	
Disease involving small bowel only, n (%)	Not applicable	22 (39%)	
Disease involving colon and small bowel, n (%)	Not applicable	31 (54%)	
25(OH)D, ng/mL, mean*	30.0±12.5	24.6±8.0	
Vitamin D insufficiency (<30 ng/mL), n (%)	11 (58%)	41 (72%)	52 (68%)
Vitamin D deficiency (<20 ng/mL), n (%)	4 (21%)	19 (33%)	23 (30%)
6MP/azathioprine, n (%)			44 (58%)
Infliximab/adalimumab, n (%)			28 (37%)
IBD-related surgery, n (%)			20 (26%)

25(OH)D: 25-hydroxyvitamin D; IBD: inflammatory bowel disease. *P=0.032.

TABLE 2. Demographic features and vitamin D levels

	Vitamin D		P value
	<20 ng/mL (n=23)	>20 ng/mL (n=56)	
Age, y	35.7±11.6	33.0±9.5	0.285
Disease duration (months)	79.6±72.3	68.7±63.7	0.515
Gender (%)			
Male	33%	67%	0.719
Female	29%	71%	
CD location (%)			
L1	41%	59%	0.621
L2	25%	75%	
L3	29%	71%	
Immunomodulator use (%)	34%	66%	0.394
Biologic use (%)	39%	61%	0.191
Intestinal resection (CD) (%)	33%	67%	0.432

CD: Crohn's disease.

There was no significant difference in the prevalence of vitamin D deficiency by age, gender or duration of disease. The use of immunomodulators, biologic therapy or previous history of intestinal resection were not significantly associated with vitamin D deficiency. In patients with CD the location of disease did not have an association with serum vitamin D levels (Table 2).

Vitamin D & disease activity

Those patients who were in clinical remission (HBI ≤3 for CD and a partial Mayo Score ≤2 with no subscore >1

for UC) had higher levels of vitamin D compared with those who were not in remission (28.0±10.3 vs 21.6±6.0 ng/mL, P=0.001). Clinical remission was significantly associated with vitamin D sufficiency (P=0.011) (Table 3).

By univariate analysis only lower levels of vitamin D (21.6±6.0 vs 28.0±10.3; P=0.001) and higher levels of CRP (16.8±31.6 vs 4.9±4.1; P=0.009) were statistically associated with disease activity, however, in binary logistic regression only lower levels of vitamin D were independently associated with disease activity with a RR of 1.1/ per unit (P=0.018; 95% CI 1.02-1.20).

TABLE 3. Association between Vitamin D levels and disease activity and quality of life

	No clinical remission	Clinical remission	<i>P</i> value	SIBDQ <50	SIBDQ >50	<i>P</i> value
25(OH)D, ng/mL, mean	21.6±6.0	28.0±10.3	0.001	23.4±6.9	27.9±10.8	0.041
Vitamin D <20 ng/mL, n	12	11	0.011*	12	11	0.242*
Vitamin D >20 ng/mL, n	12	41		20	33	

25(OH)D, 25-hydroxyvitamin D; SIBDQ, Short Inflammatory Bowel Disease Questionnaire.

Remission was defined as Harvey-Bradshaw index (HBI) score ≤3 for Crohn's disease and a partial Mayo Score ≤2 with no subscore >1 for ulcerative colitis. *Chi-square test.

TABLE 4. Association between Vitamin D levels and serological biomarkers

	Vitamin D <20 ng/mL	Vitamin D >20 ng/mL	<i>P</i> value	Vitamin D <30 ng/mL	Vitamin D >30 ng/mL	<i>P</i> value
Hemoglobin	13.5±1.4	13.5±1.4	0.926	13.7±1.4	13.2±1.4	0.171
Albumin	3.9±0.5	4.0±0.4	0.095	4.0±0.4	4.1±0.3	0.297
Ferritin	57.5±62.7	72.0±86.5	0.473	64.6±63.3	74.1±109.0	0.631
ESR	16.4±19.9	15.7±15.3	0.873	15.6±16.9	16.7±16.5	0.782
CRP	11.6±19.6	7.4±18.3	0.366	10.7±22.3	4.3±2.9	0.048

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Vitamin D & HRQOL

IBD patients with SIBDQ scores <50 had significantly lower mean vitamin D levels compared with patients who had SIBDQ scores ≥50 (23.4±6.9 vs 27.9±10.8 ng/mL, *P*=0.041). However, there was no significant difference in the prevalence of vitamin D deficiency between these two groups (Table 3).

Vitamin D & other markers

A significantly higher proportion of patients with vitamin D insufficiency had higher levels of CRP (10.7±22.3 vs 4.3±2.9 mg/L, *P*=0.048), however, there was no difference for vitamin D deficiency (<20 ng/mL). The presence of anemia, lower levels of albumin and higher levels of ferritin and ESR did not correlate significantly with lower levels of vitamin D (Table 4).

DISCUSSION

The role of vitamin D is increasingly recognized in immunomodulation and in a variety of diseases states, including IBD⁽²⁴⁾. In a cohort of patients with IBD in an outpatient setting we found 30% of patients had vitamin D deficiency (<20 ng/mL), which increased to 68% when considering vitamin D insufficiency (≥20 but <30 ng/mL). Our results highlight the fact that vitamin D deficiency is common in IBD patients even when the disease is managed in an outpatient setting and remain high even in summer. These results were consistent with a large, retrospective study of 504 adult patients with IBD from Wisconsin (UC n=101, CD n=403), in which ~50% of patients had vitamin D deficiency⁽³³⁾.

Inadequate exposure to sunlight is an important cause of vitamin D deficiency in IBD patients; several studies, particularly from northern climates, have consistently demonstrated an association between winter season, a period of low sunlight and UVB exposure, and vitamin D deficiency^(10, 23, 30). In this study all samples were collected in the summer to reduce the influence of lack of UVB exposure in our data, suggesting that the observed low levels of vitamin D were not a result of low sunlight levels.

While most studies have examined the prevalence in patients with well-established IBD, vitamin D deficiency does not appear to be a consequence of long-standing disease alone. In a cohort of newly diagnosed patients from Canada, only 22% were found to have sufficient levels of vitamin D⁽¹⁹⁾. Similarly, in our cohort of patients there was no apparent correlation between vitamin D deficiency and duration of the disease.

The association between vitamin D levels in CD of the small bowel and malabsorption of oral vitamin D is yet unclear. It has been suggested that malabsorption of oral vitamin D can occur in CD⁽¹⁰⁾, however, this association has not been demonstrated elsewhere⁽³⁰⁾. In our study we did not find an association between vitamin D deficiency and small bowel CD. However, it should be noted that due to the relatively small number of patients with CD had isolated large bowel disease (n=4; 7%), our study was not sufficiently powered to determine this effect.

Terminal ileal resection was associated with vitamin D deficiency in some studies^(20, 31), which is thought to be a result of the interruption of the enterohepatic circulation in the terminal ileum, reducing the absorption of fats and fat-soluble vitamins, such as vitamin D⁽²⁴⁾. However, the effect of ileal resection in vitamin D deficiency has not been consistently observed⁽³³⁾ and our results did not find an association between ileal resection and vitamin D deficiency.

Published data supporting a clinical association between vitamin D deficiency and disease activity in IBD are also conflicting. No correlation between vitamin D levels and disease activity was observed in two cross-sectional studies^(4, 21) while a retrospective study concluded that vitamin D deficiency was associated with increased disease activity in patients with CD, but not with UC⁽³³⁾. A recent study prospectively analyzed the association between vitamin D deficiency and the need for IBD-related surgery or hospitalizations in a large cohort of 3,217 patients and concluded that vitamin D deficiency was associated with an increased risk of surgery and hospitalization compared with those patients with adequate vitamin D levels⁽²⁾. In our study the prevalence of patients in clinical remission was significantly higher in patients with adequate vitamin D levels. Additionally we found an independent association between lower levels of vitamin D and disease activity and even though the impact was not very high, this could suggest that vitamin D has a protective effect and that low vitamin D levels are probably a risk factor for surgery and hospitalization in IBD patients. The fact that other variables, particularly CRP, did not associate independently with clinical disease activity may be related to the fact that we only included outpatients with mild to moderate disease severity.

In our study, IBD patients with low HRQOL (SIBDQ score <50) had significantly lower mean vitamin D levels (in the range of vitamin D insufficiency: ≥ 20 and < 30 ng/mL). Only one comparative study could be found which concluded that vitamin D deficiency was independently associated with lower HRQOL in CD, but not in UC⁽³³⁾. These results highlight the importance of vitamin D insufficiency in IBD patients, as QOL is an important outcome in these patients⁽⁹⁾.

In patients with IBD, lower serum vitamin D levels have been associated with increased ferritin and CRP levels⁽³¹⁾. However, a recent study demonstrated an inverse correlation between serum vitamin D levels and markers of intestinal inflammation (fecal calprotectin) but no association between vitamin D levels and serological inflammation markers⁽⁸⁾. In our study, only CRP was shown to correlate with vitamin D insufficiency and none of the serological inflammation markers correlated with vitamin D deficiency; this may be supported by the theory that serum vitamin D levels may influence local tissue inflammation more than systemic inflammation⁽⁸⁾, but more studies are needed to elucidate the relationship.

There are some limitations to this study: the relatively small number of patients reduced the statistical power to detect a correlation between vitamin D and QOL, while the selection of only outpatients with mild to moderate disease severity may have introduced potential selection bias. Another limitation was non-assessment of anthropometric measurements (weight, height, BMI) and food questionnaire, however, some authors suggest that traditional food sources contribute to less than 200 IU/day to vitamin D intake⁽³⁴⁾.

Strengths of the study included the use of strict exclusion criteria to remove comorbid confounding factors, as well as the fact that sampling was performed in the summer to ensure that the influence of daylight hours was consistent.

In conclusion, vitamin D deficiency was common in patients with IBD and appears to be related to clinical disease activity and QOL. However, although there is evidence for a role of vitamin D in IBD pathogenesis, it has been unclear if vitamin D deficiency results from chronic gastrointestinal inflammation⁽¹⁾. Our study allowed us to identify an association between vitamin D insufficiency, clinical disease activity and QOL, but the causality can only be determined through prospective studies. Given the high prevalence of vitamin D deficiency in patients with IBD, there is a clear need for increased awareness of regular vitamin D screening and appropriate supplementation of vitamin D in the management of these patients.

Authors' contributions

Dias de Castro F performed the study, data analysis, and a literature search and drafted the manuscript; Magalhães J participated in the design and data analysis; Boal Carvalho P participated in the design of the study and performed statistical analysis; Mota P revised the manuscript and performed sample analysis, Moreira MJ revised the manuscript and participated in the design study; Cotter J participated in the design of the study, critically revised the manuscript and approved the final version to be submitted.

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RESUMO - Contexto - A doença inflamatória intestinal, que compreende a doença de Crohn e a colite ulcerosa, é um grupo de entidades incapacitantes associada a uma resposta imunitária desregulada. A vitamina D tem sido associada à resposta imune e funções gastrointestinais. **Objetivo** - Investigar a correlação entre os níveis séricos de vitamina D, a atividade clínica da doença e a qualidade de vida em doentes com doença inflamatória intestinal. **Método** - Estudo transversal que incluiu doentes em ambulatório com doença inflamatória intestinal avaliando a atividade clínica da doença e a qualidade de vida (Short Inflammatory Bowel Disease Questionnaire [SIBDQ]). Os níveis séricos de vitamina D foram determinados através dos níveis de 25-hidroxivitamina D; a deficiência de vitamina D foi definida para valores <20 ng/mL. **Resultados** - Foram incluídos 76 doentes, 19 com colite ulcerosa (25%) e 57 com doença de Crohn (75%). No global, os valores séricos médios de 25-hidroxivitamina D foram baixos (26,0±10,0 ng/mL), os doentes com doença de Crohn apresentaram níveis mais baixos do que os doentes com colite ulcerosa (24,6±8,0 vs 30,0±12,5 ng/mL; $P=0,032$). O déficit de vitamina D foi identificado em 30% dos doentes. Os doentes em remissão clínica apresentaram níveis mais elevados de vitamina D (28,0±10,3 vs 21,6±6,0 ng/mL, $P=0,001$). Doentes com SIBDQ <50 apresentaram níveis significativamente inferiores de vitamina D em comparação com doentes com SIBDQ ≥50 (23,4±6,9 vs 27,9±10,8 ng/mL, $P=0,041$). **Conclusão** - Uma percentagem elevada de doentes apresentou deficiência de vitamina D, em particular doentes com doença de Crohn. A atividade clínica e a qualidade de vida dos doentes com doença inflamatória intestinal correlacionou-se com níveis mais baixos de vitamina D, ilustrando uma clara necessidade de suplementação desta vitamina em doentes com doença inflamatória intestinal.

DESCRITORES - Doenças inflamatórias intestinais. Vitamina D. Qualidade de vida.

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