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BRIEF ARTICLE

# Serum 25-hydroxyvitamin D concentration and inflammatory bowel disease characteristics in Romania

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## Abstract

**AIM:** To describe the relationship between vitamin D levels and inflammatory bowel disease (IBD) characteristics in northeastern Romanian patients.

**METHODS:** This was a prospective study of 47 consecutive IBD patients admitted to The Institute of Gastroenterology and Hepatology in Iasi, Romania between March 2011 and June 2012. The diagnosis of IBD was established based on endoscopic, histologic and radiologic findings. Demographic data, disease characteristics, ongoing treatments and biological parameters of patients (including markers of inflammation: C-reactive protein level, fibrinogen level, and erythrocyte sedimentation rate) were recorded. Serum vitamin D levels were measured and compared with age- and sex-matched healthy volunteers from the same geographic area. Vitamin D levels were defined as sufficient (> 30 ng/mL), insufficient (20-30 ng/mL), or severely deficient (< 20 ng/mL).

**RESULTS:** Thirty-three of the IBD patients included in this study had ulcerative colitis (UC) and 14 had Crohn's disease (CD). Only 24% of the UC patients and 21% of the CD patients had sufficient vitamin D levels. The vitamin D levels were significantly lower in the CD patients with moderate to severe disease activity compared to the CD patients in remission or with mild disease activity (16 ± 6 ng/mL *vs* 26 ± 7 ng/mL; 16 ± 6 ng/mL *vs* 31 ± 9 ng/mL, respectively, $P < 0.05$). Vitamin D levels in the UC patients were not influenced by disease activity and no correlation was observed with the inflammation markers tested (C-reactive protein, fibrinogen, and erythrocyte sedimentation rate). No association was observed between vitamin D levels and smoking status or ongoing medication (5ASA, steroids, and anti-TNFα). Newly diagnosed IBD patients had lower vitamin D levels than patients with established cases, though these differences were not significant (UC: 22 ± 9 ng/mL *vs* 26 ± 12 ng/mL; CD: 18 ± 6 ng/mL *vs* 27 ± 11 ng/mL, respectively). Although no association was found between the season during which the visit was scheduled and vitamin D levels, the UC patients assessed during the winter tended to have lower levels than those assessed during the summer (22 ± 9 ng/mL *vs* 28 ± 13 ng/mL, respectively).

**CONCLUSION:** Vitamin D levels are significantly reduced in IBD patients in northeastern Romania, with the lowest levels occurring in CD patients with moderate to severe disease activity.



**Key words:** Inflammatory bowel disease; Vitamin D level; Northeastern Romania; Crohn's disease activity; Seasonality

**Core tip:** This is the first prospective study assessing serum vitamin D levels in a Romanian population with

inflammatory bowel disease. The results of the study highlight the low prevalence of sufficient vitamin D levels in patients with Crohn's disease and ulcerative colitis. Furthermore, vitamin D levels were significantly lower in newly diagnosed cases, suggesting that disease treatment can help restore levels to some extent.

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## INTRODUCTION

Inflammatory bowel disease (IBD) is a debilitating condition characterized by a dysregulated mucosal immune response to intestinal microorganisms in a genetically susceptible host. While its pathogenesis is only partially understood, studies have shown that a complex combination of genetic, immune, environmental and microbial factors contribute to IBD. It is thought that IBD results from an inappropriate immune response to luminal antigens in the gut[1]. This disease is an important public health problem, affecting up to 0.5% of the population in developed countries and with increasing incidence in developing nations[2-4].

Recent studies describing the immunomodulatory function of vitamin D have suggested that vitamin D activity could play an extenuating role in the occurrence and progression of these autoimmune diseases[5-7]. Epidemiological studies suggest that the prevalence of vitamin D deficiency is high in patients with Crohn's disease (CD). Vitamin D deficiency is associated with a decreased exposure to sunlight, decreased oral vitamin D intake, malabsorption of vitamin D due to short gut syndrome or small bowel disease, bacterial overgrowth, and the use of cholestyramine for IBD symptom management[8]. Although patients with IBD are known to have an increased incidence of vitamin D deficiency, it remains unclear whether the deficiency contributes to and/or results from the disease. In this study, the vitamin D levels of northeastern Romanian IBD patients were compared with age- and sex-matched control subjects to assess the association between vitamin D levels and disease characteristics.

## MATERIALS AND METHODS

### Patient selection

This was a prospective study of outpatient and hospitalized IBD patients from the Institute of Gastroenterology and Hepatology Iasi in northeastern Romania between March 2011 and June 2012. The study was reviewed and approved by the local ethics review board. The diagnosis of IBD was established based on endoscopic, histologic and radiologic findings. Demographic data, disease characteristics, ongoing treatment, and biological parameters (including markers of inflammation, such as C-reactive protein level, fibrinogen level, and erythrocyte sedimentation rate) were recorded.

### Disease characteristics

Disease location was classified according to the Montreal IBD classification system[9]. The disease activity for ulcerative colitis (UC) was determined using a total Mayo score[10], with a score of $\geqslant 3$ identifying a clinically active disease state (3-5, mild; 6-8, moderate; 9-12, severe). The Crohn's disease activity index was utilized to categorize CD activity[11], where clinically active disease was defined by a score $\geqslant 150$ (150-220, mild to moderate; 220-450, moderate to severe; $> 450$, fulminant to severe). Serum 25-hydroxyvitamin D concentrations were determined for all patients at the Bioclinica Laboratory using the high performance liquid chromatography method. Patients with confounding factors for serum vitamin D levels (*i.e.,* renal failure, liver disease, pregnancy and lactation, medications such as anticonvulsants and vitamin D supplements, and prominent malabsorption) were excluded. Ninety-four healthy age- and sex-matched volunteers from the same geographic area and without disorders of the gastrointestinal tract or bone, or other confounding factors served as control subjects. The vitamin D levels were compared across groups for effects related to sex, season, and IBD. CD and UC patients were analyzed separately for disease location, new/established disease, disease severity, and the impact of treatment on the vitamin D level. New disease (newly diagnosed) patients were those for whom the diagnosis of IBD was made just before enrolling the study, during that hospitalization, or within the previous four weeks. Established disease patients were those for whom the diagnosis of IBD was made more than four weeks prior. The relationship between markers of inflammation (*e.g.,* C-reactive protein level, fibrinogen level, and erythrocyte sedimentation rate), disease duration, smoking status, and vitamin D levels in all patients were analyzed.

### Definition of vitamin D status

Although the definition of an acceptable 25-hydroxyvitamin D level is a matter of debate, a level greater than 30 ng/mL is considered optimal for maintaining a normal immune system. Therefore, we classified vitamin D levels as sufficient ($> 30$ ng/mL), insufficient (20-29 ng/mL), and deficient ($< 20$ ng/mL) for the purposes of this study.

### Statistical analysis

All statistical analyses were performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, United States). The chi-square distribution test was performed for the majority of the analyses, and the Fisher's exact test was used in some cases when sample size was small. The threshold for statistical significance was set at $P < 0.05$, and data are

**Table 1 Patient demographics *n* (%)**

| | Ulcerative colitis (*n* = 33) | Crohn's disease (*n* = 14) | Control subjects (*n* = 94) |
|---|---|---|---|
| Age, mean ± SD | 42 ± 14 | 36 ± 9 | 42 ± 12 |
| Sex, F/M | 16/17 | 6/8 | 44/50 |
| Disease duration in years, mean ± SD | 3 ± 5 | 3 ± 3 | |
| Newly diagnosed patient[1] | 15 (45) | 6 (43) | |
| Ulcerative colitis | | | |
| Proctitis | 8 (24) | | |
| Left colitis | 12 (36) | | |
| Pancolitis | 13 (39) | | |
| Crohn's disease | | | |
| Ileal | | 0 (0) | |
| Colonic | | 5 (36) | |
| Ileo-colonic | | 8 (57) | |
| Isolated upper digestive | | 1 (7) | |
| 25-OH D in μg/L, mean ± SD | 24 ± 11 | 23 ± 10 | 31 ± 13 |
| Vitamin D deficiency | 10 (30) | 5 (36) | 19 (20) |
| Vitamin D insufficiency | 15 (45) | 6 (43) | 28 (30) |
| Vitamin D sufficiency | 8 (24) | 3 (21) | 47 (50) |
| Season of clinical visit | | | |
| Winter | 20 (61) | 7 (50) | 53 (56) |
| Summer | 13 (39) | 7 (50) | 41 (44) |

[1]Patients for whom the diagnosis of inflammatory bowel disease was established just prior to study inclusion.

reported as mean ± SD.

## RESULTS

A total of 47 IBD patients and 94 healthy volunteers were included in this study. Thirty-three of the IBD patients had UC and 14 had CD. Demographic data and disease characteristics from these patients are presented in Table 1. Vitamin D levels were significantly lower in IBD patients compared to healthy controls (24 ± 10 ng/mL *vs* 31 ± 13 ng/mL, $P < 0.05$). However, IBD type did not influence this decrease, as no difference was found between the CD and UC patients. A significantly greater proportion of the male healthy controls had a sufficient vitamin D level than the male IBD patients (56% *vs* 25%, $P < 0.05$), but the difference between the female healthy controls and the female UC patients and respectively female CD patients did not reach the threshold of statistical significance (43% *vs* 24% *vs* 17%, $P = 0.16$). Additionally, while vitamin D levels in the healthy control group were significantly associated with the season ($P < 0.05$), this trend was not observed in the IBD patients. Although the vitamin D levels were lower in the winter compared to those during the summer in UC patients (22 ± 9 ng/mL *vs* 28 ± 13 ng/mL) and higher in CD patients (25 ± 8 ng/mL *vs* 21 ± 11 ng/mL, respectively), these differences were not significant.

In the UC patients, a lower serum vitamin D level was detected in a subgroup with extensive colitis (20 ± 7 ng/mL) compared to patients with left side colitis (30 ± 14 ng/mL); however, the difference was not significant. Similarly, a moderately reduced serum vitamin D level was observed in CD patients with involvement of only the colon compared to patients with additional involvement of the small bowel. Furthermore, newly diagnosed patients tended to have a lower vitamin D level than patients with established cases in the CD group (18 ± 6 ng/mL *vs* 27 ± 11 ng/mL) and the UC group (22 ± 9 ng/mL *vs* 26 ± 12 ng/mL). Although the severity of the flare in UC patients did not affect serum vitamin D levels, CD patients with moderate to severe disease activity had significantly lower vitamin D levels than patients in remission or with mild disease activity (16 ± 6 ng/mL *vs* 26 ± 7; 16 ± 6 ng/mL *vs* 31 ± 9 ng/mL, respectively, $P < 0.05$). Finally, there were no statistically significant associations between vitamin D levels and smoking or medication status, or with serum levels of C-reactive protein or fibrinogen, or with erythrocyte sedimentation rate.

## DISCUSSION

The incidence and prevalence of IBD is higher in Northern Europe, North America, North Australia and New Zealand than in Asia[2,3]. Although the incidence of IBD in the Indian subcontinent is low, individuals migrating to developed countries in northern latitudes have an increased risk for developing the disease[12]. The association between vitamin D levels and sunlight exposure and IBD incidence is confounded by numerous factors, and therefore a causal relationship cannot be confirmed. The available reports on vitamin D levels in adults with IBD show a range of prevalence of vitamin D deficiency of 22% to 70% in CD cases and between 15% and 45% in those with UC[13-15]. This study found that only 24% of UC patients, 21% of CD patients, and 50% of healthy subjects were vitamin D sufficient. These results were somewhat unexpected, given that Romania is considered by some to be a sunny country, and therefore an adequate source of vitamin D.

Although low vitamin D concentrations have been reported in IBD[16,17], there are contradictory data regarding the correlation between 25-hydroxyvitamin D levels and IBD activity[18-20]. However, despite some reports showing no association[21], we anticipated that patients with small bowel CD would have lower vitamin D levels, as a study by Tajika *et al*[22] showed that 25-hydroxyvitamin D levels correlated with CD duration and activity. The current study indicates that, despite the high prevalence of vitamin D deficiency in IBD patients, serum vitamin D levels were only associated with IBD activity in CD patients, in contrast to a previous finding[19]. However, our results are in agreement with a similar study published by Lamb *et al*[23] showing that overall, vitamin D levels did not differ between patients with CD and patients with UC. Interestingly, our study indicated that newly diagnosed IBD patients tended to have lower vitamin D levels, though the small number of patients prohibited this difference from reaching statistical significance. It has been suggested that vitamin D deficiency in IBD patients is related to inadequate absorption[24]. Although this study demonstrated an increased incidence of vitamin D

deficiency in IBD patients, it is unclear whether the low vitamin D level is due to the IBD and associated inflammation of the gut, or if the IBD is a consequence of the immune disorders induced by the vitamin D deficiency.

A large population study found that high sunlight exposure was associated with a significantly decreased risk of CD[25]. Furthermore, patients with reduced sun exposure have lower serum 25-hydroxyvitamin D levels and increased disease activity[26]. While the onset and exacerbation of IBD is thought to show seasonal variation, suboptimal vitamin D levels have been observed even during the summer[27]. This study similarly failed to demonstrate a seasonality effect, though a trend for reduced deficiency rates in summer was observed in UC patients. In addition to sunlight exposure, steroid treatment for IBD may contribute to vitamin deficiency, as vitamin D-deficient patients are statistically more likely to be treated with steroids, but not other immunosuppressants such as infliximab, methotrexate, azathioprine, adalimumab or mercaptopurine[28], however, the sample size in this study was insufficient to allow for proper analysis of the impact of different treatments on vitamin D levels.

This is the first report of an assessment of vitamin D levels in IBD patients from northeastern Romania. Although the small number of patients was a limitation of the study, there are some advantages to the research design. Patients included in the study were excluded based on specific criteria, and disease activity was based on laboratory, clinical and endoscopic assessments. Furthermore, patients were compared with geographically similar control subjects, with all blood sampling performed in the same laboratory. The study highlights the low prevalence of sufficient vitamin D levels in IBD patients, and an association between vitamin D deficiency and moderate to severe CD. Future prospective cohort studies with larger patient samples are needed to determine the causal relationship between the vitamin D deficiency and the incidence of IBD. Moreover, the effect of vitamin D supplementation on IBD outcome should be investigated, which may provide insight to possible therapeutic or preventative measures for the treatment of IBD.

## COMMENTS

### Background

Inflammatory bowel diseases (IBDs) represent an important public health problem. Recent studies describing the immunomodulatory function of vitamin D suggest that it may influence the occurrence and progression of these autoimmune diseases.

### Research frontiers

Although patients with IBD are known to have reduced vitamin D levels, it is unclear whether vitamin D deficiency contributes to or results from the disease. This study analyzes the association between vitamin D levels and disease characteristics in IBD patients from northeastern Romania.

### Innovations and breakthroughs

This is the first study assessing vitamin D levels in a Romanian population. The study highlights the low prevalence of sufficient vitamin D level in IBD patients, as well the association between low vitamin D levels and moderate to severe Crohn's disease. The results are reinforced by strict exclusion criteria for patient enrollment, standardized clinical and endoscopic scoring systems for assessment of disease activity, and identical blood sampling and testing conditions for all patients and matched control subjects.

### Applications

This report identifies a correlation with IBD severity and vitamin D deficiency. These results suggest that clinicians should assess the vitamin D status of their IBD patients and recommend vitamin supplementation to those with a deficiency.

### Terminology

Vitamin D levels are assessed by serum 25-hydroxyvitamin D concentrations. Although the definition of an acceptable 25-hydroxyvitamin D level is a matter of debate, a level greater than 30 ng/mL is considered optimal for maintaining a normal immune system. This study categorized vitamin D levels as sufficient (> 30 ng/mL), insufficient (20-29 ng/mL), and deficient (< 20 ng/mL).

### Peer review

This is the first prospective study assessing vitamin D levels in a Romanian population with IBD. The results indicate that IBD is associated with an increased incidence of vitamin D deficiency. Furthermore, patients with moderate to severe cases of Crohn's disease had significantly reduced vitamin D levels compared to patients in remission or with mild cases. These data suggest that vitamin D deficiency is an important factor in IBD, however more work is needed to determine whether the deficiency contributes to or results from the disease state.

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