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Original Article

Deficiency of vitamin D and its relation with clinical and laboratory activity of inflammatory bowel diseases☆

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ABSTRACT

Objective: To evaluate the serum concentrations of vitamin D and their relation with inflammatory bowel diseases.

Methods: This is a quantitative and descriptive study, with individuals assisted by the interdisciplinary ambulatory of Inflammatory Bowel Disease of the Family and Community Health Unit of Itajaí/SC from September 2015 to October 2016. Socioeconomic data, life habits, and biochemical tests were collected, with the use of clinical indexes of classification of the disease activity: Harvey-Bradshaw Index (Crohn's Disease) and Partial Mayo Score (Chronic Nonspecific Ulcerative Colitis).

Results: Of the 60 patients evaluated, 57% ($n = 34$) had Crohn's Disease and 43% ($n = 26$) had Chronic Nonspecific Ulcerative Colitis. According to disease activity, 75% ($n = 45$) were in the remission phase, 13% ($n = 8$) had mild activity, and 9% ($n = 5$) had moderate activity. Regarding vitamin D, 63% ($n = 38$) had deficiency of this vitamin and 37% ($n = 22$) presented sufficiency. With the association of serum vitamin D concentrations and disease activity, we observed statistical significance among the variables ($p = 0.005$). Regarding biochemical exams, the majority of patients with fecal calprotectin elevation presented vitamin D deficiency ($p = 0.025$). Statistically significant correlation between HSV and vitamin D ($p = 0.0001$) was found.

Conclusion: According to the findings of this study, vitamin D deficiency is related to the clinical and laboratory activity of inflammatory bowel diseases.

☆ Study conducted at the Inflammatory Bowel Disease Ambulatory, Universidade do Vale do Itajaí, Itajaí, SC, Brazil.

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Deficiência de vitamina D e sua relação com a atividade clínica e laboratorial das Doenças Inflamatórias Intestinais

Palavras-chave:
Doença de crohn
Retocolite ulcerativa
Vitamina D

RESUMO

Objetivo: Avaliar as concentrações séricas de vitamina D e sua relação com as doenças inflamatórias intestinais.
Métodos: Estudo quantitativo e descritivo com indivíduos assistidos pelo ambulatório interdisciplinar de Doença Inflamatória Intestinal da Unidade de Saúde Familiar e Comunitária de Itajaí/SC no período de setembro 2015 até outubro 2016. Foram coletados dados socioeconômicos, hábitos de vida, exames bioquímicos e foram plicados os índices clínicos de classificação da atividade da doença: Índice de Harvey-Bradshaw (Doença de Crohn) e Escore Mayo Parcial (Retocolite Ulcerativa Inespecífica Crônica).
Resultados: Dos 60 pacientes avaliados, 57% (n = 34) eram portadores de Doença de Crohn e 43% (n = 26) de Retocolite Ulcerativa Inespecífica Crônica. De acordo com a atividade da doença, 75% (n = 45) encontravam-se em fase de remissão, 13% (n = 8) em atividade leve e 9% (n = 5) em atividade moderada. Com relação a vitamina D, 63% (n = 38) apresentavam deficiência e 37% (n = 22) demonstravam suficiência. Associando as concentrações séricas de vitamina D e a atividade da doença, observou-se significância estatística entre as variáveis (p = 0,005). Com relação aos exames bioquímicos, a maioria dos pacientes com calprotectina fecal elevada apresentou deficiência de vitamina D (p = 0,025). Houve correlação estatisticamente significativa entre VHS e vitamina D (p = 0,0001).
Conclusão: Segundo os achados do estudo, deficiência de vitamina D relaciona-se com atividade clínica e laboratorial das doenças inflamatórias intestinais.

Introduction

Inflammatory bowel diseases (IBD), which are chronic non-infectious, progressive, and autoimmune inflammations, are divided into two forms of presentation: Crohn's disease (CD), which can affect the entire extent of the gastrointestinal tract, and Chronic Nonspecific Ulcerative Colitis (CNUC), which is restricted to the colon and rectum.[1–3] The etiology of these diseases is not definitively clarified, but some studies suggest that they are related to a genetic predisposition, an interaction with external factors (*e.g.*, environmental factors), autoimmune events associated with abnormalities, and loss of intestinal mucosal balance and immune cell changes.[4,5]

Vitamin D and its prohormones and antagonists have been the subject of studies, because of their interaction with the immune system and the expression of vitamin D receptor (VDR) in various tissues of the body, such as brain, heart, skin, gonads, breasts, and immunological and intestinal cells, and their relationship with other conditions such as cancer, cardiovascular diseases, and autoimmune diseases.[6,7]

VDR is widely expressed in immune cells, especially in the activation of T-lymphocytes and dendritic cells and in the expression of antigen-presenting cells, monocytes, macrophages, and natural killer cells, in addition to stimulating the production of interleukins. These immunomodulatory properties of vitamin D may explain the likely association between its serum concentrations and the number of autoimmune disease cases, including IBD.[8]

It is not uncommon the occurrence of vitamin D deficiency among patients with IBD.[6–10] The mechanisms proposed to explain this frequent occurrence would be intestinal malabsorption (mainly in cases of CD, due to ileus involvement, a decreased enterohepatic circulation of the vitamin, and short bowel syndrome), and a low ingestion of vitamin D-rich foods. It should be noted that the modern lifestyle negatively influences vitamin D production, and factors such as sun exposure, season of the year, clothing, sun block products' use, and smoking should be taken into account.[6–10] In view of the above, this study aimed to evaluate serum vitamin D levels and its relationship with IBD in outpatients.

Method

This is a cross-sectional, descriptive study. The study population was drawn from a universe of 106 patients and, after applying inclusion and exclusion criteria, a consecutive sample of 60 patients with a diagnosis of inflammatory bowel disease (IBD) was established. Data collection was performed from September 2015 to October 2016 at the IBD interdisciplinary outpatient clinic of the Unidade de Saúde Familiar e Comunitária (USFC) of Itajaí, Santa Catarina.

The inclusion criteria were: age over 18 years, the signature of a free informed consent form, a diagnosis of IBD, vitamin D, fecal calprotectin, ferritin, ESR, and CRP values obtained simultaneously, and no nutritional supplementation with vitamin D in the last six months.

The data collection was performed after the end of the consultations in the outpatient clinic and for this purpose, we applied a semi-structured form that covered socioeconomic characteristics (identification of the patient, age group, gender, people with whom he/she lives, marital status, occupation, education, and income), life habits, and health (family history of IBD, smoking, use of a vitamin D supplement or multivitamins).

The socioeconomic classification of the evaluated patients was made through the Critério de Classificação Econômica Brasil, proposed by the Instituto Brasileiro de Geografia e Estatística (IBGE) and updated by the Associação Brasileira de Empresas de Pesquisa (ABEP), taking into account data as family income, schooling, living conditions, and possession of durable goods (house owner, or rented housing).[11]

The diagnosis of IBD was established by physicians, and data on vitamin D concentrations and disease activity were obtained through laboratory tests and by applying a clinical index of disease activity.

Serum vitamin D concentrations were assessed, and the values <30 ng/mL, 30–80 ng/mL, and >100 ng/mL, were considered as defining deficiency, sufficiency, and toxicity, respectively, in accordance with the parameters of the Laboratório da Escola de Análises Clínicas (LEAC/UNIVALI).

To evaluate the laboratory activity of the disease, fecal calprotectin, CRP, ferritin, and ESR were obtained. In the evaluation of fecal calprotectin, the criteria used were normal, <50 μg/g, undetermined, 50.1–150 μg/g, and high, >150.1 μg/g. CRP and ESR were considered as reagents for values >0.6 mg/dL and >10 mm, respectively. Ferritin was classified according to gender: for women, values between 11 and 306.8 ng/mL were considered normal; for men, these values ranged from 23.9 to 336.2 ng/mL. The reference values followed the LEAC/UNIVALI protocol.

To verify disease activity, we used the clinical index of activity proposed by Harvey-Bradshaw[12] for CD, in which scores <5 are equivalent to the remission phase; 5–7, to a light activity; and >8, to a moderate activity. For patients with CNUC, the index used was the Partial Mayo Score proposed by Turner et al.[13] This index indicates scores <2 for the phase of remission; 2–4 for light activity; and >5 for moderate activity. For statistical purposes, the disease activity index was gathered.

The Research Ethics Committee (CEP) approved the project on August 6, 2015, under Opinion No. 1,173,802.

Statistical analysis

The data collected were tabulated with the use of Microsoft Excel® and Word® programs and the statistical analysis was conducted using the STATA® v.13.0 program. For the categorical variables, absolute and relative frequencies were calculated; we also used χ^2 association tests or the Fischer exact test. For quantitative variables, Spearman's correlation was used.

Results

Of the 60 patients assisted, 57% ($n = 34$) had CD and 43% ($n = 26$) had CNUC. According to Table 1, the majority of the patients were women (65%), married or in a stable relationship (63%), and mainly with full elementary school education (68%). The analysis of the monthly family income among patients with CD revealed that the highest percentage (55%) belonged to C, D, and E classes. Among the patients with CNUC, the majority (43%) were classified as class C, followed by classes D and E, according to the Critério de Classificação Econômica Brasil.[11]

Table 1 – Socioeconomic and health variables of patients attending the DII outpatient clinic, Itajaí, Santa Catarina, 2016.

Variable	CNUC ($n = 26$)		CD ($n = 34$)		Total ($n = 60$)	
	n	%	*n*	%	*n*	%
Gender						
Female	16	62	23	68	39	65
Male	10	38	11	32	21	35
Marital status						
Married/stable relation	16	62	22	65	38	63
Single/divorced/widowed	10	38	12	35	22	37
With whom the patient lives with						
Alone	2	8	2	6	4	7
Family	24	92	32	94	56	93
Education						
Illiterate	0	0	2	6	2	3
Elementary school	14	54	17	50	31	52
High school	8	31	11	32	19	32
Higher education	4	15	4	12	8	13
Income						
A (average of R$ 20,272.56)	0	0	1	3	1	2
B (R$4427.36–R$ 8695.88)	5	19	2	6	7	12
C (R$1446.24–R$ 2409.01)	13	50	17	50	30	50
D–E (average of R$ 639.78)	8	31	14	41	22	36
Family history						
Yes	4	15	4	12	8	13
No	22	85	30	88	52	87
Smoking						
Yes	0	0	1	3	1	2
No	26	100	33	97	59	98

Source: Associação Brasileira de Empresas de Pesquisa (ABEP).

A family history of IBD (13%) and smoking (2%) were poorly reported among patients with either pathology (Table 1).

Taking into account all patients, 75% ($n = 45$) were in remission phase, 13% ($n = 8$) in mild activity, and 12% ($n = 7$) in moderate activity. In the analysis of serum vitamin D levels, 38 patients (63%) – most of the population studied – had vitamin deficiency and 22 patients (37%) showed normal levels. No patient was classified as with toxic levels.

In the association of serum vitamin D levels with the clinical activity of the disease with the application of Fischer's exact test, a statistically significant difference was found between the analyzed variables (Table 2).

Table 2 – Association between diagnoses of serum vitamin D levels and clinical and laboratory disease activity of patients treated at the IBD outpatient clinic, Itajaí, Santa Catarina, 2016.

	Sufficiency ($n=22$)		Deficiency ($n=38$)		p
	%	n	%	n	
Calprotectin (high)	26	10	74	28	0.029
ESR (above normal)	27	9	63	24	0.095
Ferritin (above normal)	33	4	21	8	0.789
Disease activity (clinical)	4	1	38	14	0.005

Table 3 – Correlation between vitamin D dosage and laboratorial disease activity of patients attended at the IBD outpatient clinic, Itajaí, Santa Catarina, 2016.

Laboratory tests	Vitamin D	
	r	p
Calprotectin	−0.3837	0.0025
ESR	−0.4832	0.0001
Ferritin	0.2351	0.0705

Of the patients with sufficient serum vitamin D levels, 95% ($n=21$) were in remission. Among vitamin D-deficient patients, 38% ($n=14$) were in the active phase of the diseases.

In the evaluation of biochemical tests, we observed that 63% ($n=38$) of the patients presented high result for fecal calprotectin, 22% ($n=13$) had an indeterminate result, and 15% ($n=9$) were normal. Regarding ESR, 45% ($n=27$) presented values within normality and 55% ($n=33$) had values above normal. For CRP, 87% ($n=52$) had normal values and 13% ($n=8$) were above the reference level. As for ferritin, 70% ($n=42$) were normal, 20% ($n=12$) with values above reference levels, and 10% ($n=6$) with values below reference levels.

Table 3 lists the relationship between the diagnosis of vitamin D and the laboratory parameters used to evaluate disease activity.

Discussion

The results show that, among the evaluated patients, there was a prevalence of female gender, patients married or in a stable relation, with full elementary education, nonsmokers, with no family history of IBD, and with a higher occurrence of CD – findings that agree with the literature.[14–17] The data of the present study were similar to those found by Rosa, Silva Junior and Rosa[14] who, in a study with 48 patients in whom 66% were female, 66% were married, with a mean of 12.38 years of schooling, 85% non-smokers, and 81% with no family history of IBD. Our data also agree with those from Souza, Belasco, and Aguilar-Nascimento[18] that, among their 220 patients studied, 57% were women, 66% were married, with a mean of 9.17 years of schooling and 62% of non-smokers.

Studies show that although there is no distinction between genders for disease involvement, the higher occurrence among women may be due to hormonal factors, which may interfere with the expression of the disease, or else due to the progress in the technologies and methods for detecting the diseases and in the establishment of diagnoses, taking into account that women are more concerned about their health.[17,19]

As for vitamin D, in the present study, most of the patients presented deficiency (63%), which agrees with the findings of Ulitsky et al.[20] that, when evaluating 504 patients with IBD (403 with CD and 101 with CNUC), found vitamin D deficiency in 49.8% of the participants. Our data also combine with the findings of Levin et al.,[21] who reported 38% of deficiency in a study with 78 participants.

Initially, hypovitaminosis D is more common in high-latitude countries; but Brazil is a low-latitude country, closer to the tropics and with a high incidence of UVB radiation, which should be a favorable factor, thanks to a satisfactory solar exposition. However, the results of the present study and those described in the literature are similar to those found in high-latitude places. This can be explained by the low day-to-day exposure to sunlight, poor exposure of the body due to clothing, and the frequent use of sunscreens.[8,22]

The active form of vitamin D is present in various tissues and organs that are not related to bone or calcium metabolism. 1,25-Dihydroxyvitamin D functions in processes such as cell differentiation, proliferation and apoptosis, hormone secretion, and in the immune system. Its deficiency has been identified as a risk factor for the emergence of chronic non-communicable diseases, cancer, and autoimmune diseases, as is the case of IBD.[23,24]

Regarding serum vitamin D levels and disease activity according to clinical symptomatology, a statistically significant relationship between the analyzed variables was found.

In agreement with the above data, Jorgensen et al.,[25] in a study with 182 CD patients, concluded that 25(OH)D levels demonstrate an inverse proportional association with disease activity; average levels of vitamin D were found in patients with CD in remission or with a moderate level of activity. Patients taking a supplement of this vitamin showed lower levels of activity and less presence of reactive CRP.

Ananthakrishnan et al.,[26] in a study with 72,719 women aged 40–73 years, demonstrated a significant association of the diagnosis of high serum levels of 25(OH)D with low risk of incidence of CD, or with its more mild manifestation.

Dias de Castro et al.,[15] in their evaluation of 76 patients (57 with CD and 19 with CNUC), investigated the correlation between serum vitamin D concentration and disease activity for these two diseases, with the application of the Harvey-Bradshaw index[12] for CD and the Mayo Partial Score[13] for CNUC, as well as serologic markers such as CRP, ferritin, and ESR. The findings demonstrated that patients in remission had higher serum vitamin D levels *versus* patients with the active disease.

The prevalence of hypovitaminosis D among patients with IBD has been related to factors such as intestinal malabsorption, especially in the active phase of the disease, where inflammation of the mucosa and low enterohepatic circulation occur, in addition to the low oral intake of this micronutrient. Insufficient intake may be related to the scarce available dietary sources, as well as to the fear of eating, a factor reported by patients with IBD.[8–10] In addition to clinical activity indexes, low plasma vitamin D levels are also associated with the long duration of the disease and with an increase

in inflammatory and serological markers such as ferritin, CRP, ESR, and fecal calprotectin.[20]

Taking into account the biochemical tests used to confirm disease activity in the present study, we found that among patients with vitamin D deficiency, all of them had reactive CRP values. This same finding was observed by Dias de Castro et al.,[15] in their analysis of PCR results; these authors also found a significant association between low levels of vitamin D and high levels of CRP.

Regarding ESR values, it was observed that, among patients with vitamin D deficiency, 73% had high values, with a statistically significant association. Ulitsky et al.[20] confirmed these data: in patients with low serum 25(OH)D levels, these authors found an association with increased levels of ESR. However, the use of routine inflammatory markers for the evaluation of disease activity, even if associated with clinical activity indexes, has been considered as of little specificity. According to Silva and Melo Junior,[27] in the active phase of the diseases, and despite the increase in serum inflammatory markers, this alteration may be due to the frequent use of corticosteroids in the treatment of these diseases. In view of this, fecal markers (among them fecal calprotectin) have revealed greater accuracy in the evaluation of inflammation.

Fecal calprotectin is an antimicrobial protein released into the intestine, upon exposure of its mucosa to inflammation. It is a fast, sensitive, specific, accessible, and non-invasive marker for the detection and monitoring of IBD activity.[28]

Establishing a relationship between vitamin D and fecal calprotectin values in the present study, we found that most patients with vitamin D deficiency showed elevated fecal calprotectin results. Similar results were found by Garg et al.[29] in their evaluation of 40 patients with CD and of 31 patients with CNUC; these authors inversely correlated levels of vitamin D and fecal calprotectin. Similar findings were also observed by Torki et al.[30]: among the 133 patients studied, classified as in the active phase of the disease, there was a greater presence of abnormal fecal leukocytes *versus* patients in remission, 43.3% *vs.* 6.7% respectively.

According to the findings of our study, vitamin D deficiency correlates with clinical and laboratory activities of IBD. It is important that new research is carried out, correlating serum vitamin D levels with the activity of IBD, considering the small number of patients evaluated in the present study, and considering the role of this nutrient in immunomodulatory activity.

Conflicts of interest

The authors declare no conflicts of interest.

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