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Vitamin D deficiency among inflammatory bowel disease patients in Argentina: a cross-sectional study

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ABSTRACT – Background – An association has been established between low serum values of vitamin D and inflammatory bowel disease. There is a lack of evidence on whether this association is still observed in regions where sun exposure throughout the year is higher. **Objective** – To compare the prevalence of vitamin D deficiency between inflammatory bowel disease patients and healthy controls. **Methods** – Inflammatory bowel disease patients were consecutively enrolled as cases. Age and gender-matched healthy subjects who agreed to undertake a determination of serum vitamin D were enrolled as controls. Demographic features, medical treatment, need for hospital admission at diagnosis, steroid treatment, smoking, need for surgical treatment were evaluated as factors associated with vitamin D deficiency. **Results** – Overall, 59 patients with a diagnosis of either Crohn's disease or ulcerative colitis were enrolled, as well as 56 controls. Median age was 41 years (19-79) and 56% were male. Vitamin D deficiency was observed in 66.1% of inflammatory bowel disease patients versus 21.42% of healthy controls (OR 7.15 (3.1-16.48), *P*=0.001). Among inflammatory bowel disease patients, male gender, disease duration, moderate-to-severe disease and hospital admission at the moment of diagnosis were found to be associated with vitamin D deficiency. On multivariate analysis, only longer disease duration [(OR 1.01 (1-1.06)] and hospital admission at diagnosis [(OR 5.63 (1.01-31.61)] were found to be significantly associated with the latter. **Conclusion** – Vitamin D deficiency was more frequent among inflammatory bowel disease patients. Longer disease duration and need for hospital admission at diagnosis were associated to vitamin D deficiency among these patients.

HEADINGS – Ulcerative colitis. Crohn's disease. Vitamin D.

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of immune-related disorders that may affect different anatomical sites throughout the digestive tract: as a matter of fact, two well-defined clinical entities constitute the vast majority of IBD cases: Crohn's disease (CD) which can affect virtually any site of the digestive tract and can also involve different layers of the gastrointestinal wall and ulcerative colitis (UC), which affects only the mucosa and is distributed solely throughout the colon[1].

The etiology of IBD is not well understood. It is believed that they derive from an aberrant chronic immune response towards an unknown luminal antigen, in genetically-predisposed subjects[2]. As a consequence, there is a myriad of both pro-inflammatory and anti-inflammatory biologic agents which are inappropriately secreted or inactivated among IBD subjects[3].

Vitamin D3 – or cholecalciferol – is a liposoluble vitamin which has been classically related to phosphocalcic metabolism[4]. However, in recent years a considerable amount of evidence has suggested that vitamin D3 has several important immunological functions: it can promote lymphocyte differentiation, can induce interleukin-10 production as well as decrease the production of pro-inflammatory cytokines such as Interferon γ[5].

Several studies of different methodological nature have suggested that vitamin D3 deficiency may have a significant role in terms of the magnitude of the inflammatory response observed among IBD patients. For instance, there seems to be a correlation between vitamin D3 values in serum and the severity of the inflammatory response among CD patients[6]. This correlation has also been observed among UC patients.

As it is known, vitamin D3 activity is related to solar exposure[7]. Most of the evidence regarding vitamin D3 and IBD comes from Northern Hemisphere countries, in which solar exposure and thus vitamin D deficiency can be a prevalent condition. Coincidentally, IBD incidence is slightly higher in many countries from the Northern Hemisphere than from the Southern Hemisphere.

There is also a lack of local evidence regarding the prevalence of vitamin D deficiency among IBD patients and possible risk factors that could be potentially associated with vitamin D deficiency. Hence, we sought to compare vitamin D3 serum values between a cohort of IBD patients versus healthy volunteers and to determine which clinical features among IBD patients were linked to a higher odds of low vitamin D values.

METHODS

Study design and population

A cross-sectional study was undertaken. The study protocol was properly reviewed and approved by our Institution's Internal Review Board. Adult patients with a diagnosis of either UC or

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CD were consecutively enrolled from June 2014 to January 2016. The vast majority of these patients were initially diagnosed and followed up on a regular basis at our Institution – only 5% (n=3) of these patients were referred for treatment from another Institution. Also, age and gender-matched asymptomatic individuals were enrolled for vitamin D determination; these were regarded as controls. We excluded patients with conditions that can be associated with vitamin D deficiency: cirrhosis, chronic kidney disease, hypoparathyroidism.

Outcome measures

After signing informed consent, both cases and controls were subject to a blood extraction to determine serum vitamin D3 levels. A cutoff value of 30 ng/mL was considered for the definition of vitamin D deficiency. Vitamin D3 levels were compared between cases and controls. The proportion of IBD patients with vitamin D deficiency was estimated. The following variables were registered and compared between IBD patients with and without vitamin D deficiency: age, gender, disease distribution, disease duration, need for hospital admission at diagnosis, smoking, need for biological therapy, steroid treatment, clinical severity at the moment of vitamin D determination. For the latter, either Crohn's Disease Activity Index (CDAI) or Mayo score were used: moderate-to-severe disease were defined as a CDAI >220 and Mayo score >6.

Statistical analysis

Stata software was used for this purpose (v11.1, Statacorp, College Station, Texas, USA). Categorical variables were described as percentages; numerical variables were described as mean with their standard deviation or – in cases of non-parametrical variables, as median with their range. For the comparison of categorical variables, Fisher exact test was used. In the case of numerical variables, either Student t test or Mann-Whitney test were used. Odds Ratios (OR) with their corresponding 95% Confidence Intervals (95%CI) were estimated. A univariate analysis was performed to determine the variables significantly associated with vitamin D deficiency among IBD patients, followed by a multivariate analysis including all variables with a p value of less than 0.1 on univariate analysis. Multivariate analysis was performed following a logistic regression model.

RESULTS

From June 2014 to January 2016, 59 patients with a diagnosis of either CD or UC were consecutively enrolled as cases, as well as 56 healthy controls. All patients undertook serum vitamin D determination. Clinical characteristics of IBD patients are shown in TABLE 1. Median age was 41 years (19-79) and 56% (n=33) were male. Overall, 76.27% (n=45) had a diagnosis of UC and 23.73% (n=14) of CD; 34% (n=20) were receiving immunomodulatory treatment with either azathioprine or 6-mercaptopurine, whereas 23.73% (n=14) were under concomitant treatment with biologics.

Vitamin D deficiency was observed in 66.1% (n=39) of IBD patients versus 21.42% (n=12) of healthy controls (OR 7.15 (3.1-16.48), p 0.001), as shown in FIGURE 1. Mean vitamin D values were 23.5±9.3 UI/mL and 38.5±7.6 UI/mL, respectively (P<0.05). FIGURE 2 shows the comparison of vitamin D deficiency between UC and CD patients, showing no significant differences in terms of vitamin D deficiency (P=0.2).

TABLE 1. Main characteristics of patients with inflammatory bowel disease.

	% (n/N)
Age	41 (19-79)
Gender (%M)	56 (33/59)
Diagnosis	
Ulcerative colitis	76.27 (45/59)
Crohn's disease	23.73 (14/59)
Age at diagnosis	31 (16-64)
Disease extension	
Crohn's disease	
Ileal	14.28 (2/14)
Ileocolonic	28.57 (4/14)
Colonic	57.15 (8/14)
Ulcerative colitis	
Rectal	15.55 (7/45)
Left-sided colitis	20 (9/45)
Extensive colitis	64.45 (29/45)
Smoking	13.56 (8/59)
Treatment with 5-ASA	
Crohn's disease	78.57 (11/14)
Ulcerative colitis	97.78 (44/45)
Need for steroid treatment	
Crohn's disease	85.71 (12/14)
Ulcerative colitis	66.67 (30/45)
Treatment with immunomodulator	
Crohn's disease	42.85 (6/14)
Ulcerative colitis	31.11 (14/45)
Treatment with biologics	
Crohn's disease	50 (7/14)
Ulcerative colitis	15.55 (7/45)
Need for admission at diagnosis	27.11 (16/59)
Need for surgical treatment	
Crohn's disease	21.42 (3/14)
Ulcerative colitis	6.66 (3/45)

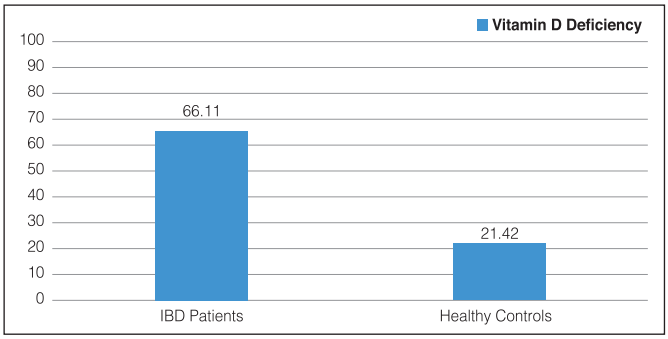

FIGURE 1. Comparison of vitamin D deficiency between inflammatory bowel disease patients and healthy controls.

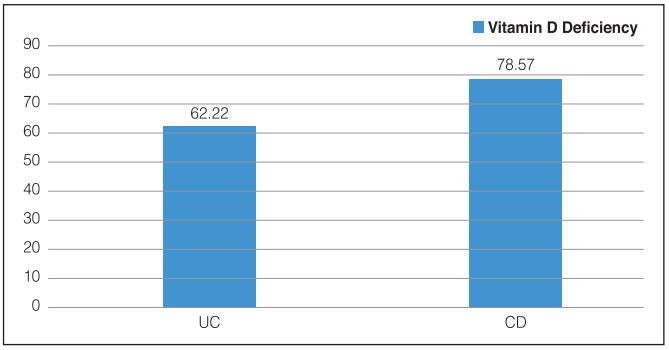

FIGURE 2. Comparison of vitamin D deficiency between ulcerative colitis and Crohn's disease patients.

When analyzing the features among IBD patients significantly related to vitamin D deficiency (TABLE 2), male gender (53.85% vs 25%, *P*=0.04), longer disease duration [12 (4-22) vs 8 (2-16) years, *P*=0.05], need for steroid treatment (79.49% vs 55%, *P*=0.05), moderate-to-severe disease activity at the moment of vitamin D serum determination (69.23% vs 35%, p 0.01) and hospital admission at the moment of diagnosis (35.91% vs 10%, *P*=0.03) were found to be associated. On multivariate analysis (TABLE 3), only longer disease duration [(OR 1.01 (1-1.06)] and hospital admission at diagnosis [(OR 5.63 (1.01-31.61)] were found to be independently associated with vitamin D deficiency.

TABLE 2. Comparison of Clinical Features between IBD patients with and without Vitamin D deficiency.

	Vitamin D deficiency (%, n/N)	Normal Vitamin D values (%, n/N)	OR (95%CI)	*P*
Age	42 (20-62)	45 (18-69)	N/A	0.27
Gender (%M)	53.85 (21/39)	25 (5/20)	3.5 (1.06-11.52)	0.04
Hospital admission on diagnosis	35.91 (14/39)	10 (2/20)	5 (1.2-27.02)	0.03
Need for steroid treatment	79.49 (31/39)	55 (11/20)	3.17 (1-10.81)	0.05
Disease duration	12 (4-22)	8 (2-16)	N/A	0.05
Need for biological treatment	28.21 (11/39)	15 (3/20)	2.22 (0.52-9.39)	0.25
Smoking	12.82 (5/39)	15 (3/20)	0.83 (0.17-3.96)	0.8
Moderate-to-severe disease activity*	69.23 (27/39)	35 (7/20)	4.17 (1.33-13.11)	0.01
Need for surgical treatment	12.82 (5/39)	10 (2/20)	1.32 (0.23-7.63)	0.7

*At the moment of vitamin D determination.

TABLE 3. Multivariate analysis results.

Variable	OR (CI 95%)
Gender	3.3 (0.56-19.58)
Hospital admission on diagnosis*	5.63 (1.01-31.61)
Need for steroid treatment	2.71 (0.68-10.83)
Disease duration*	1.01 (1-1.06)
Moderate-to-severe disease activity at the moment of vitamin D determination	2.37 (0.7-8.26)

*Significant values from a statistical point of view.

DISCUSSION

Our study confirms the increased prevalence of vitamin D deficiency among IBD patients as well as its association with certain features showing disease activity and severity. These findings are consistent with what other authors have suggested in previously published papers[8-10].

It is well known that vitamin D exerts a significant function regulating the phosphocalcic metabolism; its deficiency is a key component of osteopenia and osteoporosis – a common finding among IBD patients[11]. However, growing evidence point towards other key functions vitamin D has, such as anti-inflammatory, anti-proliferative as well as anti-apoptotic functions[12]. Vitamin D can modulate both adaptive and innate immune response by means of its influence on T and B lymphocytes as well as dendritic cell and macrophage function: these cells can express vitamin D receptors on its surface, which can bind cholecalciferol and 25 (OH)-cholecalciferol and turn them into 1,25 (OH)-cholecalciferol, an active metabolite with autocrine and paracrine actions. Vitamin D3 has been shown to suppress Th1 lymphocytic response, leading to a decrease in the excretion of pro-inflammatory cytokines such as interferon γ, interleukin-2 and tumor necrosis factor α[13].

Additionally, vitamin D inhibits dendritic cell differentiation[14]; furthermore, dendritic cells can induce the conversion of 25-OH cholecalciferol into 1,25 OH-cholecalciferol, which in turn helps promote monocyte differentiation as well as CD4+ inhibition. The evidence derived from experimental models have proved a crucial association between chronic inflammation and vitamin D. However, these models do not necessarily prove a causal association between vitamin D deficiency and IBD, nor it answers the therapeutic benefit of vitamin D administration among IBD patients.

Our results show a significant difference in terms of mean serum vitamin D concentration between IBD patients and otherwise healthy controls. This finding has been previously observed in several observational studies[8-10]. However, the vast majority of such studies were undertaken in geographical locations where both vitamin D deficiency and IBD incidence are relatively high; this could lead to a potential association bias, a bias that can be avoided with data from geographical places where sun exposure – and consequently, vitamin D levels – are higher. There is a relative lack of evidence from mild-temperature places such as South American countries.

We have found some relevant clinical features that IBD patients with vitamin D deficiency show. It is interesting that, on univariate analysis, key factors related to a more severe disease – in both CD as well as UC – such as need for steroid treatment during disease

evolution, disease duration, moderate-to-severe disease activity at the moment of vitamin D determination and need for hospital admission at the moment of diagnosis were significantly related to vitamin D deficiency. On multivariate analysis, the need for hospital admission at the moment of IBD diagnosis as well as the disease duration were independently associated with the odds of vitamin D deficiency. These findings could have two potentially feasible explanations. First of all, the probable relationship between the degree of vitamin D deficiency and IBD severity; for instance, among CD patients, those with need for surgical resection, or gastrointestinal stenosis, or need for steroid treatment at the moment of diagnosis were significantly related to a more profound vitamin D deficiency[15,16]. Additionally, those IBD patients on remission fail to show a similar prevalence of vitamin D deficiency than patients with active disease. These observations support the idea that the absence of vitamin D anti-inflammatory properties enhance IBD inflammatory activity and thus become a risk factor of a more severe disease course.

On the other hand, the association between vitamin D deficiency and disease severity may be due to the intermittent or continuous exposure to high doses of steroids that these patients may have. Most patients who require admission, especially at the time of diagnosis, may receive intravenous steroids, which are then switched to orally administered steroids; it could also be argued that those patients with longer duration of disease may experience a higher amount of relapses and thus, may receive a non-neglectable amount of steroids. As it has been demonstrated by Skversky et al.[17], chronic exposure to steroids constitutes an independent predictor of severe vitamin D deficiency. The question, hence, is whether vitamin D deficiency is a cause of a more severe disease or instead, vitamin D deficiency is a consequence of the inevitable exposure to medications that patients with a more severe evolution suffer – a question that observational studies like ours do not fully address.

Limitations should be mentioned. Mainly, sample size was relatively small, with a rather low proportion of patients with severe disease, as witnessed by the relatively low proportion of patients who required biological treatment and/or surgical interventions. This could underestimate the true weight that the latter may have as predictors of vitamin D deficiency. On the other hand, this is one of the few studies on the subject performed in a South American setting, apart from a recently published study by Kotze et al.[18].

In conclusion, we found a higher prevalence of vitamin D deficiency among IBD subjects when compared to healthy controls. Moreover, both hospital admission at the moment of diagnosis as well as longer disease duration were found to be significantly associated with the odds of showing vitamin D deficiency among IBD patients, regardless of their disease activity and severity.

Authors' contribution

Torella MC: patient enrollment, bibliographic search, draft design. Lasa J: design of the study, statistical analysis. Rausch A: patient enrollment, draft design. Zubiaurre I: bibliographic search, critical review of manuscript draft.

Torella MC, Rausch A, Lasa J, Zubiaurre I. Deficiência de vitamina D entre pacientes com doença inflamatória intestinal na Argentina: um estudo transversal. Arq Gastroenterol. 2018,55(3):216-20.

RESUMO – **Contexto** – Uma associação foi estabelecida entre os baixos valores séricos de vitamina D e doença inflamatória intestinal. Falta evidência se esta associação ainda é observada em regiões onde a exposição ao sol durante todo o ano é maior. **Objetivo** – Comparar a prevalência de deficiência de vitamina D entre pacientes com doença inflamatória intestinal e indivíduos controles saudáveis. **Métodos** – Pacientes com doença inflamatória intestinal foram consecutivamente selecionados. Indivíduos saudáveis combinados da mesma idade e gênero que concordaram em fornecer uma determinação da vitamina D do soro foram considerados como controles. Características demográficas, tratamento médico, necessidade de admissão hospitalar no diagnóstico, tratamento de esteroides, tabagismo, necessidade de tratamento cirúrgico foram avaliados como fatores associados à deficiência de vitamina D. **Resultados** – No geral, 59 pacientes com diagnóstico de doença de Crohn ou colite ulcerosa foram observados, bem como 56 controles. A idade mediana era de 41 anos (19-79) e 56% eram do sexo masculino. A deficiência de vitamina D foi observada em 66,1% dos pacientes com doença inflamatória intestinal versus 21,42% dos controles saudáveis (OR 7,15 (3.1-16.48), *P*=0,001). Entre os pacientes com doença inflamatória intestinal, sexo masculino, duração da doença, doença de moderada a severa e admissão hospitalar no momento do diagnóstico foram associados com a deficiência de vitamina D. Na análise multivariada, apenas a duração da doença [(OR 1; 1 (1-1,06)] e a admissão hospitalar no diagnóstico [(OR 5,63 (1,01-31,61)] foram encontradas significativamente associadas ao último. **Conclusão** – A deficiência de vitamina D foi mais frequente entre os pacientes com doença inflamatória intestinal. Maior duração da doença e necessidade de admissão hospitalar no diagnóstico foram associadas à deficiência de vitamina D entre esses pacientes.

DESCRITORES – Colite ulcerativa. Doença de Crohn. Vitamina D.

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