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Vitamin D deficiency in outpatients with inflammatory bowel disease: prevalence and association with clinical-biological activity

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ABSTRACT

Introduction: there are few data on the prevalence of vitamin D deficiency in patients with inflammatory bowel disease (IBD) in Spain. A deficiency could be associated with a worse course of the disease.

Aim: to determine the prevalence of 25-hydroxyvitamin D (25OHD) deficiency in a cohort of outpatients with IBD and assess its association with clinical and biological activity, quality of life and psychological symptoms.

Methods: a cross-sectional, single-center observational study was performed. The study variables were obtained via clinical interviews, medical chart review and validated questionnaires (Hospital Anxiety and Depression Scale and Short Quality of Life in Inflammatory Bowel Disease Questionnaire). 25OHD was measured in the same laboratory by an electro-chemiluminescence immunoassay.

Results: the study included 224 patients. The prevalence of vitamin D deficiency in Crohn's disease and ulcerative colitis was 33.3% and 20.3%, respectively. In Crohn's disease, vitamin D deficiency was associated with a higher clinical activity ($p < 0.001$) and a higher concentration of fecal calprotectin ($p = 0.01$). In ulcerative colitis, it was associated with clinical activity ($p < 0.001$), the use of steroids during the last six months ($p = 0.001$) and hospital admission during the previous year ($p = 0.003$). A sub-analysis of 149 patients failed to detect an association between vitamin D and quality of life or the scores of the Hospital Anxiety and Depression Scale.

Conclusions: vitamin D deficiency is common in patients with inflammatory bowel disease. An association was found between vitamin D concentration and clinical activity indexes, as well as fecal calprotectin levels in Crohn's disease.

Key words: Vitamin D. Crohn's disease. Ulcerative colitis. Inflammatory bowel disease.

INTRODUCTION

Non-classical or extra-skeletal effects of vitamin D have aroused scientific interest over recent years. Numerous studies in experimental models of colitis assign vitamin D an important role in the regulation of both innate and acquired immunity (1). The action of its active metabolite, 1,25-dihydroxyvitamin-D, on the vitamin D receptor that is present in different cells of the immune system modulates the immune response towards a net anti-inflammatory state. After its endogenous synthesis or intestinal absorption, vitamin D is transported to the liver, where it undergoes a first hydroxylation by the action of the enzyme 25-hydroxylase. The metabolite, 25 hydroxyvitamin D (25OHD), is the most common circulating form of vitamin D, which best defines the status of an individual (2).

The prevalence of vitamin D deficiency in people with inflammatory bowel disease (IBD) varies from 16% to 95% and it is usually more frequent in Crohn's disease (CD) than in ulcerative colitis (UC) (3). A recent meta-analysis showed that the prevalence is also greater than that found in a healthy population (4). Prevalence data on vitamin D deficiency in patients with IBD are scarce in Spain (5). A few observational, heterogeneous or cross-sectional studies have attempted to determine the association

between vitamin D deficiency and clinical and prognostic variables of IBD (clinical disease activity, quality of life, hospitalization or need for surgery). However, no regular association has been found (6). Furthermore, different clinical indexes and systemic biological parameters of activity have been used, such as C reactive protein (CRP). Only three studies included fecal calprotectin (FC) as a more sensitive parameter of inflammatory activity (7-9).

The possible relationship between quality of life and vitamin D deficiency in patients with IBD has not been clarified, as the results from various studies are discordant (10,11). In addition, patients with IBD have an increased risk of anxiety and depression (12). A few observational studies have detected an association between vitamin D deficiency and depression, as well as a possible therapeutic role for vitamin D in this situation (13). However, no data are available with regard to the possible association between IBD, anxiety-depression and vitamin D.

The main aim of the study was to determine the prevalence of vitamin D deficiency in a series of outpatients with IBD from a hospital in southern Spain and examine the association with clinical and biological parameters, including FC. The secondary endpoint was to assess the association between vitamin D concentration and quality of life related to health and psychological symptoms.

MATERIAL AND METHODS

This cross-sectional, observational study was performed in a third-level hospital in Spain (latitude 36.72) between the 1st of March of 2016 and 30th of April of 2017.

Patients

The study comprised consecutive outpatients older than 18 years of age with a diagnosis of IBD (UC and CD) according to standard criteria (14), who were able to understand and complete the information form and health questionnaires. The exclusion criteria included the following: associated coeliac disease or short bowel syndrome, treatment with non-steroidal anti-inflammatory drugs during the previous month, liver or kidney failure, pregnancy or lactation, and cases undergoing anti-epileptic treatment. The consumption of vitamin D supplements was not a reason for

exclusion. At the time of study inclusion, the indexes of clinical activity were calculated and the clinical and demographic variables were recorded. The completed questionnaires (quality of life and psychological symptoms) were collected one week after study inclusion and a blood sample was taken at the same time. The laboratory measurements included those routinely used for outpatient follow-up plus the determination of 25OHD and FC. The patients were classified according to the Montreal classification (15).

Evaluation of vitamin D levels

Serum 25OHD was quantified by an electro-chemiluminescence immunoassay (Cobas® e602, Roche, Switzerland). Levels of 25OHD < 20 ng/ml were considered as deficient; 20-29.9 ng/ml, as insufficient; and ≥ 30 ng/ml, as adequate, in accordance with the criteria of the Endocrine Society (16). The season when the measurement was taken was also noted; winter was considered to be from November until April and summer from May until October. Patients were considered as having vitamin D supplements if they had received daily treatment with at least 800 IU of vitamin D during the last month.

Evaluation of IBD activity, physical activity, quality of life and psychological symptoms

The clinical activity was assessed using the Harvey-Bradshaw index (HBI) for patients with CD and the Partial Mayo score for patients with UC. A CRP ≥ 10 mg/dl was considered as pathological (17). The FC was measured via an ELISA (Calprest® Eurospital, Trieste, Italy). The Calprest values ranged from 15.6 mcg/g to 500 mcg/g. Samples with values > 500 mcg/g were subsequently diluted to obtain values above 1,000 mcg/g. In agreement with a recent study from our latitude and using the same FC commercial technique (18), 170 mcg/g was used as the cut point to differentiate between the biological viewpoint and active disease and remission. Quality of life was measured using the Spanish version of the Short Quality of Life in Inflammatory Bowel Disease Questionnaire (SIBDQ-9). Psychological symptoms were assessed using the Hospital Anxiety and Depression scale (HADS). The level of physical activity was

assessed with the international physical activity questionnaire (IPAQ) and the results were calculated in METS (multiples of the basal metabolic rate) (42).

Statistical analysis

For the descriptive analysis, continuous variables are presented as the mean and standard deviation when normally distributed, or the median and the interquartile range otherwise. Qualitative variables are expressed as a frequency distribution. Prevalence and the corresponding 95% confidence intervals were estimated. Normality was determined using the Shapiro-Wilk test. The Chi-square test with Fisher's correction was used when necessary for the analysis of qualitative variables. The Student's t-test or the corresponding non-parametric Mann-Whitney test were used for the analysis of the differences between continuous quantitative variables in the two independent groups. Differences between quantitative variables in three independent groups were assessed using the ANOVA test if the distribution was normal, or the Kruskall Wallis test if not. Finally, contrasts were performed *a posteriori* using the Bonferroni correction. The analysis was performed using the statistical software R Project, version 3.4.4.

Ethical considerations

The study protocol was approved by the Provincial Research Ethics Committee of Malaga. The data were recorded anonymously in a coded electronic database. The project complies with the principles of the Declaration of Helsinki and the norms of good clinical practice.

RESULTS

Patients: clinical and demographic data

Initially, 289 consecutive outpatients with IBD who were regularly followed-up by our service were invited to participate in the study. Of these, 40 were not included for the final analysis. The reasons for exclusion included: refusal to participate (n = 10), age < 18 years (n = 4), language barrier or inability to read and understand the questionnaires (n = 10), short bowel (n = 2), gestation or lactation (n = 3), use of non-

steroidal anti-inflammatory drugs (n = 4), alteration of the liver profile (n = 2), associated coeliac disease (n = 1), kidney failure (n = 3) and treatment with anti-epileptic drugs (n = 1). Of the remaining 249 patients, 25 were excluded as they had no laboratory measurements. Thus, the final study included 224 patients (150 with CD and 74 with UC). However, 75 patients failed to complete all the questionnaires on quality of life, physical activity and psychological symptoms. Accordingly, the sub analysis of these variables was performed with 149 patients (107 CD and 42 UC). Table 1 shows the main clinical and demographic characteristics.

Prevalence of vitamin D deficiency

The prevalence of vitamin D deficiency and insufficiency (95% confidence interval) in the entire series was 29% (23-35) and 34.4% (28-43), respectively. With regard to the patients with CD, 68% had deficient or insufficient levels of vitamin D, 33.3% (25-41) deficient and 38% (30-46) insufficient. With regard to the patients with UC, 20.3% (10-30) had deficient levels and 27% (16-38) insufficient levels. The median 25OHD concentration in patients with CD was significantly lower than in patients with UC (24.38 [14.38] ng/ml *vs* 30.20 [15.83] ng/ml, p = 0.002). No differences were found with regard to the percentage of measurements of 25OHD in summer and winter (p = 0.1). However, a seasonal effect was noted, with a lower mean 25OHD in winter months than summer months for both CD (21.53 ± 9.22 ng/nl *vs* 29.11 ± 11.93 ng/ml, p < 0.001) and UC (26.51 ± 11.11 *vs* 34.76 ± 9.6, p < 0.001). In addition, the proportion of patients with vitamin D deficiency was greater in winter than in summer for both CD (48.5% *vs* 21.4%; p < 0.001) and UC (35.2% *vs* 6%; p = 0.002).

Associations between 25OH vitamin D and clinical and demographic variables

Tables 2-4 summarize the association between the demographic variables and the clinical and biological parameters according to the concentration of 25OHD of the entire patient cohort, the CD cohort and the UC cohort, respectively.

Demographic variables, smoking and body mass index

No association was found between the 25OHD concentration and age, duration of disease, active smoking or body mass index (BMI). The proportion of male UC patients with a 25OHD deficiency was significantly lower than for female UC patients (p = 0.02).

Clinical activity and biological parameters

The proportion of patients with a vitamin D deficiency was greater among those with disease activity according to the HBI and Partial Mayo, in the entire cohort (p < 0.001) as well as in each separate entity (CD, p < 0.001 and UC, p = 0.008). The FC concentration decreased significantly as the serum 25OHD category increased, in both the entire cohort (p = 0.002) and in patients with CD (p = 0.026) (Fig. 1). The median FC concentration in patients with CD and 25OHD < 20 ng/ml was almost twice that of the patients with levels > 30 ng/ml (56 [88.5] mcg/g *vs* 108.25 [180.5] mcg/g, p = 0.01). No significant differences were found between the median FC concentrations in patients with UC (p = 0.39).

Significant differences were found between the median CRP levels between the various groups (0.04). The median CRP in the subgroup with a deficient 25OHD concentration was higher than in the group with adequate levels (2.9 [3.8] mg/l *vs* 2.9 [0.2] mg/l, p = 0.001). Considering CD and UC separately, no significant differences were found in the median CRP concentrations between the various subgroups of 25OHD concentration.

The 25OHD concentration was further analyzed according to the biological activity of the disease and CRP and FC. In patients with CD, the median 25OHD in cases with FC > 170 mcg/g was significantly lower than in patients with values < 170 mcg/g (21 [10.44] ng/ml *vs* 25.45 [15.16] ng/ml; p = 0.03) (Fig. 2). Likewise, in patients with UC, the mean 25OHD was significantly lower in patients with FC > 170 mcg/g than in those with lower values (23.04 ± 10.34 ng/ml *vs* 32.14 ± 10.68 ng/ml; p = 0.004) (Fig. 3). No significant differences were found in the median and mean 25OHD levels between the patients with CRP values above or below 10 mg/l in CD or UC.

Inflammatory bowel disease phenotype (Montreal classification) and prior surgery

The patients with CD who had previously undergone surgery had a lower median 25OHD concentration than patients who had not undergone surgery (23.31 [13.47] ng/ml *vs* 25.47 [15.27] ng/ml; p = 0.022). The median 25OHD concentration was significantly lower in CD patients with isolated ileum involvement compared to patients who had exclusive colon involvement (22.26 [14.56] ng/ml *vs* 27.45 [12.57] ng/ml; p = 0.002]. There were no differences with regard to the presence of perianal disease (p = 0.85). The site of the UC did not affect the mean 25OHD levels (p = 0.75). The age at diagnosis was not significantly associated with the vitamin D concentration in CD (p = 0.21) or UC (p = 0.38). With regard to the CD phenotype, the median 25OHD concentrations were significantly lower in those with a fistulising pattern compared to an inflammatory pattern (20.17 [11.73] ng/ml *vs* 25.94 [16.23] ng/ml; p = 0.004) and stenotic pattern (20.17 [11.73] ng/ml *vs* 24.13 [8.89] ng/ml; p = 0.004).

Disease treatment, steroid use, hospital admission and use of supplements

No differences were found in either the CD or UC cohort with regard to the proportion of patients on biological therapy or receiving immunosuppressive agents, steroids or vitamin D supplements. Overall, a greater proportion of patients with 25OHD deficiency were receiving a biological treatment as compared to the group with adequate levels (p = 0.03). The proportion of patients using steroids in the last six months was greater in the groups with insufficient or deficient levels as compared to the entire cohort (p = 0.01) and the UC group (p = 0.001). The proportion of patients who had been admitted to hospital in the last year and who had vitamin D deficiency/insufficiency was greater in the entire cohort (p = 0.01) and in patients with UC (p = 0.003). In all the patients taking supplements, vitamin D was associated with the concomitant use of steroids.

Quality of life, physical activity and psychological symptoms

No significant differences were found between the median scores of METS in the physical activity questionnaire between the patients with clinical remission and the patients with clinical activity (2,106 [2,746.5] *vs* 1,950 [1,587.8]; p = 0.17). No differences were found between the mean scores of the questionnaires for quality of

life or physical activity, or in the median scores on the subscales for anxiety and depression in the HADS questionnaire between the various categories of 25OHD concentrations.

DISCUSSION

This study highlights the high prevalence of insufficient vitamin D concentrations in outpatients with IBD in our area. This finding was particularly notable in patients with CD, with a joint prevalence of 68% (33.3% deficiency). This prevalence rate in CD is almost exactly the same as that found by Raferty in 119 Irish patients with CD (8). It is also similar to that reported for a North American population (19) and lower than that seen in a recent multicenter Norwegian study (53% deficiency) (7). There are few data available for patients with UC, with prevalence rates ranging from 15% to 44% (7,20). Thus in agreement with our findings. On the other hand, we found a significantly lower median vitamin D concentration in CD compared to UC. This was not found by the various studies analyzing this issue (21,22).

A Spanish population-based study on the prevalence of hypovitaminosis D (which used the same methodology as we did) included over 1,200 non-institutionalized patients with no chronic diseases that affected phosphocalcium metabolism (40). Just over half the patients resided in the province where the study was undertaken. The prevalence of vitamin D deficiency (< 20 ng/ml) was almost the same (33.9%) as that observed in CD in our study. The lack of important differences in the proportion of vitamin D deficiency between healthy people and CD patients was also described by De Bruyn et al. in a case-control study in a Dutch population (34). The similar prevalence rates can be explained by the fact that most of the patients included were in clinical remission, had mild activity and the mean age of the patients in the Spanish population-based study (a risk factor for deficiency in their study) was 50 years of age. In addition, the seasonal effect was evident, with significantly higher vitamin D values in summer, although the deficiency prevalence in winter months in our study in CD patients (48.5%) was higher (37.2%) (40).

A cross-sectional study that was also undertaken in Spain examined the relation between vitamin D deficiency and bone mineral density in 64 patients with CD. There

was a deficiency prevalence of 60% (5). However, the reduced sample size and the absence of information about the season during which the measurements were taken or the percentage of patients with clinical activity hindered a comparison with our findings. In our study, as in other similar studies (22,28), the season the measurements were taken conditioned the results. There were significantly greater 25OHD concentrations when the samples were measured in the summer. Likewise, the percentage of patients with 25OHD concentrations below 20 ng/ml were greater in winter, for both UC and CD. This difference in seasonality has not been seen by others at different latitudes (7,11). Various cross-sectional studies have suggested an association between deficient vitamin D serum concentrations and a greater clinical and biological activity in CD and UC, although, overall, data are inconsistent (4,6). These studies differ greatly in terms of design, method of measuring 25OHD, composition of the study population and the clinical indexes and biological parameters of activity used.

In our patients, vitamin D deficiency was significantly associated with the presence of clinical activity in CD and UC, as measured by the HBI and Partial Mayo score. This aspect is discordant among the various studies, as some indicate an association with the CDAI (24), HBI (7) or the simple ulcerative colitis index (25), whereas others fail to show this association (8,23). In an attempt to correct the subjective component of the clinical indexes, we divided the patients according to FC and CRP levels. The median and the mean 25OHD in CD and UC, respectively, were greater in the groups considered to be non-active according to the FC criteria (< 170 mcg/g). This same finding was reported in another study on CD (8) which used a higher cut point for FC (250 mcg/g).

There is a general lack of an association between the vitamin D concentration and the CRP (7,8,11,26), although the occasional study did find a significant association (24). This may be due to the inclusion of few active patients and the lack of an increase in CRP in many patients with endoscopy-demonstrated activity. Our study identified a significant association between the CRP concentration and the vitamin D level in the entire cohort but not in the individual groups of patients with UC or CD separately. FC has been shown to be better than CRP and clinical disease activities at discriminating

intestinal inflammation, with a good correlation with endoscopic and histological scoring systems for IBD (27). Garg et al. (9) found a negative correlation between the 25OHD concentration and FC levels in 40 patients with CD. An Irish study detected a gradient in the FC concentration between the different subgroups of patients according to their vitamin D levels (8). We also noted this situation in the entire cohort of 224 patients and in the patients with CD, but not in UC cases. Only two studies have detected an association between vitamin D deficiency and FC levels in UC (7,9).

The association between vitamin D deficiency and some of the phenotypic characteristics of CD varies. The patients in our study with CD who had previously undergone surgery had significantly lower concentrations of 25OHD than the patients who had not undergone surgery. Moreover, lower 25OHD levels were found in the ileum compared to the colon. This finding has been noted in other studies (22,29,30). In addition, our patients with a fistulising pattern had significantly lower levels than those with an inflammatory or stenotic pattern.

Quality of life has been associated with 25OHD concentration (10,21) and one study even identified an improvement in quality of life after repletion of levels above 30 ng/ml (31). Given the relationship between vitamin D and depression and anxiety seen in some observational studies (12), we wanted to include this factor in our study. However, neither quality of life (assessed with the SIBDQ-9) nor the psychological symptoms (evaluated with the HADS) were associated with the 25OHD concentration in our series.

Kabani et al. performed a prospective study involving 965 patients with IBD and found a significant association between vitamin D deficiency levels and a greater consumption of health resources (32). We found an association with the use of steroids in the previous six months and hospitalization in the last year, although only in UC patients. A few other variables have been associated with low levels of vitamin D in IBD. Notable among these are longstanding disease (36), age (19,32), sex, smoking (33,34), steroid use, obesity (35) and non-Caucasian race (22,35). As the great majority of patients in our series were Caucasian, we are unable to assess this aspect. Neither the presence of active smoking, a greater BMI, nor a longer disease duration were associated with vitamin D levels in our study. Furthermore, no association was

detected between the vitamin D status and biological therapy or treatment with immunosuppressive drugs or steroids. However, recent studies have suggested a possible contribution of adequate vitamin D levels to the durability of biological treatment (37,38).

This study has a few limitations. Firstly, the cross-sectional nature of the study makes it impossible to draw conclusions regarding causality. Other limitations include the fact that it was a single-center study and there was no group of healthy controls. Furthermore, the gold standard for the measurement of vitamin D, liquid chromatography/tandem mass spectrometry, was not used in this study (39). However, the electro-chemiluminescence immunoassay method used is nevertheless the most widely employed and applicable in the clinical practice. Furthermore, it is calibrated with international standards. There may also have existed a certain degree of selection bias, as the outpatients from a regional reference hospital were more complex. The study population was almost solely Caucasian, which makes it impossible to compare our findings with those of other cohorts with a greater ethnic variation. Another possible bias that is not contemplated in most studies is the influence of the clinical activity on the lower physical exercise and thus, a reduced possibility of solar exposure. The sub-analysis of 149 patients in our series showed no significant differences in the median scores on the IPAQ between active patients and patients in remission. This can mainly be explained by the fact that the study involved active outpatients, mostly with mild or mild-to-moderate activity, who were able to carry out similar physical exercises to the patients in remission. Thus, we do not consider that physical activity has influenced the results.

The strengths of the study relate to the inclusion of a large and representative number of outpatients in follow-up for IBD and the prospective collection of the clinical data by the same team of IBD specialists. In addition, the difference with regard to seasonal measurements of vitamin D was also studied and FC was used as a more sensitive marker of clinical activity than CRP or indexes of clinical activity that are commonly used.

In conclusion, both deficient and insufficient levels of vitamin D are prevalent in IBD outpatients in our health area and there was a notable association with a greater

disease activity**.** However, certain questions remain to be resolved. The first of these is which IBD patients should receive supplements. Currently, there is no agreement with regard to the recommendations drawn up by the main scientific societies, which are based solely on maintaining musculoskeletal health. The Endocrine Society (41) recommends objective vitamin D levels above 30 ng/ml. On the other hand, the more conservative recommendations of the Institute of Medicine establish a cut point of concentrations below 20 ng/ml for starting treatment. No scientific evidence exists for vitamin D supplements as anti-inflammatory agent or adjuvant to other treatments for IBD. Furthermore, the concentrations of vitamin D that should be achieved in these cases are unknown. Clarifying this issue requires well-designed, prospective intervention studies, with endoscopic variables and sensitive biological markers such as FC. Objective vitamin D levels that are higher than necessary to maintain good bone health are also required. These studies will have to overcome potential ethical conflicts related with the treatment of the control group as well as safety from any potential toxic effects arising from overdoses of vitamin D.

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Table 1. Demographic, clinical and biological characteristics plus current treatment according to type of IBD

Variables	*UC (n = 74)*	*CD (n = 150)*	*p*
Age (years)*	42.67 (18.14)	36 (17.69)	0.002
Sex n (%)			
Female	38 (51.4)	74 (49.3)	0.89
Male	36 (48.6)	76 (50.7)	
Race n (%)			0.62
Caucasian	73 (98.7)	143 (95.3)	
Arab	1 (1.3)	6 (4)	
Black		1 (0.7)	
BMI†	25.34 ± 4.42	24.18 ± 4.13	0.05
BMI > 25 (kg/m^2), n (%)	36 (48.6)	55 (36.7)	0.11
Duration (years)*	5.5 (8.95)	6.25 (8.91)	0.584
Flares in last year, n (%)	43 (58.1)	80 (53.3)	0.57
Active smoker, n (%)	5 (6.8)	35 (23.3)	0.002
UC extensión, n (%)			
E2	29 (39.2)		
E3	45 (60.8)		
CD site, n (%)			
Ileum		58 (38.7)	
Colon		24 (16)	
Ileocolonic		68 (45.3)	
CD behavior, n (%)			
Inflammatory		90 (60)	
Stenotic		34 (22.6)	
Fistulising		26 (17.4)	
Perianal disease, n (%)		41 (27.3)	
Clinical activity, n (%) Remission			
Active	55 (74.3)	104 (68.7)	0.53
	19 (25.7)	46 (30.7)	

CRP (mg/l), n (%)			
< 10	65 (87.8)	133 (88.7)	0.83
> 10	9 (12.2)	17 (11.3)	
Fecal calprotectin (mcg/g), n (%)			
< 170			
> 170	58 (78.4)	114 (76)	0.74
	16 (21.6)	36 (24)	
Current medication, n (%)			
Steroids	6 (8.1)	12 (8)	1
AZA/MTX/6-MP	25 (33.8)	76 (50.7)	0.02
Biological	15 (20.3)	63 (42)	0.001
Prior surgery, n (%)		61 (40.6)	
Ileocecal resection		44	
Ileal resection		10	
Ileal + right colon resection		7	
Vitamin D supplements	6(8.1)	12 (8)	1
Vitamin D (ng/ml)*	30.2 (15.68)	24.38 (14.15)	0.002
Variables	*UC (n = 42)*	*CD (n = 107)*	*p*
SIBDQ-9 score*	65.15 (13.1)	63.9 (11.8)	0.76
HADS (anxiety)*	8 (8)	7 (7)	0.56
HADS (depression)*	5 (7)	5 (6)	0.43

*Median (interquartile range). †Mean ± standard deviation. n (%): absolute frequency (percentage). BMI: body mass index; HADS: hospital anxiety and depression scale; SIBDQ-9: Short Quality of Life in Inflammatory Bowel Disease Questionnaire; CRP: C reactive protein.

Table 2. Association between the demographic variables and the clinical and biological parameters according to the concentration of 25OHD in the entire cohort (n = 224)

Variable	Deficiency < 20 g/ml (n = 65)	Insufficiency 20-29 ng/ml (n = 77)	Adequate ≥ 30 ng/ml (n = 82)	p
Age*	38.8 (18.2)	38 (15.6)	37.5 (23.7)	0.83
Sex (male), n (%)	26 (23.2)	39 (34.8)	47 (42)	0.11
BMI (kg/m^2)*	23.2 (6.2)	25 (5.7)	24.3 (4.9)	0.13
Active smoker, n (%)	17 (42.5)	14 (35)	9 (22.5)	0.06
Disease duration (years)*	7.8 (11.8)	6.5 (8.3)	5 (8.7)	0.59
Active disease, n (%)	34 (52.3)	24 (36.9)	7 (10.8)	< 0.001
CRP (mg/l)*	2.9 (3.8)	2.9 (2.1)	2.9 (0.2)	0.04
Fecal calprotectin (mcg/g)*	107.8 (187.5)	84 (160.5)	47.2 (85.3)	0.002
Steroids in last 6 months, n (%)	18 (40)	19 (42.2)	8 (17.8)	0.012
Immunosuppression, n (%)	29 (28.7)	37 (36.6)	35 (34.7)	0.79
Biological, n (%)	31 (39.7)	25 (32.1)	22 (28.2)	0.03
Steroids, n (%)	8 (44.4)	7 (38.9)	3 (16.7)	0.15
Hospital admissions (previous year), n (%)	17 (48.6)	11 (31.4)	7 (20)	0.01
Vitamin D supplements, n (%)	8 (44.4)	7 (38.9)	3 (16.7)	0.15
Sub-analysis (n = 149)	Deficiency < 20 g/ml (n = 43)	Insufficiency 20-29 ng/ml (n = 60)	Adequate ≥ 30 ng/ml (n = 46)	p
Quality of life†	63.64 ± 9	64.22 ± 9.56	65 ± 9.78	0.78
HADS (A)*	7 (7.5)	8 (7)	8 (7)	0.9
HADS (D)*	4 (7)	5.5 (6.2)	5 (5)	0.84
Physical activity (METS)†	1,750 (1,878)	2,390 (2,343)	2,139 (2,192)	0.82

n (%): absolute frequency (percentage). *Mean ± standard deviation. †Median (interquartile range). CRP: C reactive protein.

Table 3. Association between the demographic variables and the clinical and biological parameters according to the concentration of 25OHD in patients with Crohn's disease (n = 150)

Variable	Deficiency (< 20 g/ml) (n = 50)	Insufficiency 20-29 ng/ml (n = 57)	Adequate ≥ 30 ng/ml (n = 43)	p
Age*	37.7 (15.7)	36.4 (16.4)	30.7 (16.8)	0.17
Sex (male), n (%)	23 (30.3)	30 (39.5)	23 (30.3)	0.72
BMI (kg/m^2)*	23 (5.9)	25.1 (5.1)	23 (4.3)	0.08
Active smoker, n (%)	15 (42.9)	14 (40)	6 (17.1)	0.18
Disease duration (years)*	6.4 (10.5)	8 (8.3)	5.1 (8.4)	0.52
Active disease, n (%)	26 (56.5)	18 (39.1)	2 (4.3)	< 0.001
CRP (mg/l)*	2.9 (3.8)	2.9 (3.1)	2.9 (0.4)	0.14
Fecal calprotectin (mcg/g)*	108.2 (180.5)	92 (128.4)	56 (88.5)	0.026
Steroids in last 6 months, n (%)	12 (42.9)	10 (35.7)	6 (21.4)	0.45
Immunosuppression, n (%)	26 (34.2)	28 (36.8)	22 (28.9)	0.95
Biological, n (%)	27 (42.9)	21 (33.3)	15 (23.8)	0.11
Steroids, n (%)	6 (50)	4 (33.3)	2 (16.7)	0.45
Hospital admissions (previous year), n (%)	12 (50)	6 (25)	6 (25)	0.15
Vitamin D supplements, n (%)	6 (50)	4 (33.3)	2 (16.7)	0.45
Sub-analysis (n = 149)	Deficiency < 20 g/ml (n = 37)	Insufficiency 20-29 ng/ml (n = 43)	Adequate ≥ 30 ng/ml (n = 27)	p
Quality of life†	63.9 ± 9.62	64.57 ± 9.1	64.58 ± 9.9	0.9
HADS (A)*	7 (7)	8 (7)	9 (7.5)	0.9
HADS (D)*	4 (6)	5 (7.5)	5 (5)	0.8
Physical activity (METS)†	1,704 (1,843)	2,236 (2,316)	2,520 (2,088)	0.72

n (%): absolute frequency (percentage). *Mean ± standard deviation. †Median (interquartile range). CRP: C reactive protein.

Table 4. Association between the demographic variables and the clinical and biological parameters according to the concentration of 25OHD in patients with ulcerative colitis (n = 74)

Variable	Deficiency < 20 g/ml (n = 15)	Insufficiency 20-29 ng/ml (n = 20)	Adequate ≥ 30 ng/ml (n = 39)	p
Age*	41 (22)	42.7 (10)	44.8 (21.5)	0.78
Sex (male), n (%)	3 (8.3)	9 (25)	24 (66.7)	0.02
BMI (kg/m^2)*	23.9 (9.4)	23.8 (9.3)	25.2 (5.5)	0.73
Active smoker, n (%)	2 (40)	0 (0)	3 (60)	0.32
Disease duration (years)*	9 (12.4)	4.5 (7.1)	5 (8.8)	0.55
Active disease, n (%)	8 (42.1)	6 (31.6)	5 (26.3)	0.008
CRP (mg/l)*	4.8 (3.9)	2.9 (0.5)	2.9 (0.2)	0.18
Fecal calprotectin (mcg/g)*	78.4 (207.8)	44.5 (205.8)	47 (81.8)	0.39
Steroids in last 6 months, n (%)	6 (35.3)	9 (52.9)	2 (11.8)	0.001
Immunosuppression, n (%)	3 (12)	9 (36)	13 (52)	0.30
Biological, n (%)	4 (26.7)	4 (26.7)	7 (46.7)	0.75
Steroids, n (%)	2 (33.3)	3 (50)	1 (16.7)	0.14
Hospital admissions (previous year), n (%)	5 (45.5)	5 (45.5)	1 (9.1)	0.003
Vitamin D supplements, n (%)	2 (33.3)	3 (50)	1 (16.7)	0.14
Sub-analysis (n = 149)	Deficiency < 20 g/ml (n = 6)	Insufficiency 20-29 ng/ml (n = 17)	Adequate ≥ 30 ng/ml (n = 19)	p
Quality of life†	62 ± 3.2	63.3 ± 10.8	65.6 ± 9.78	0.6
HADS (A)*	12 (6.5)	8 (6)	8 (7)	0.7
HADS (D)*	7.5 (6)	6 (6)	4 (4.5)	0.4
Physical activity (METS)†	2,454 ± 1,594	2,274 ± 1,659	2,377 ± 1,724	0.9

n (%): absolute frequency (percentage). *Mean ± standard deviation. †Median (interquartile range). CRP: C reactive protein.

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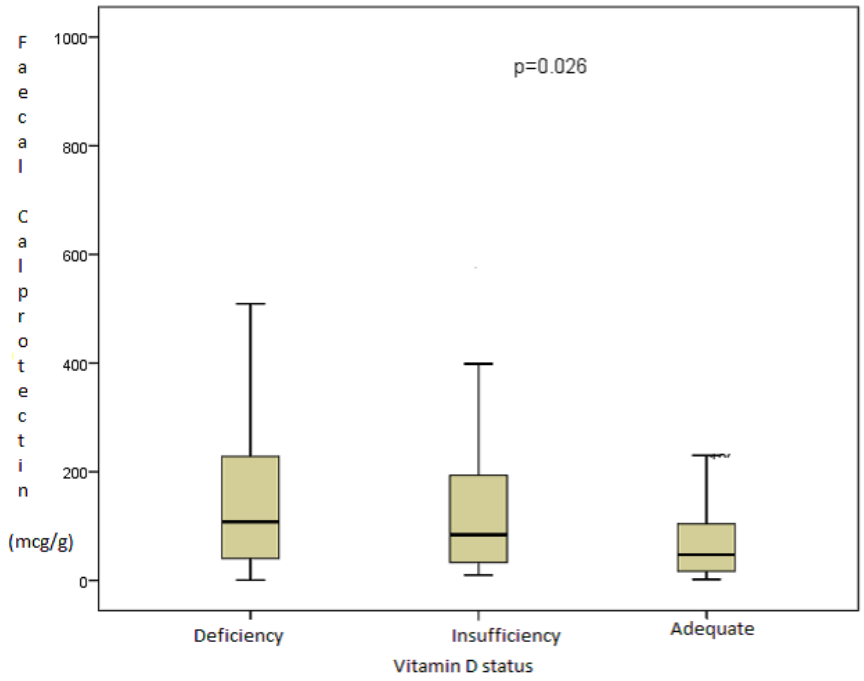

Fig. 1. Concentration of fecal calprotectin according to the vitamin D status of the patients with Crohn's disease.

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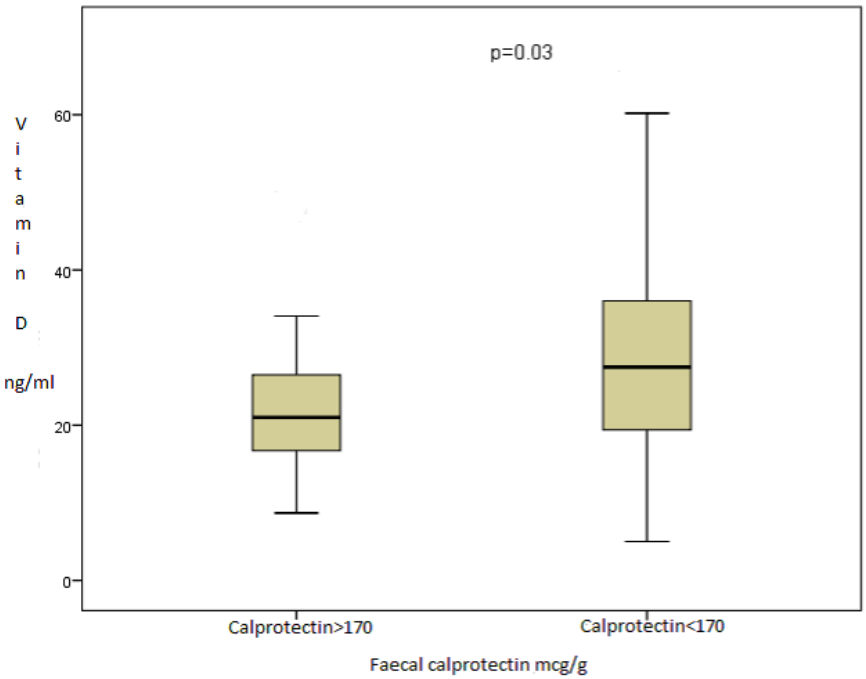

Fig. 2. Concentration of vitamin D in patients with fecal calprotectin above or below 170 mcg/g in Crohn's disease.

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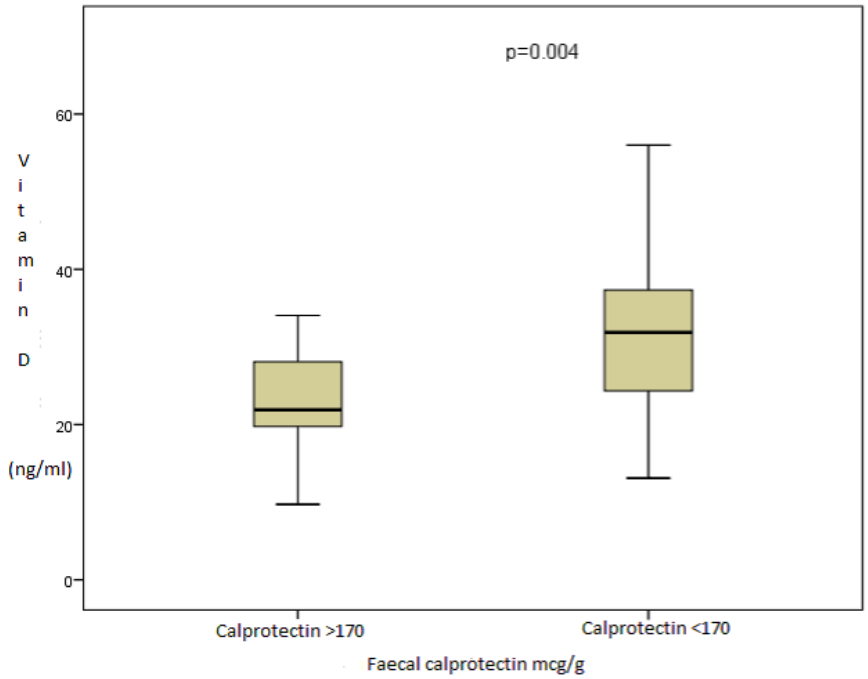

Fig. 3. Concentration of vitamin D in patients with fecal calprotectin above or below 170 mcg/g in ulcerative colitis.