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Vitamin D Deficiency in a Portuguese Cohort of Patients with Inflammatory Bowel Disease: Prevalence and Relation to Disease Activity

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Keywords

Crohn disease · Disease activity · Epidemiology · Inflammatory bowel disease · Ulcerative colitis · Vitamin D

Abstract

Background and Aims: Vitamin D deficiency is more common in inflammatory bowel disease (IBD) patients than in the general population. However, there are conflicting data about predictive factors of vitamin D deficiency and its potential association with disease activity. The aims of this study were to determine the prevalence and predictive factors of vitamin D deficiency and to evaluate a possible association with disease activity. ***Methods:*** A prospective observational study was conducted, including patients with IBD from January to July 2016. The Endocrine Society guidelines were considered for defining levels of serum 25-hydroxyvitamin D (25-OH-D) as follows: deficient (<20 ng/mL, <10 ng/mL being severe deficiency), insufficient (21–29 ng/mL), and adequate (>30 ng/mL). ***Results:*** A total of 152 patients (52% men; 47.2 ± 17.3 years) were included, of whom 70% had Crohn's disease (CD). Thirty-seven percent of patients were on immunosuppressors and 17% were on biologics. The majority were outpatients (88.2%). Mean 25-OH-D levels were 17.1 ± 8 ng/mL (CD: 16.7 ± 8 ng/mL vs. ulcerative colitis: 17.6 ± 7 ng/mL, $p = 0.1$). Inadequate levels were present in 90.8% of patients (deficiency: 68.4%; insufficiency: 22.4%). A significant negative correlation between 25-OH-D levels and age ($r = -0.2$, $p = 0.04$), C-reactive protein (CRP) levels ($r = -0.22$, $p = 0.004$), and Harvey-Bradshaw index (HBi) ($r = -0.32$, $p = 0.001$) was found. Patients with severe deficiency showed a higher CRP (0.6 vs. 1.4 mg/dL, $p = 0.03$), erythrocyte sedimentation rate (ESR) (22 vs. 31 mm/h, $p = 0.03$), and HBi (2 vs. 5, $p < 0.001$) and lower hemoglobin (13.6 vs. 12.7 g/dL, $p = 0.02$). There was no association between vitamin D deficiency and gender, type, extent, and duration of disease, surgery, and other measures of disease activity, such as ESR, hemoglobin (these 2 items except for severe deficiency), fecal calprotectin, or Truelove and Witts classification. ***Conclusions:*** There is a high prevalence of inadequate levels of vitamin D in IBD patients, particularly deficiency (68.4%). There seems to exist an association between lower levels of vitamin D and higher disease activity, especially in CD.

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Deficiência de vitamina D numa coorte de doentes Portugueses com doença inflamatória intestinal: prevalência e relação com a atividade da doença

Palavras Chave
Doença de Crohn · Atividade da doença · Epidemiologia · Doença inflamatória do intestino · Vitamina D

Resumo
Introdução: A deficiência de vitamina D é mais comum na doença inflamatória intestinal (DII) que na população geral. Contudo, existem dados controversos sobre fatores preditivos da deficiência de vitamina D e a potencial associação com a atividade da doença. Os objetivos deste estudo foram determinar a prevalência e fatores preditivos da deficiência de vitamina D e aferir possível associação à atividade da doença. ***Métodos:*** Desenhou-se um estudo observacional prospetivo incluindo doentes com DII entre janeiro e julho/2016. Foram consideradas as orientações da *The Endocrine Society* para definir níveis de 25-hidroxivitamina D (25-OH-D) sérica como: deficientes (<20 ng/mL, sendo <10 ng/mL deficiência grave [DG]), insuficientes (21–29 ng/mL) e adequados (>30 ng/mL). ***Resultados:*** Foram incluídos 152 doentes (52% homens; 47.2 ± 17.3 anos), dos quais 70% com Doença de Crohn (DC). Do total, 37% estavam medicados com immunossupressores e 17% com biológicos. A maioria (88.2%) estava em ambulatório. O nível sérico de 25-OH-D foi 17.1 ± 8 ng/mL (DC:16.7 ± 8 ng/mL vs. Colite ulcerosa: 17.6 ± 7 ng/mL, $p = 0.1$). Verificaram-se níveis inadequados em 90.8% (deficiência: 68.4%; insuficiência: 22.4%). Registou-se correlação negativa significativa entre níveis de 25-OH-D e idade ($r = –0.2$, $p = 0.04$), proteína C-reativa (PCR) ($r = –0.22$, $p = 0.004$) e índice *Harvey-Bradshaw* (iHB) ($r = –0.32$, $p = 0.001$). Doentes com DG apresentaram níveis mais elevados de PCR (0.6 vs. 1.4 mg/dL, $p = 0.03$), velocidade de sedimentação (VS) (22 vs. 31 mm/h, $p = 0.03$) e iHB (2 vs. 5, $p < 0.001$), e mais baixos de hemoglobina (13.6 vs. 12.7 g/dL, $p = 0.02$). Não se verificou associação entre deficiência de vitamina D e sexo, tipo, extensão e duração da doença, cirurgia, e outras medidas de atividade da doença como VS, hemoglobina (estas duas exceto para DG), calprotectina fecal ou classificação *Truelove* e *Witts*. ***Conclusões:*** Registou-se prevalência alta de níveis inadequados de vitamina D na DII, particularmente de deficiência (68.4%). Parece existir associação entre níveis mais baixos de vitamina D e maior atividade da doença, nomeadamente na DC.

Introduction

Vitamin D deficiency has become an increasingly relevant topic in medical practice and literature, particularly during the last years, and since 2010 more than one thousand papers subordinated to this subject have been published and indexed in PubMed per year. A high prevalence of vitamin D deficiency has been reported not only in sick populations [1], particularly hospitalized patients, but also in healthy individuals, as demonstrated in a recent study that defines it as being pandemic in Europe [2]. A contemporary study [3], performed in the north of Portugal, in 2016, reported a prevalence of 48 and 74% of vitamin D deficiency in a healthy adult population (18–67 years), in summer and winter, respectively. There is evidence of an association between lower levels of vitamin D and higher risk of numerous diseases, such as cancer, mental disorders, infection, cardiovascular diseases, type 2 diabetes mellitus, and autoimmune disorders [4].

Inflammatory bowel disease (IBD) refers to a group of chronic autoimmune diseases, consisting mainly of Crohn's disease (CD) and ulcerative colitis (UC), which involve a dysregulation of the immune system with consequences in the intestinal wall [5]. Vitamin D deficiency has also been reported in these patients, although published data are conflicting as the prevalence of vitamin D deficiency in patients with IBD ranges from 16 to 95% [6–14]. It is also not clear in which type of IBD the prevalence of vitamin D deficiency is higher [8, 15]. Facing the need to clarify this controversy, a systematic review with a meta-analysis was conducted in 2015. It included 14 studies with a total of 1,891 patients and reported that patients with IBD had 64% higher odds of vitamin D deficiency when compared with controls [15]. An association with disease activity has been described more inconsistently, with some authors arguing that there is a relation between lower levels of vitamin D and higher disease activity [6, 16–21], while others have not found any relation [22–24]. There are 2 published Portuguese studies on this subject, both from the north of the country. Castro et al. [6] encountered a prevalence of vitamin D deficiency of 30% (samples were collected in the summer and patients included were only in ambulatory care) in a cohort of 76 patients with IBD, particularly in those with CD, and found a correlation between lower levels of vitamin D and higher disease activity and worse quality of life. Santos-Antunes et al. [7] included 68 patients with IBD with indication to start anti-TNF therapy and found a prevalence of vitamin D deficiency

of 93%. The Endocrine Society guidelines recommend vitamin D screening only in high-risk individuals, where IBD patients are included [1].

The aim of this study was to determine the prevalence of vitamin D deficiency in a cohort of Portuguese IBD patients and identify whether there was an association between vitamin D levels and disease activity or not.

Methods

A prospective observational and cross-sectional study was performed in a district Hospital in the region of Lisbon between January and July 2016. Winter was considered from December to April and summer from May to July.

Inclusion and Exclusion Criteria

Patients aged 18 years and older with a diagnosis of IBD according to ECCO guidelines [25, 26] were consecutively included; either they were in an ambulatory setting or hospitalized. Exclusion criteria included medical conditions that interfere with vitamin D levels, such as chronic kidney disease, liver cirrhosis, exocrine pancreatic insufficiency, pregnancy, lactation, the use of medications, such as anticonvulsants, and supplements with vitamin D.

Demographic and Clinical Variables

Demographic and clinical data were collected by interview and included age, gender, type, extent, location, and behavior of the disease according to the Montreal Classification [25, 26], duration of disease, IBD-related surgeries, actual hospitalization or ambulatory care, and medication for IBD.

Vitamin D and Laboratory Variables

All samples were collected and analyzed at the Hospital Central Laboratory. Vitamin D was assessed by the serum 25-hydroxyvitamin D (25-OH-D) through the LIAISON® 25 OH Vitamin D Assay which is a chemiluminescent immunoassay.

Categorization of Vitamin D Levels

The Endocrine Society guidelines [1] were considered for evaluating the levels of 25-OH-D: deficiency (<20 ng/mL, <10 ng/mL being a severe deficiency), insufficiency (21–29 ng/mL), and adequacy (>30 ng/mL). Inadequacy includes deficiency and insufficiency.

Definition of Disease Activity

Disease activity was measured both clinically and analytically. The clinical indices used in the study were the Truelove and Witts classification (TLWc) for UC and the Harvey-Bradshaw index (HBi) for CD. According to the TLWc, UC was classified as inactive, mild, moderate, and severe. A score of the HBi >4 was considered as active disease. Laboratory markers of disease activity were measured by C-reactive protein (CRP; normal range <0.29 mg/dL), erythrocyte sedimentation rate (ESR; normal range <20 mm/h), hemoglobin (Hb; normal range for men <13 g/dL and for women <12 g/dL), and fecal calprotectin (FC; normal range <100 μg/g).

Endpoints

Our primary endpoints were to determine the prevalence of vitamin D deficiency and to evaluate an association between vitamin D levels and disease activity. Our secondary endpoint was to analyze if there were predictors of vitamin D deficiency.

Data and Statistical Analysis

Normally distributed variables were described using the mean and standard deviation; variables with a skewed distribution were described using the median and range. Crude associations between pairs of variables were analyzed using the Student *t* test and the χ^2 test. Nonparametric tests (Mann-Whitney *U* test) were used when normality could not be assumed. All tests were two-sided. *p* values <0.05 were considered statistically significant. We did not perform any correction for multiple testing because we considered our analyses explorative. IBM SPSS Statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA, released in 2011) was used for all statistical analyses.

Ethical Considerations

The study was approved by the Institutional Ethics Committee of our hospital. All patients signed an informed consent form.

Results

Demographic and Clinical Data

A total of 152 patients were included in the study, of whom 79 (52%) were male and the median age was 47.2 ± 17.3 years (range 17–89). Of these, 106 (70%) had CD, 44 (29%) UC, and 2 (1%) unclassified IBD, with a mean disease duration of 8.4 ± 7.9 years (range 0–45). About one-third of patients (37%, 55 patients) were medicated with immunosuppressors (azathioprine or methotrexate), 17% (26 patients) with anti-TNF, which were either infliximab or adalimumab, and 9% (14 patients) were on combination therapy with azathioprine (9 under infliximab and 5 under adalimumab). There were 17% (26 patients) medicated with corticosteroids and 78.3% (119 patients) with salicylates. A minority of patients (11.8%, 18 patients) was hospitalized. Of CD patients, 92 (86.2%) had small bowel involvement, with 51 (48.1%) of them showing ileocolic involvement (L3 according to the Montreal Classification), 22 patients (20.8%) had perianal disease, and 33 (21.7%) had had small bowel resection. Of UC patients, 18 (40.8%) had pancolitis (E3 according to the Montreal Classification). More detailed information about demographic and clinical data is displayed in Table 1.

Prevalence of Vitamin D Deficiency and Vitamin D Levels

Mean vitamin D levels were 17.1 ± 8 ng/mL, slightly higher in UC (17.6 ± 7 ng/mL) than in CD (16.7 ± 8 ng/

Table 1. Baseline characteristics of patients: demographic, clinical, and laboratorial data (n = 152)

Age, years	47.2±17.3 (17–89)
Male sex	79 (52)
Type of disease	
Crohn disease	106 (70)
Ulcerative colitis	44 (29)
Disease duration, years	8.4±7.9 (0–45)
Current medication	
Immunosuppressors	55 (37)
Biologics	26 (17)
Corticosteroids	26 (17)
Surgery	33 (21.7)
Inpatients	18 (11.8)
Crohn disease location[a]	
L1	41 (31.7)
L2	14 (13.2)
L3	51 (48.1)
L4	17 (16)
Crohn disease behavior[a]	
B1	58 (54.7)
B2	22 (20.8)
B3	26 (24.6)
Perianal disease	22 (20.8)
Ulcerative colitis extent[a]	
E1	9 (20.5)
E2	17 (38.7)
E3	18 (40.8)
C-reactive protein, mg/dL	0.75±1.8
Sedimentation rate, mm/h	24.1±23
Hemoglobin, g/dL	13.4±1.8
Fecal calprotectin, mg/kg	728±1200
Harvey-Bradshaw index	2.7±3
Truelove and Witts, mild/moderate/severe	7/8/2

Values are means ± standard deviations (ranges) or n (%) unless otherwise indicated. [a] According to the Montreal Classification.

mL); this difference was not statistically significant (p = 0.1). Globally, the prevalence of vitamin D deficiency was 68.4% and was higher in CD (72%) than in UC (65%), but this difference was not statistically significant (p = 0.4). Taking all patients into consideration, 17.7% had severe deficiency, and this prevalence tended to be significantly higher in CD (24%) than in UC (11%, p = 0.06). Inadequate levels of vitamin D were present in 90.8% of patients, a percentage very similar in CD and UC (91 vs. 93%, respectively, p = 1). More detailed information about the prevalence of inadequate vitamin D levels can be found in Table 2.

Table 2. Prevalence of inadequate vitamin D levels

	Total	CD	UC	p value
Inadequate levels	90.8	91	93	1
Insufficiency	22.4	20	28	0.3
Deficiency	68.4	72	65	0.4
Severe deficiency	17.7	24	11	0.06

Values are %. CD, Crohn's disease; UC, ulcerative colitis.

Vitamin D Deficiency and Disease Activity

The influence of vitamin D levels on disease activity was evaluated numerically and categorically. According to the clinical indices, there were 47 patients (30.9%) with active disease, of whom 30 had CD. In UC, 36.9% had active disease (88.2% had mild or moderate activity), and in CD 28.3% had a HBi compatible with active disease. Considering this clinical definition of active disease, there was no association between active disease and vitamin D deficiency (p = 1); however, patients with active disease more frequently had severe vitamin D deficiency than those in remission (33 vs. 13%, p = 0.004).

Patients with vitamin D deficiency more commonly had markers of higher disease activity than patients without vitamin D deficiency, except for FC. They had more active disease determined by the TLWc (65 vs. 62%, p = 0.4) or the HBi (2.8 vs. 2.5, p = 0.6), higher CRP levels (0.85 vs. 0.53 mg/dL, p = 0.3) and ESR (24.9 vs. 22.4 mm/h, p = 0.5), and lower Hb levels (13.3 vs. 13.6 g/dL, p = 0.4), although these differences were not statistically significant. Nonetheless, when considering patients with severe vitamin D deficiency, these differences were all statistically significant, except for the TLWc: they also had more active disease determined by the TLWc (12 vs. 7%, p = 0.07) or the HBi (5 vs. 2, p = 0.001), higher CRP levels (1.4 vs. 0.6 mg/dL, p = 0.03) and ESR (31 vs. 22 mm/h, p = 0.03), and lower Hb levels (12.7 vs. 13.6 g/dL, p = 0.02).

It was possible to determine correlations between levels of vitamin D and some demographic, clinical, and analytical variables. Patients with lower levels of vitamin D were significantly older (r = –0.20, p = 0.04) and had a higher HBi (r = –0.32, p = 0.001) and CRP levels (r = –0.22, p = 0.004). More detailed information about the relation between vitamin D deficiency and disease activity is presented in Table 3.

Table 3. Influence of markers of disease activity on vitamin D deficiency and severe deficiency

	Deficiency		*p* value	Severe deficiency		*p* value
	no	yes		no	yes	
Mean CRP, mg/dL	0.53	0.85	0.3	0.6	1.4	0.03
Mean ESR, mm/h	22.4	24.9	0.5	22	31	0.03
Mean Hb, g/dL	13.6	13.3	0.4	13.6	12.7	0.02
Mean FC, mg/kg	1,117	556	0.02	754	598	0.4
Mean HBi	2.5	2.8	0.6	2	5	0.001
TLWc (inactive vs. active)	62%	65%	0.4	7%	12%	0.07

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; FC, fecal calprotectin; HBi, Harvey-Bradshaw index; TLWc, Truelove and Witts classification.

Predictors of Vitamin D Deficiency and Severe Deficiency

There were no statistically significant differences in relation to baseline demographic and clinical characteristics and medication of patients with and without vitamin D deficiency except for the use of corticosteroids, which was more common in patients with vitamin D deficiency (85 vs. 65%, $p = 0.04$), and the season when vitamin D deficiency was diagnosed, with winter being the most frequent one (78 vs. 57%, $p = 0.005$).

When considering patients with severe deficiency of vitamin D, more pronounced differences were noticed. Apart from a diagnosis during the winter and the use of corticosteroids also being more frequent in these patients (27 vs. 10%, $p = 0.008$ and 33 vs. 15%, $p = 0.05$, respectively), other differences were noticed. Patients on biologics more often had severe deficiency than patients who were not under this medication (37 vs. 16%, $p = 0.01$), and inpatients more commonly had severe deficiency than outpatients (50 vs. 15%, $p = 0.001$). There were 2 other differences, although they were not statistically significant, namely that patients with CD more frequently had a severe deficiency (24 vs. 11% of UC patients, $p = 0.06$) and patients with an age above 60 years also had more severe deficiency than patients under 60 years (30 vs. 17%, $p = 0.07$). More detailed information about predictors of vitamin D deficiency is presented in Table 4.

Discussion

The prevalence of vitamin D deficiency is high and is considered a public health problem since it has implications in many diseases, besides the well-known consequences on bone disease. Vitamin D, or calciferol, is a generic term and refers to a group of lipid-soluble compounds, 25-OH-D being the major circulating form of vitamin D and 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) its most active form [27]. Vitamin D has a well-known role in mineral metabolism and bone health, and its supplementation in young children is well established for preventing rickets [28]. In the last decade, the perspective on the influence of vitamin D on health has changed due to the discovery of vitamin D receptor and vitamin D activating enzyme 1-α-hydroxylase (CYP27B1) in many cell types, such as the intestine, pancreas, prostate, and immune system [29, 30]. Specifically, in immunology, the synthesis of $1,25(OH)_2D$ by immune cells and peripheral tissues has been proposed to have immunomodulatory properties similar to locally active cytokines [31, 32].

Vitamin D deficiency has been reported to be very prevalent among patients with IBD. Although a high prevalence of vitamin D deficiency is also being described in the general population, it seems to be higher in patients with IBD, with a calculated odds ratio of 1.64 [15]. In fact, different prevalence rates of vitamin D deficiency were published, namely 16–95% [6–14], but the later studies, which include a systematic review [15], reported high prevalence rates. Our study is in accordance with the most recent data, revealing a prevalence of 68% of vitamin D deficiency, and almost one-fifth of patients had a severe deficiency, with only around 9% of patients having adequate levels of vitamin D. In comparison with the 2 published Portuguese studies [6, 7], this prevalence lies in between, which can be explained by the differences in the inclusion criteria: our study included patients with IBD in different clinical settings, while one of the studies included just outpatients [6] and the other included only patients with more severe disease [7].

Table 4. Influence of demographic and clinical variables on vitamin D deficiency and severe deficiency

	Deficiency, %	*p* value	Severe deficiency, %	*p* value
Age				
>60 years	69	0.8	17	0.07
<60 years	72		30	
Gender				
Female	71	0.4	22	0.4
Male	66		18	
Season				
Winter	78	0.005	27	0.008
Summer	57		10	
Type of disease				
Crohn disease	69	0.9	24	0.06
Ulcerative colitis	68		11	
Hospital setting				
Inpatients	72	0.8	50	0.001
Outpatients	68		15	
Surgery				
Yes	66	0.8	24	0.4
No	69		19	
Current medication, yes/no				
Immunosuppressors	63/71	0.4	19/20	0.9
Biologics	76/67	0.5	37/16	0.01
Corticosteroids	85/65	0.04	33/15	0.05

The mean values of vitamin D assessed in our study, 17.1 ± 8 ng/mL, were classified as deficient. A relevant question that is being raised in several recent papers is whether we are overdiagnosing vitamin D deficiency. Even among healthy individuals, the prevalence of vitamin D deficiency is so high that it has been referred to as pandemic in Europe and North America [2, 33, 34]. Some of the factors that may contribute to this high prevalence in heathy individuals in different studies are seasonality, differences in the analytical method to measure vitamin D, heterogeneous populations included in the studies (sex, life stage/age, and ethnicity), and different cutoffs for defining deficiency. It is interesting to note that, over the last 2 decades, the recommended cutoff values and recommended diary intake of vitamin D to reach an adequate level have changed to higher values [33]. The reason for this is probably related to the great amount of studies reporting an increased prevalence of vitamin D deficiency in several diseases, including IBD [10, 33].

IBD patients are at risk of vitamin D deficiency, and many factors are likely to contribute, such as malabsorption, reduced sunlight exposure, insufficient physical activity, low vitamin D intake, smoking, and corticoid use [8]. Among the described factors, this study supports 2 of them as factors that can predispose to vitamin D deficiency, namely reduced sunlight exposure and corticoid use.

There was a tendency towards a difference in the prevalence of vitamin D deficiency between CD and UC. When analyzing all patients with deficiency, the difference was small (72% of deficiency in CD and 65% in UC, $p = 0.4$), but when the subset of patients with severe deficiency was analyzed, this difference was considerable, although not statistically significant, severe deficiency being more frequent in CD patients than in UC patients (24% in CD vs. 11% in UC, $p = 0.06$). In contrast to our findings, the largest meta-analysis on this topic reported a higher odds ratio for vitamin D deficiency in UC than in CD (2.24 and 1.63, respectively), although the authors assume that this could be, at least in part, due to a sample size effect, because there were fewer total patients and fewer events in the UC meta-analysis than in the CD meta-analysis [15]. A relation to disease activity could not be determined due to a lack of this information in the majority of the studies included in this meta-analysis.

One of the most interesting observations in this study is that lower levels of vitamin D are associated with in-

creased disease activity, measured in different ways (both clinical and laboratorial), a finding that has not been so clearly established in most of the studies. The high prevalence of vitamin D deficiency could hinder identification of possible predictive factors and a relation with disease activity. Consequently, analyses of associations with lower levels of vitamin D were conducted in a numeric and a categorical way (the latter using the definition of severe deficiency). We found that lower levels of vitamin D were associated with older age, higher CRP levels, and a higher HBi. In those patients fitting the category of severe deficiency, it was noted that they more frequently presented the following characteristics: active disease, when measured by clinical indices, higher ESR and lower Hb levels, use of biologics or corticosteroids, and being hospitalized. These results suggest that low levels of vitamin D are linked to high disease activity. There is no consensus on this issue in the literature, although many studies have already reported a relation between low levels of vitamin D and more clinical activity [6, 16–21], while others have not [22–24]. This relation is more consistently reproduced when activity is subjectively measured, by clinical indices, than when activity is objectively measured, by systemic inflammation markers, such as CRP or ESR (as fecal calprotectin is measured in almost none of the studies). For example, in CD, many studies report a link between vitamin D deficiency and increased clinical activity, either measured by the HBi [8, 16, 21] or Crohn's Disease Activity Index [17, 18]. In UC, data are more scarce, and, until now, only 2 studies reported an inverse relation between vitamin D levels and disease activity, measured by clinical scores [21, 34]. The relation with systemic inflammation is not that linear, presumably because even patients with active disease can have normal CRP values [18], and very seldom have higher CRP levels been associated with vitamin D deficiency [22] and insufficiency [6]. To the best of our knowledge, there are no studies about the relation between ESR and anemia and severe vitamin D deficiency. Possible explanations are that only a few studies measured those variables (or at least referred to them), and there was a relatively high proportion of patients with active disease in our study (around one-third of the total). In our study, FC was not associated with vitamin D deficiency. FC is a sensitive (60–70%) and specific marker of active disease, better than CRP [25]. We assume that this lack of relation is associated with the fact that median levels of FC were high in our study (298 μg/g, n = 105), and as the prevalence of deficiency was also high, it was statistically more difficult to establish an association. The study by Kabbani et al. [21] including 965 patients also associated low vitamin D levels with a higher need of biologics, corticosteroids, and hospitalizations, and we obtained a similar finding, namely that patients with these characteristics more commonly had severe vitamin D deficiency.

Other strengths of our study were the number of included patients, the highest until now in a Portuguese population and one of the highest in unicentric studies, and the fact that patients were included in a prospective way. Also, this is the first study performed in the south of the country.

There are limitations to our investigation. We included a heterogenic group of patients, incorporating CD and UC patients, with a wide range of age, and hospitalized and ambulatory patients, which, on the one hand, could improve the analysis but, on the other hand, could result in many confounders, which we tried to diminish by analyzing some subgroups of patients. Another limitation is the fact that we measured vitamin D levels both in summer and winter, and, as expected, there was a statistically significant difference in the levels between the 2 seasons, demonstrating the importance of seasonality for vitamin D biology.

There are already some studies which report that supplementation with vitamin D could have good outcomes, although these effects have been measured by symptoms and have not been demonstrated by laboratory markers or endoscopy [35–39]. Also, the exact supplementation dose of vitamin D has not yet been determined. Routine screening is not yet recommended in European guidelines unless there is suspicion of bone disease or prolonged corticosteroid use [40].

Conclusions

Vitamin D deficiency is very prevalent in Portuguese IBD patients, in CD as well as in UC patients. Winter and corticosteroid medication are predictors of vitamin D deficiency. In addition, hospitalization and biologics medication are predictors of severe vitamin D deficiency. It is important to determine the level of deficiency of vitamin D, because the lower the level of vitamin D, the more evident the link to higher disease activity, especially in CD patients. Future research should focus on the potential therapeutic effect of vitamin D supplementation.

Statement of Ethics

The study was approved by the Institutional Ethics Committee of our hospital. All patients signed an informed consent form.

Disclosure Statement

The authors have no conflicts of interest to declare.

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