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Alimentary Tract

Factors affecting vitamin D deficiency in active inflammatory bowel diseases

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ABSTRACT

Background: Hypovitaminosis D is prevalent in inflammatory bowel disease (IBD) and may be associated with disease activity.
Aim: This study evaluated vitamin D (VitD) status in an Italian cohort of IBD patients, not taking VitD supplementation. We investigated risk factors for VitD deficiency and its correlation with disease activity.
Methods: VitD levels were measured in 300 consecutive outpatients (42% with Crohn's Disease (CD) and 58% with ulcerative colitis (UC), 56% male) from a tertiary referral center. Data from the IBD cohort were compared with those of 234 healthy controls, matched by sex, age, and the month in which VitD levels were measured.
Results: The mean VitD level in IBD patients was significantly lower than in controls (18.9 ng/ml vs. 25 ng/ml, $p < 0.001$) when accounting for gender, age, and season. VitD deficiency was present in 62% of IBD patients. Risk factors for deficiency were: age <40 and ≥60 years, winter, previous surgery, C-reactive protein (CRP) ≥0.5 mg/dl, and erythrocyte sedimentation rate ≥20 mm/h. In multivariate analysis, VitD levels were negatively influenced by disease location and CRP in UC.
Conclusions: Although VitD deficiency was more prevalent than expected in healthy controls living in a Mediterranean country not at high risk of hypovitaminosis D, it was more common and severe in IBD patients. This study also found an association between VitD status and disease activity

1. Introduction

The prevalence of vitamin D (VitD) deficiency varies in different series of inflammatory bowel disease (IBD) patients in relation to geographical location, dietary habits, prevalence of micronutrient supplementation, small bowel involvement and resection in Crohn's Disease (CD), and race [1–5]. As a consequence, the prevalence of VitD deficiency ranges from less than 20% to over 90% in different series, but is consistently more frequent in IBD patients than in controls. Low VitD is considered a risk factor for IBD and the geographical area in which observations were carried out correlates positively with the incidence of disease [6,7]. An association has also been found between inadequate VitD levels and higher risk for an active, aggressive disease course and surgery [8–11]. Conversely, high VitD levels have been shown to lower the risk of IBD. Supplementation in some but not all instances proved to be of potential therapeutic benefit [12–14]. The mechanisms by which VitD is involved in the occurrence/prevention of IBD and in inflammation reduction has only been partially elucidated. The VitD receptor and cytochrome CYP27B1, which produces the active metabolite 1,25-dihydroxyVitD, are widely expressed in immune and intestinal epithelial cells, implying a crucial role of VitD in gut homeostasis. Upregulation of anti-inflammatory IL-10 production, induction of regulatory T cells, and partial suppression of the pro-inflammatory IL-6 and IL-17 pathways have been reported in animal studies [15,16]. Effects on innate immune signaling, upregulation of tight and adherens junction proteins, reduction of intestinal permeability, and protective effects against TNF-a-induced injury are likely involved [17–20]. More recently, adequate VitD levels have also

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been reported to result in a favorable modification of the intestinal microbiota [21].

The aim of the present study was to identify or confirm risk factors for VitD deficiency in a large series of IBD patients from a single Italian tertiary referral center, and correlate VitD levels with disease behavior.

2. Materials and methods

Between February 2013 and June 2017, we enrolled 300 consecutive IBD patients who were visited in our IBD referral center who were not taking VitD supplements, and for whom VitD measurements were available. Diagnosis of UC/CD was based on standard clinical, endoscopic, histological, and cross-sectional imaging evidence.

Serum 25-hydroxyVitD, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were simultaneously measured in all patients. Age at diagnosis, localization and behavior of disease according to Montreal classification [22], current therapy, intestinal surgery, need of steroids, disease duration, body mass index, and smoking status were also recorded.

Disease activity was calculated using the Harvey-Bradshaw index (HBI) for CD patients, and the partial Mayo score for UC patients [23,24]. Patients were also classified according to the season of observation, classified as either winter/spring (December–May) or summer/fall (June–November), in order to analyze seasonal variations of VitD and minimize the carry over effect of summertime exposure on fall vitamin concentrations. Data from 163 (54.3%) patients were collected in winter/spring, and from 137 (45.7%) patients in summer/fall.

The VitD levels in IBD patients were compared to those of 234 healthy blood donors (mean age: 44 ± 12.6 years, age range 18–68 years) matched by age (±2 years), sex, and month in which the blood sample was collected. As an inclusion criterion, controls could not be taking VitD supplements. Since controls all were blood donors, no matched control data were available for the 66 IBD patients who were over 69 years old. One hundred twenty-three (52.6%) controls were male and data from 129 (55.1%) were obtained in winter/spring.

VitD levels were measured as previously reported [25]. Baseline VitD status was classified into 4 categories (severe deficiency ≤10 ng/ml, deficiency 11–20 ng/ml, insufficient levels 21–30 ng/ml, and adequate levels >30 ng/ml) [26].

3. Statistical analysis

Data were analyzed using Student's t-test, chi-square test, and linear correlation. The odds ratio (OR) and 95% confidence interval (CI) for VitD deficiency were also calculated.

A proportional logistic regression model was applied to categorical variables, such as VitD status, to determine the effect of various covariates. The effect of each covariate was controlled for age, season, and duration of the illness. Stepwise regression using AIC (Akaike Information Criterion) was used to eliminate uninfluential covariates. For continuous response variables the effects of covariates were obtained using a multivariate linear model and stepwise elimination of uninfluential covariates.

Analyzing case-control data, the difference in VitD levels between cases and controls was used as a dependent variable in a multivariate linear regression framework. Stepwise elimination of uninfluential covariates was used to determine the best model to explain the variation of the difference in VitD levels between cases and controls. All analyses were performed using R statistical package v. 3.3.1.

Table 1
Clinical characteristics in ulcerative colitis (UC) and Crohn's Disease (CD).

	UC n = 174	CD n = 126	p Value
Sex: males/females *n*	98/76	70/56	ns
Age yrs mean ± SD	51 ± 17.9	51 ± 16.7	ns
Smoking: no/ex/yes[a] *n*	41/53/17	26/20/39	<0.001
BMI kg/m^2 mean ± SD[b]	24.8 ± 4.3	24 ± 3.7	ns
Disease duration yrs *mean ± SD*	10.4 ± 9.8	13.2 ± 11.8	<0.003
Age at diagnosis yrs *mean ± SD*	40.7 ± 17	38.1 ± 15.8	ns
UC extent: E1/E2/E3 *n*	20/71/83	–	–
CD extent: L1/L2/L3/L4 *n*	–	48/18/58/2	–
CD behavior: B1/B2/B3 *n*	–	59/48/19	–
Perianal disease *n*	–	20	–
Previous surgery *n(%)*	11 (6.3%)	41 (32.5%)	<0.001
Previous steroidal therapy *n (%)*	79 (45.4%)	67 (53.2%)	ns
Partial Mayo score *mean ± SD*	1.2 ± 1.7	–	–
Harvey-Bradshaw index *mean ± SD*	–	3.3 ± 2.9	–
ESR mm/h *mean ± SD*	18.2 ± 18.9	18.4 ± 17.7	ns
CRP mg/dl *mean ± SD*	0.57 ± 0.9	0.87 ± 1.3	0.026

[a] Data available in 196 patients.
[b] Data available in 237 patients.

4. Results

4.1. General characteristics and demographics.

The mean age of IBD patients was 51 ± 17.4 years (range: 16–89 years). One hundred seventy-four patients (58%) had ulcerative colitis (UC) and 126 (42%) had Crohn's Disease (CD). In relation to gender, 98 (56.3%) UC patients and 70 (55.6%) CD patients were male. Patient demographics and disease characteristics are reported in Table 1.

When VitD levels were measured, 87.7% of IBD patients were receiving aminosalicylates, 11% immunosuppressants, 7% steroids, 5.7% biologics, and 4% combined immunomodulant therapy. Six percent were not receiving therapy. Eleven (6.3%) UC patients, and 41 (32.5%) CD patients had undergone previous IBD- related surgery.

4.2. VitD in IBD patients

The mean VitD concentration was 18.9 ± 10.2 ng/ml in the 300 IBD patients; 21.1 ± 11 ng/ml in UC and 16 ± 8.2 ng/ml in CD ($p < 0.001$) (Table 2). VitD deficiency was present in 62% of IBD patients, and was more frequent in CD than UC (75.4% vs 52.3%; OR 2.8, 95% CI 1.7–4.6, $p < 0.001$) (Table 3).

VitD levels of the entire IBD population were lower in winter (16.2 ± 8.8 ng/ml) than in summer (22.2 ± 10.8 ng/ml). The same was observed in UC (16.9 ± 9.5 vs 25 ± 10.9 ng/ml, $p < 0.001$) but not in CD (15.3 ± 10.4 vs 17.1 ± 8.7 ng/ml, p = ns) (Table 2). The OR of VitD deficiency in IBD patients during winter versus summer was 3.6 (95% CI 2.2–5.9, $p < 0.001$) (Table 3).

VitD status was not significantly different between male and female IBD patients (19.4 ± 10.5 ng/ml vs 18.3 ± 9.9 ng/ml, respectively). The same proved true in UC (21.7 ± 10.1 vs 20.3 ± 12) and in CD (16.3 ± 8.8 ng/mlvs 15.6 ± 7.5 ng/ml), when analysed separately. No significant differences were observed when considering BMI and smoking status.

According to age, VitD concentration was as follows: <40 years 18.8 ± 8.9 ng/ml, 41–59 years 20.2 ± 10.4 ng/ml and ≥ 60 years 17.6 ± 10.8 ng/ml. The OR of VitD deficiency in patients <40 and ≥60 years was 1.7 (95% CI 1.1–2.8, p = 0.023) (Table 3). Despite statistical significance in CD, the correlation coefficients between age and VitD status were low (IBD r = −0.07; CD r = −0.21; UC r = −0.05).

No significant differences were observed in relation to disease extension, behaviour, duration of the disease, or age at diagnosis. About two-thirds (63.3%) of IBD patients had CRP ≥ 0.5 mg/dl.

Table 2
Vitamin D status in UC and CD in winter-spring and summer-autumn.

	UC n=174	CD n=126	p value
VitD	21.1 ± 11	16 ± 8.2	< 0.001*
VitD in Wintertime	16.9 ± 9.5	15.3 ± 7.9	ns*
1 - 10 ng/ml	23 (27.1%)	23 (29.5%)	
11 - 20 ng/ml	38 (44.7%)	39 (50%)	ns**
21 - 30 ng/ml	16 (18.8%)	11 (14.1%)	
> 30 ng/ml	8 (9.4%)	5 (6.4%)	
VitD in Summertime	25 ± 10.9	17.1 ± 8.7	< 0.001*
1 - 10 ng/ml	5 (5.6%)	14 (29.2%)	
11 - 20 ng/ml	25 (28.1%)	19 (39.6%)	
21 - 30 ng/ml	41 (46.1%)	11 (22.9%)	< 0.001**
> 30 ng/ml	18 (20.2%)	4 (8.3%)	

*VitD levels expressed in ng/ml, mean values ± SD. Absolute number of patients with differing VitD levels, percent of patients within brackets. *Student T Test,** Chi-square test.

Table 3
Risk factors of VitD deficiency in IBD patients.

		VitD ≤20 ng/ml	OR	95%CI	p Value
Crohn's Disease	vs UC	95 (75.4%)	2.8	1.7–4.6	<0.001
Wintertime	vs summertime	123 (75.5%)	3.6	2.2–5.9	<0.001
Age <40 and ≥60 yrs	vs age 40–59 yrs	124 (67%)	1.7	1.1–2.8	0.023
CRP ≥0.5 mg/dl	vs CRP <0.5 mg/dl	81 (73.6%)	2.3	1.4–3.8	0.002
ESR ≥20 mm/h	vs ESR <20 mm/h	73 (75.3%)	5.8	3.4–9.9	<0.001
Surgery	vs no surgery	40 (76.9%)	2.3	1.2–4.7	0.017

Absolute number of patients, percentage of patients within brackets.

Their mean VitD concentration was 16.2 ± 8.8 ng/ml versus 20.5 ± 10.6 ng/ml in patients with normal CRP values (p < 0.001). The OR of VitD deficiency in patients with elevated CRP was 2.3 (95% CI 1.4–3.8, p = 0.002). ESR ≥20 mm/h was present in 32.3% of patients. Their mean VitD levels were lower, 15.7 ± 8.8 ng/ml (p < 0.001) than those in patients with normal ESR, 20.5 ± 10.5 ng/ml (OR 5.8, 95% CI 3.4–9.9, p < 0.001) (Table 3). An HBI score ≥5, observed in 32 (25.4%) patients, was associated with lower VitD levels than those with HBI <5 (13.1 ± 7 vs 17 ± 8.4 ng/ml, p = 0.01). A similar, but not significant trend was observed in UC patients with a Mayo score ≥2 and <2 (19.6 ± 11.4 vs 21.6 ± 10.8 ng/ml, p = ns). A weak negative correlation between CRP, ESR values, HBI scores, and VitD levels was present (respectively r = −0.14, p = .015; r = −0.13, p = .023; r = −0.19, p = 0.032).

Multivariate analysis showed that VitD levels in UC patients were negatively influenced by disease extent and abnormal CRP values, after controlling for age, gender, and season. UC patients with extensive disease show a decrease in the log odds of having normal VitD values of 68%, compared to left colitis and proctosigmoiditis. Abnormal CRP reduced the odds of normal VitD values by 29% in UC patients. Conversely, in CD, multivariate analysis did not detect significant effects of disease behaviour, location, and CRP on baseline VitD levels. Controlling for age, sex, and season, CD patients had 58% lower odds of having normal VitD levels, as compared to UC.

In relation to therapy, mean VitD levels were similar in all patient groups, irrespective of treatment with aminosalicylates (19.4 ± 10.4 ng/ml), steroids (17.7 ± 9.5 ng/ml), or immunosuppressants (20.1 ± 9.4 ng/ml). Those treated with biologics had slightly lower values of VitD (15.5 ± 7.5 ng/ml, p = n.s.).

Previous surgery was associated with a higher risk of VitD deficiency in univariate analysis (OR 2.3, 95% CI 1.2–4.7, p = 0.017) (Table 3). The mean VitD concentration in patients who had undergone surgery was 16 ± 10.2 ng/ml, versus 19.6 ± 9.4 ng/ml in those who had not undergone surgery (p = 0.021).

4.3. Controls vs IBD (234 matched pairs)

The mean VitD level in the overall control group was 25 ± 9.4 ng/ml, significantly higher than that in IBD patients (p < 0.001) (Table 4). The prevalence of VitD deficiency was 32.1% in the control group and 59.8% in IBD patients (OR 3.2, 95% CI: 2.2–4.6, p < 0.001) (Table 5).

Unlike IBD patients, control females had lower VitD concentrations than males: 23.7 ± 8.2 ng/ml and 26.1 ± 10.2 ng/ml, respectively (Table 4). The OR of VitD deficiency for IBD males and females as compared to controls was 3.2 for both genders (Table 5).

VitD was similar among younger subjects in the control group (<30 years) versus older controls (21.3 ± 6.4 ng/ml and 25.6 ± 9.6 ng/ml, respectively). IBD patients had significantly lower VitD values than age-matched controls in all decades, with the exception of young people (<30 years) in which the significance level was not attained (Table 4).

Controls had a mean VitD concentration of 21.5 ± 6.8 ng/ml in winter and 29.3 ± 10.3 ng/ml in summer (p < 0.001). Throughout the year, VitD values were significantly higher in controls than in

Table 4
Mean VitD values in IBD patients and Controls.

	N	IBD	Controls	p Value
Overall series	234	19.3 ± 10.1	25 ± 9.4	<0.001
Males	123	19.8 ± 10.5	26.1 ± 10.2	<0.001
Females	111	18.8 ± 9.7	23.7 ± 8.2	<0.001
Winter–spring	129	16.6 ± 9	21.5 ± 6.8	<0.001
Summer-fall	105	22.7 ± 10.3	29.3 ± 10.3	<0.001
<30 yrs	34	19.2 ± 9.4	21.3 ± 6.4	ns
30–39 yrs	49	18.5 ± 8.6	27.1 ± 10.6	<0.001
40–49 yrs	67	20.5 ± 10.2	25.6 ± 8.2	0.002
50–59 yrs	48	19.7 ± 10.9	25.2 ± 6.9	0.004
60–69 yrs	36	17.8 ± 11.3	24.2 ± 13.5	0.03
CD	99	16.6 ± 8.2	24.1 ± 10.4	<0.001
UC	135	21.3 ± 10.8	25.7 ± 9	<0.001

Absolute number of matched pairs of patients and controls. VitD levels expressed in ng/ml, mean values ± SD.

Table 5
Odd Ratio of VitD deficiency in IBD patients compared to controls.

	VitD ≤ 20 ng/ml	OR	95%CI	p Value
IBD	140 (59.8%)	3.2	2.2–4.6	<0.001
CD	71 (71.7%)	6.1	3.3–11.3	<0.001
UC	69 (51.1%)	2	1.2–3.3	0.005
Males	73 (59.3%)	3.2	1.9–5.3	<0.001
Females	67 (60.4%)	3.2	1.8–5.5	<0.001
Winter–spring	94 (72.9%)	3.3	2–5.5	<0.001
Summer-fall	46 (43.8%)	4	2.1–7.7	<0.001

Absolute number of patients, percent of patients within brackets.

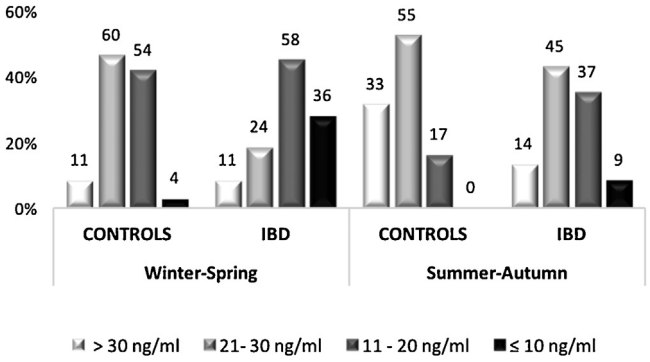

Fig. 1. Distribution of VitD levels in different seasons of the year (winter/spring and summer/autumn) in control subjects and IBD patients. White columns represent normal concentrations (>30 ng/ml), light grey, insufficient levels (21–30 ng/ml); dark grey, deficiency (11–20 ng/ml); and black, severe deficiency (≤10 ng/ml).

IBD patients ($p < 0.001$ in both summer and winter) (Table 4, Fig. 1). The OR of VitD deficiency in IBD patients compared to controls was higher in summer than winter (4 and 3.3, respectively) (Table 5).

CD patients with ileocolonic (L3) or penetrating (B3) disease showed larger differences of VitD concentration versus controls when compared to CD patients with other disease locations or behaviour ($p = 0.047$), or when compared to UC patients.

UC patients with abnormally high CRP, but not those with CD, showed larger differences of VitD concentration versus controls, compared to patients with normal CRP ($p = 0.004$).

Previous surgery did not significantly influence the differences between cases and controls (CD, $p = 0.2715$ and UC, $p = 0.5107$).

5. Discussion

This study evaluated the VitD status in a large Italian cohort of IBD patients not receiving VitD supplements, by comparing IBD patient data with data collected in the same month from age- and gender-matched healthy controls. The use of a control population which consisted of blood donors not receiving VitD supplements strengthens the reliability of data, but also implied the exclusion of older cohort of patients from the study.

About 90% of IBD patients had serum concentrations below 30 ng/ml. Two-thirds had VitD deficiency, which was severe in 22%. VitD status was more likely to be altered in CD, with VitD deficiency present in up to 80% of patients in winter. In the control group the prevalence of VitD deficiency, at approximately 30%, was also high and in line with figures recently reported in Italy by Lippi et al. [27], though slightly lower than figures reported in other European Countries (40.4%) [28].

The risk of VitD deficiency in IBD patients versus controls was higher (OR 3.2) than that reported in a recent meta-analysis (OR 1.64) [29], which may be due to the strict exclusion of subjects taking any form of vitamin supplementation from this study. Indeed, the prevalence of hypovitaminosis D in our cohort (68%) was similar to that reported in the UK and in Maryland [29,30], and slightly higher than that reported in other studies from Wisconsin and Norway [31,32]. In these studies, however, data were not compared to those in the normal population.

The high prevalence of VitD deficiency in our IBD population may be due to different factors. First of all, enrolment in the study was limited to IBD patients not taking VitD supplements, which was not the case in most other studies. Data were collected in a tertiary referral centre which has a high prevalence of severe, complex cases, which represents a predictable selection bias. Similarly, the ages included in the study population, in which elderly people represented about 20% of the cohort, increase the prevalence of VitD deficiency. Finally, an additional contributing factor is that VitD is regularly added to a variety of food in northern Countries, but not in Italy.

The present data suggest that the belief that Mediterranean Countries are not at high risk of hypovitaminosis D due to adequate sun exposure should be reconsidered. Our results are consistent with previous studies reporting that CD patients are at higher risk of deficiency than those with UC. Small bowel involvement and previous surgery are particularly important risk factors for VitD deficiency.

A relation between disease activity (defined by HBI for CD patients, and the partial Mayo score for UC) and VitD status was observed, though it was less than what might be expected. CD patients, but not UC patients, with active disease had significantly lower VitD concentrations than those in remission. Nonetheless in the present study high levels of CRP and ESR were associated with an increased risk of VitD deficiency, especially in UC. This is in line with other studies reporting an inverse correlation between VitD status and disease activity [9,13,31,33,34]. Kabbani et al. found an association between VitD deficiency and clinical status, disease activity scores, and the need for steroids, biologics, surgery, and hospitalization in a large study covering a 5-year period [35]. Less than optimal sun exposure [36], which is prevalent in people with active disease, plays a primary role. Similarly, inadequate sun exposure in IBD patients also accounts for the higher OR of hypovitaminosis in summer, when differences versus controls are more marked.

In addition, patients with active IBD often present with unnecessary dietary restrictions, leading to an inadequate intake of calcium and VitD. Many patients fear that food containing lactose may worsen abdominal symptoms and diarrhoea, and this leads to the avoidance of the primary dietary source of calcium and VitD [37], especially in the presence of active disease. Malabsorption due to ileal disease or resection, and the use of cholestyramine to treat diarrhoea are also important considerations in CD.

In the present IBD study, younger and older cohorts had lower mean VitD values than those in the 40–60 age range, which contrasts with findings reported by Kabbani, who found a significantly

higher prevalence of VitD deficiency in young males [35]. This discrepancy could result from confounding factors, since people taking VitD supplementation were included by Kabbani et al., and the cohort of elderly people was underrepresented. In all age groups, IBD patients had significantly lower VitD levels as compared to controls, except in those less than 30 years old. The finding that young controls were often VitD deficient was unexpected and largely unexplained. However, peculiar dietary habits may be involved, as indirectly suggested by the low consumption of vegetables and fruit as compared to other age groups which was reported by Eurostat (European Core Health Indications, ECHI 41) [38].

Gender did not represent an adjunctive risk factor in IBD, whereas control females had lower VitD concentrations than males. The differences observed between IBD and controls, and between UC and CD, most likely result from the presence/absence of the disease and type of IBD rather than gender.

Disease duration was not an adjunctive risk factor for VitD deficiency, which is consistent with other studies no bold type [35,39], and neither was age at diagnosis. Conversely, extensive UC and ileo-colonic CD were associated with an increased risk of low VitD levels.

As expected, VitD status did not correlate with therapy, as the same drugs may be used for both the induction and maintenance of remission. Patients treated with biologics had overall lower VitD concentrations. The same was reported by other authors who considered biologics, but not other drugs, to be an independent risk factor for VitD deficiency [8]. The relationship between VitD levels and anti-TNF therapy is intriguing, as the two factors may have reciprocal effects. Patients on biologics are more likely to be affected by active, severe disease, maximizing the risk of deficiency. Conversely, low VitD levels negatively affected immunoresponse and were shown to reduce the efficacy of anti-TNF therapy both for inducing and maintaining remission [40,41].

In conclusion, the present study shows the high prevalence of VitD deficiency in IBD patients who live in Italy, a Country in which inadequate sunlight exposure is not considered a risk factor. Thus, it would be beneficial for all IBD patients, especially those affected by CD, to be checked regularly for VitD status and given supplements as needed, not only during the phases of disease activity or when treated with steroids [42].

Conflict of interest

None declared.

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References

[1] Forrest KY, Stuhldreher WL. Prevalence and correlates of Vitamin D deficiency in US adults. Nutr Res 2011;31:48–54.
[2] Mouli VP, Ananthakrishnan AN. Review article: Vitamin D and inflammatory bowel diseases. Aliment PharmacolTher 2014;39:125–36.
[3] Fu YT, Chatur N, Cheong-Lee C, Salh B. Hypovitaminosis D in adults with inflammatory bowel disease: potential role of ethnicity. Dig Dis Sci 2012;57:2144–8.
[4] Narula N, Marshall JK. Management of inflammatory bowel disease with vitamin D: beyond bone health. J Crohns Colitis 2012;6:397–404.
[5] Sentongo TA, Semaeo EJ, Stettler N, Piccoli DA, Stallings VA, Zemel BS. Vitamin D status in children, adolescents, and young adults with Crohn disease. Am J Clin Nutr 2002;76:1077–81.
[6] Armitage EL, Aldhous MC, Anderson N, Drummond HE, Riemersma RA, Ghosh S, et al. Incidence of juvenile- onset Crohn's disease in Scotland: association with northern latitude and affluence. Gastroenterology 2004;127:1051–7.
[7] Jaimea F, Riutorta MC, Alvarez-Lobosb M, Hoyos-Bachilogluc R, Camargo CA, Borzutzky A. Solar radiation is inversely associated with inflammatory bowel disease admissions. Scand J Gastroenterol 2017;52:730–7.
[8] Ulitsky A, Ananthakrishnan AN, Naik A, Skaros S, Zadvornova Y, Binion DG, et al. Vitamin D deficiency in patients with inflammatory bowel disease: association with disease activity and quality of life. JPEN 2011;35:308–16.
[9] Blanck S, Aberra F. Vitamin D deficiency is associated with ulcerative colitis disease activity. Dig Dis Sci 2013;58:1698–702.
[10] Boyd CA, Limdi JK. VitD deficiency and disease outcomes in South Asian patients with IBD. Dig Dis Sci 2013;58:2124–5.
[11] Limketkai BN, Bayless TM, Brant SR, Hutfless SM. Lower regional and temporal ultraviolet exposure is associated with increased rates and severity of inflammatory bowel disease hospitalisation. Aliment Pharmacol Ther 2014;40:508–17.
[12] Ananthakrishnan AN, Khalili H, Higuchi LM, Bao Y, Korzenik JR, Giovannucci EL, et al. Higher predicted Vitamin D status is associated with reduced risk of Crohn's disease. Gastroenterology 2012;142:482–9.
[13] Jørgensen SP, Agnholt J, Glerup H, Lyhne S, Villadsen GE, Hvas CL, et al. Clinical trial: vitamin D3 treatment in Crohn's disease — a randomized double-blind placebo-controlled study. Aliment Pharmacol Ther 2010;32:377–83.
[14] Hassan V, Hassan S, Seyed-Javad P, Ahmad K, Asieh H, Maryam S, et al. Association between serum 25 (OH) vitamin D concentrations and inflammatory bowel diseases (IBDs) activity. Med J Malaysia 2013;68:34–8.
[15] Wu S, Liao AP, Xia Y, Li YC, Li JD, Sartor RB, et al. Vitamin D receptor negatively regulates bacterial-stimulated NF-kappaB activity in intestine. Am J Pathol 2010;177:686–97.
[16] Ryz NR, Patterson SJ, Zhang Y, Ma C, Huang T, Bhinder G, et al. Active 1,25-dihydroxyvitamin D3 increases host susceptibility to citrobacter rodentium by suppressing mucosal Th17 responses. Am J Physiol Gastrointest Liver Physiol 2012;303:G1299–311.
[17] White JH. Vitamin D deficiency and the pathogenesis of Crohn's disease. J Steroid Biochem Mol Bio 2018;175:23–8.
[18] Raftery T, Martineau AR, Greiller CL, Ghosh S, McNamara D, Bennett K, et al. Effects of vitamin D supplementation on intestinal permeability, cathelicidin, and disease markers in Crohn's Disease: results from a randomized double-blind placebo-controlled study. United Eur Gastroenterol J 2015;3:294–302.
[19] Meckel K, Li YC, Lim J, Kocherginsky M, Weber C, Almoghrabi A, et al. Serum 25-hydroxy vitamin D concentration is inversely associated with mucosal inflammation in patients with ulcerative colitis. Am J Clin Nutr 2016;104:113–20.
[20] Olsen KS, Aksnes L, Froyland L, Lund E, Rylander C. Vitamin D status and PUFA ratios in a national representative cross-section of healthy, middle-aged Norwegian women-the Norwegian women and cancer post-genome cohort. Scand J Public Health 2014;42:814–20.
[21] Barbáchano A, Fernández-Barral A, Ferrer-Mayorga G, Costales-Carrera A, Larriba MJ, Muñoz A. The endocrine vitamin D system in the gut. Mol Cell Endocrinol 2017;453:79–87.
[22] Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19(Suppl. A):5A–36A.
[23] Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980;1(8167):514.
[24] Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317(26):1625–9.
[25] Minisola S, Cianferotti L, Biondi P, Cipriani C, Fossi C, Franceschelli F, et al. Correction of status by calcidiol: pharmacokinetic profile, safety, and biochemical effects on bone and mineral metabolism of daily and weekly dosage regimens. Osteoporosis Int 2017;28:3239–49.
[26] Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81.
[27] Lippi G, Nouvenne A, Ticinesi A, Bonelli P, Salvagno GL, Cervellin G, et al. The burden of Vitamin D deficiency in a mediterranean country without a policy of food fortification. Acta Biomed 2015;86(1):59–62.
[28] Cashman KD, Dowling KG, Škrabáková Z, Gonzalez-Gross M, Valtueña J, De Henauw S, et al. Vitamin D deficiency in Europe: pandemic? Am J Clin Nutr 2016;103(April (4)):1033–44.
[29] Del Pinto R, Pietropaoli D, Chandar AK, Ferri C, Cominelli F. Association between inflammatory bowel disease and Vitamin D deficiency: a systematic review and meta-analysis. Inflamm Bowel Dis 2015;21(11):2708–17.
[30] Chatu S, Chhaya V, Holmes R, Neild P, Kang JY, Pollok RC, et al. Factors associated with Vitamin D deficiency in a multicultural inflammatory bowel disease cohort. Frontline Gastroenterol 2013;4:51–6.
[31] Ananthakrishnan AN, Cagan A, Gainer VS, Cai T, Cheng SC, Savova G, et al. Normalization of plasma 25-hydroxy vitamin D is associated with reduced risk of surgery in Crohn's disease. Inflamm Bowel Dis 2013;19(9):1921–7.
[32] Jørgensen SP, Hvas CL, Agnholt J, Christensen LA, Heickendorff L, Dahlerup JF. Active Crohn's disease is associated with low Vitamin D levels. J Crohns Colitis 2013;7(10):e407–13.
[33] Suibhne TN, Cox G, Healy M, O'Morain C, O'Sullivan M. Vitamin D deficiency in Crohn's disease: prevalence, risk factors and supplement use in an outpatient setting. J Crohns Colitis 2012;6(2):182–8.
[34] Torki M, Gholamrezaei A, Mirbagher L, Danesh M, Kheiri S, Emami MH. Vitamin D deficiency associated with disease activity in patients with inflammatory bowel diseases. Dig Dis Sci 2015;60(10):3085–91.
[35] Kabbani TA, Koutroubakis IE, Schoen RE, Ramos-Rivers C, Shah N, Swoger J, et al. Association of Vitamin D level with clinical status in inflammatory bowel disease: a 5-year longitudinal study. Am J Gastroenterol 2016;111(5):712–9.

[36] Vernia P, Burrelli Scotti G, Dei Giudici A, Chiappini A, Cannizzaro S, Afferri MT, et al. Inadequate sunlight exposure in patients with inflammatory bowel disease. J Dig Dis 2018;19(1):8–14.
[37] Vernia P, Loizos P, Di Giuseppantonio I, Amore B, Chiappini A, Cannizzaro S. Dietary calcium intake in patients with inflammatory bowel disease. J Crohns Colitis 2014;8(4):312–7.
[38] https://ec.europa.eu/health/indicators/indicators_en.
[39] Frigstad SO, Høivik M, Jahnsen J, Dahl SR, Cvancarova M, Grimstad T, et al. Vitamin D deficiency in inflammatory bowel disease: prevalence and predictors in a Norwegian outpatient population. Scand J Gastroenterol 2017;52(January (1)):100–6.
[40] Winter RW, Collins E, Cao B, Carrellas M, Crowell AM, Korzenik JR. Higher 25-hydroxyvitamin D levels are associated with greater odds of remission with anti-tumour necrosis factor-α medications among patients with inflammatory bowel diseases. Aliment Pharmacol Ther 2017;45(5):653–9.
[41] Zator ZA, Cantu SM, Konijeti GG, Nguyen DD, Sauk J, Yajnik V, et al. Pre-treatment 25-hydroxyvitamin D levels and durability of anti-tumor necrosis factor-α therapy in inflammatory bowel diseases. J Parenter Enteral Nutr 2014;38(3):385–91.
[42] Harbord M, Annese V, Vavricka SR, Allez M, Barreiro-de Acosta M, Boberg KM, et al. The first European evidence-based consensus on extraintestinal manifestations in inflammatory bowel disease. J Crohns Colitis 2016;10(3):239–54.