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Association between vitamin D deficiency and anemia in inflammatory bowel disease patients with ileostomy



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ABSTRACT

Background: Vitamin D deficiency is commonly seen in patients with inflammatory bowel disease (IBD). Vitamin D deficiency in IBD patients with ileostomy has not been systemically studied. The aim of the study was to assess the frequency and risk factors associated with low 25(OH) D₃ levels in those patients.

Methods: 112 eligible IBD patients with ileostomy were studied. Demographic, clinical, and endoscopic variables were analyzed. Vitamin D levels before and after ileostomy were compared when available. Levels of serum 25(OH)D₃ <20 ng/mL were classed as being deficient. **Results:** 112 eligible ileostomy patients were included. The mean vitamin D level was 21.47 ± 1.08 ng/dl. Low levels of vitamin D (<30 ng/dl) were present in 92 patients (82%). Vitamin D deficiency (<20 ng/dL) was seen in 55 patients (49%). There was no difference between patients with or without vitamin D deficiency regarding demographic variables, medication use and duration of ileostomy. Neo-ileal inflammation on endoscopy was not associated with vitamin D deficiency ($p=0.155$). Lower levels of phosphorus ($p=0.020$) or hemoglobin ($p=0.019$) and shorter duration of IBD ($p=0.047$) were found in patients with vitamin D deficiency. In multivariate analysis, lower levels of phosphorus (odds ratio [OR]: 1.83, 95% confidence interval [CI]: 1.16–2.89, $p=0.009$) and hemoglobin (OR: 1.32, 95% CI: 1.08–1.60, $p=0.006$) remained significantly associated with vitamin D deficiency.

Conclusion: Vitamin D deficiency is common in IBD patients with ileostomy and is associated with low hemoglobin levels. Further studies are needed to evaluate vitamin D supplementation as a possible adjuvant in the treatment of anemia of chronic disease in IBD patients.

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Associação entre deficiência de vitamina D e anemia em pacientes com doença inflamatória intestinal submetidos a ileostomia

R E S U M O

Palavras-chave:

Anemia
Ileostomia
Deficiência de Vitamina D

Introdução: A deficiência de vitamina D em pacientes com doença inflamatória intestinal submetidos a ileostomia não foi estudada sistematicamente. O objetivo desse estudo foi avaliar a frequência e os fatores de risco associados com a deficiência de vitamina D nesses pacientes.

Resultados: 112 pacientes elegíveis foram incluídos. A média dos níveis de vitamina D na população estudada foi de 21.47 ± 1.08 ng/dl. Níveis de vitamina D abaixo do normal (<30 ng/dl) e deficiência de vitamina D (<20 ng/dl) foram encontrados em 92 pacientes (82%) e em 55 pacientes (49%) respectivamente. Encontrou-se uma associação entre deficiência de vitamina D e níveis mais baixos de fósforo ($p=0.020$), hemoglobina ($p=0.019$) e duração da doença inflamatória intestinal ($p=0.047$). Na análise multivariada, níveis mais baixos de fósforo (odds ratio [OR]: 1.83, 95% confidence interval [CI]: 1.16–2.89, $p=0.009$) e hemoglobina (OR: 1.32, 95% CI: 1.08–1.60, $p=0.006$) permaneceram associados com deficiência de vitamina D.

Conclusão: A deficiência de vitamina D é comum em pacientes com doença inflamatória intestinal submetidos a ileostomia e está associada com níveis baixos de hemoglobina. Mais estudos são necessários para avaliar se a suplementação de vitamina D pode ser um adjuvante no tratamento de anemia da doença crônica nesses pacientes.

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Introduction

Vitamin D is a steroid hormone responsible for calcium hemostasis and metabolism. It also has immunoregulatory functions and anti-inflammatory effects.¹ The main source of vitamin D derives from the conversion of 7-dehydrocholesterol in the skin to cholecalciferol (D_3) by sunlight. Vitamin D is also acquired from the diet and it is absorbed in the duodenum and jejunum. As a liposoluble vitamin, it depends on bile acids for its absorption. The bile acid pool is maintained by the enterohepatic circulation and relays on the absorption of bile acids in the terminal ileum.

Vitamin D deficiency is common worldwide. In the United States, the reported frequency of vitamin D deficiency is 18–40% in adult females and 11–26% in adult males, with variation depending on age, season and geographical location.² Vitamin D deficiency has a significant impact on health, including low bone mineral density, increased risk of fractures and falls.³ In addition, adequate blood vitamin D levels and intake of vitamin D may decrease the risk of cancer,⁴ type I diabetes,⁵ multiple sclerosis⁶ and rheumatoid arthritis.⁷

Low vitamin D levels are common in patients with inflammatory bowel disease (IBD), occurring in 45–63% of the patients.^{8,9} The mechanisms for vitamin D deficiency in IBD patients are multifactorial. Patients with IBD are subject to surgery, particularly ileal resection for Crohn's disease, and may be at increased risk of vitamin D deficiency. IBD patients often require surgery during the course of their disease¹⁰ and ileostomy is performed in a subset of patients with CD or ulcerative colitis (UC).¹¹

Surgical procedures such as ileostomy may pose an additional risk for vitamin D deficiency in IBD patients. Studies

evaluating the rates and associated risk factors of vitamin D deficiency in this population are lacking. Thus the aims of this study were to evaluate the frequency of vitamin D deficiency in IBD patients with an ileostomy and to identify risk factors for vitamin D deficiency in these patients.

Patients and methods

Patients

This study was approved by the Cleveland Clinic Institutional Review Board (IRB). Three hundred IBD patients with permanent ileostomy were retrospectively identified from the electronic medical records. A total of 112 patients with IBD and at least one serum $25(OH)D_3$ level after the construction of ileostomy were included in the study. Inclusion criteria were: (1) diagnosis of IBD; (2) the presence of permanent or temporary ileostomy; and (3) at least one serum $25(OH)D_3$ level measured after the ostomy. Exclusion criteria were ileostomy for bowel malignancy or for familial adenomatous polyposis or etiologies other than IBD.

Variables

A total of 32 demographic, clinical and endoscopic variables were studied. Demographic variables included age, gender, race, body mass index (BMI), smoking status and geographical location (North vs. South). The Northern location was defined as location above the latitude of 37 degrees North. The Southern location was defined as a location below the latitude of 37 degrees North.

The following clinical variables were included: duration of disease, duration of disease until submission to ileostomy, duration of ileostomy, season when vitamin D was measured and clinical indication for ileostomy and blood levels of 25(OH)D₃, albumin, hemoglobin (Hb), calcium, parathyroid hormone (PTH), alkaline phosphatase and C-reactive protein (CRP). History of use of calcium supplements, vitamin supplements, corticosteroid, immunomodulators, anti-tumor necrosis factor (TNF) biologics, antibiotics or non-steroidal anti-inflammatory drugs (NSAID) were also evaluated. Endoscopic variables included the presence or absence of any mucosal inflammation on ileoscopy.

Vitamin D status was assessed by measuring the most recent 25(OH)D₃ level. Vitamin D levels ≥ 30 ng/mL were considered normal. A low vitamin D was defined as the level below 30 ng/mL. Low vitamin D levels were further categorized into vitamin D insufficiency when levels were between 20 and 29 ng/dl and vitamin D deficiency when levels were less than 20 ng/dl.

To evaluate the presence of anemia, the most recent Hb level within 6 months of vitamin D level measurement was taken into account. Anemia was defined as Hb <12.0 g/dL in females and Hb <13 g/dL in males. The presence of iron deficiency anemia (IDA) and anemia of chronic disease (ACD) was defined based on serum iron levels, transferrin, transferrin saturation and ferritin. The definition of ACD and IDA was as follows according to Weiss and Goodough¹²: (1) transferrin saturation $<16\%$ with normal or elevated serum ferritin levels (>100 ng/mL) characterized as ACD; (2) low levels of both transferrin saturation ($<16\%$) and serum ferritin (<30 ng/mL) characterized as IDA. Transferrin saturation $<16\%$, reduced transferrin concentration, and serum ferritin >30 ng/mL but <100 ng/mL characterized a mixed pattern of IDA and ACD.

Outcome measurements

The primary outcomes were the frequency and risk factors of vitamin D deficiency in IBD patients with ileostomy.

Statistical analysis

All statistical analyses were performed using SPSS software version 22 (IBM Corp., Armonk, NY). Mean \pm SD or $n\%$ was used to present continuous variables. To identify potential risk factors for vitamin D deficiency, univariable analysis was used. Student's *t* test (or Wilcoxon rank sum test when appropriate) was used for continuous variables, while Chi-square test (or Fishers exact test, when appropriate) was used for categorical variables. Variables that were significantly ($p < 0.05$) associated with vitamin D deficiency on univariate analysis were included in the multivariate analysis along with variables previously shown in the literature to affect vitamin D levels.

Results

A total of 112 eligible patients with IBD and ileostomy were included in this study, of which 107 had CD and 5 had UC. The mean age of the cohort studied was 53.4 ± 1.3 years (range

24–91 years) and 70 (62.5%) patients were females. The mean duration of IBD diagnosis was 24.6 ± 1.2 years (range 2–60 years) and the mean duration of ileostomy was 12.7 ± 0.9 years (range 2–45 years). The main indications for ileostomy in the cohort were failure of medical therapy in 90 patients (80.4%) and bowel obstruction in 22 (19.6%). In the subgroup of patients with UC, the main indication for end ileostomy was complications of the ileal pouch (3/5). Five patients had temporary ileostomy and 107 had permanent ileostomy.

Frequency of vitamin D deficiency

The mean vitamin D level of the whole cohort was 21.47 ± 1.08 ng/dl. Low vitamin D (<30 ng/dl) levels were present in 92 (82.1%) patients. Thirty-seven patients (33.0%) were classified as having vitamin D insufficiency (level between 20 and 29 ng/dl) and 55 (49.1%) as vitamin D deficiency (<20 ng/dl).

We performed a subanalysis of the trend of vitamin D status before and after ileostomy, based on available data in 26 (23.2%) of the 112 patients. The mean level of vitamin D was significantly higher after ileostomy compared to before ileostomy (22.4 ± 1.8 ng/dL, vs. 17.5 ± 1.8 ng/dL, $p = 0.007$) as shown in Fig. 1.

Univariate assessment of risk factors for vitamin D deficiency

The 112 patients were divided into those with vitamin D deficiency (<20 ng/mL) and those without vitamin D deficiency (>20 ng/mL) to analyze the risk factors associated with vitamin D deficiency.

In the univariate analysis, levels of phosphorus were significantly lower in the vitamin D deficiency group ($p < 0.020$). Numerically lower levels of calcium and higher levels of PTH were also found in these patients although this did not reach statistical significance (Table 1).

In addition, Hb levels were significantly lower in the vitamin D deficiency group ($p = 0.019$) (Table 1). A total of 47 (42.0%) of the 112 were found to have anemia, defined as Hb <12 ng/dL in females and Hb <13 ng/dL in males. Among the 47 patients with diagnosis of anemia, 37 had iron studies including iron levels, transferrin, transferrin saturation and ferritin. ACD was detected in 21 (63.6%) patients, IDA was detected in 6 (18.2%) patients and mixed pattern anemia was also detected in 6 (18.2%) patients. No statistical difference was found between patients with and without vitamin D deficiency regarding the prevalence of the different types of anemia (ACD vs. IDA vs. mixed pattern anemia) ($p = 0.204$, Table 1).

Patients with vitamin D deficiency had IBD diagnosis for a shorter period of time ($p = 0.047$), but no significant differences were found neither in the duration of ileostomy ($p = 0.080$), the interval between IBD diagnosis ($p = 0.819$) and ileostomy nor the presence of inflammation on ileoscopy ($p = 0.155$) as shown in Table 1.

There was no difference in age, gender, race, BMI, smoking status, geographical location, season when vitamin D was measured, albumin, alkaline phosphatase, CRP, the use of calcium supplements, vitamin supplements, steroid, immunomodulators, anti-TNF biologics, antibiotics and

Table 1 – Demographic, clinical, endoscopic and histologic characteristics of ileostomy patients with and without vitamin D deficiency.

Variables	All cases (total 112)	Vitamin deficiency (<20 ng/mL) n = 55	No vitamin D deficiency (≥ 20 ng/mL) n = 57	p-value
Mean age, years	53.39 \pm 1.32	52.04 \pm 1.87	54.87 \pm 1.87	0.317 ^a
Male gender	42	18 (32.7%)	24 (42.1%)	0.203 ^b
BMI	26.19 \pm 0.58	26.46 \pm 0.94	25.94 \pm 0.70	0.659 ^a
Race, n%				
Non-Hispanic	27	14 (25.5%)	13 (22.8%)	0.827 ^b
Caucasian	85	41 (74.5%)	44 (77.2%)	
North state location	105	51 (92.7%)	54 (94.7%)	0.480 ^b
Season, n%				
Spring	26	11 (20.0%)	15 (26.3%)	
Summer	30	15 (27.3%)	15 (26.3%)	0.598 ^b
Fall	31	14 (25.5%)	17 (29.8%)	
Winter	25	15 (27.3%)	10 (17.5%)	
Smoking, n%				
Current	21	14 (25.5%)	7 (12.3%)	
Quit	33	13 (23.6%)	20 (35.1%)	0.146 ^b
Never	58	28 (50.9%)	30 (52.6%)	
Excessive use of alcohol, n%	37	15 (27.3%)	22 (38.6%)	0.232 ^b
Indication for stoma				
Refractory IBD	90	43 (78.2%)	47 (82.5%)	0.971 ^b
Mechanical obstruction	22	12 (21.8%)	10 (17.5%)	
Years from IBD diagnosis	24.60 \pm 1.24	22.09 \pm 1.84	27.02 \pm 1.62	0.047 ^a
Years after ileostomy	12.72 \pm 0.91	12.50 \pm 1.37	12.92 \pm 1.92	0.819 ^a
Years between diagnosis and ileostomy	11.18 \pm 1.07	9.27 \pm 1.44	13.02 \pm 1.54	0.080 ^a
Ileal inflammation (ileoscopy)	26	10 (18.2%)	16 (28.1%)	0.266 ^b
Use of steroids	83	39 (70.9%)	44 (77.2%)	0.520 ^b
Use of aspirin	43	23 (41.8%)	20 (35.1%)	0.295 ^b
Use of antibiotics	107	52 (94.5%)	55 (96.5%)	0.483 ^b
Use of NSAIDS	62	31 (56.4%)	31 (54.4%)	0.492 ^b
Use of biologics	49	20 (36.4%)	29 (50.9%)	0.132 ^b
Use of immunomodulators	63	28 (50.9%)	35 (61.4%)	0.177 ^b
Use of calcium	78	35 (63.6%)	43 (75.4%)	0.125 ^b
Use of vitamin D	88	40 (72.7%)	48 (84.2%)	0.105 ^b
Calcium	81.25 \pm 1.83	77.75 \pm 2.86	84.63 \pm 2.23	0.060 ^c
PTH	103.11 \pm 14.01	111.64 \pm 21.73	87.23 \pm 16.78	0.512 ^c
Phosphorus	3.35 \pm 0.10	3.08 \pm 0.10	3.58 \pm 0.17	0.020 ^c
Alkaline phosphatase	132.36 \pm 9.06	143.73 \pm 16.06	117.53 \pm 8.46	0.096 ^c
Hemoglobin	10.92 \pm 0.22	10.38 \pm 0.32	11.42 \pm 0.30	0.019 ^c
Anemia type ^d				
Chronic disease	21	15 (75.0%)	6 (46.2%)	
Iron deficiency	6	2 (10.0%)	4 (30.8%)	0.204 ^{b,c}
Mixed pattern	6	3 (15.0%)	3 (23.1%)	
Albumin	3.47 \pm 0.08	3.37 \pm 0.13	3.55 \pm 0.15	0.429 ^a
CRP > 1 ^e	66	37 (67.3%)	29 (50.9%)	0.073 ^{b,c}

BMI, body mass index; 5 ASA, 5-aminosalicylic acid; NSAID, non-steroidal anti-inflammatory drugs; PTH, parathyroid hormone.

^a The p value was calculated by t-test.

^b The p value was calculated by chi-square test.

^c Some variables may have less than 112 due to missing data.

^d Anemia type was available in 33 patients, 20 in vitamin D deficiency and 13 in no vitamin D deficiency groups.

^e CRP was available in 104 patients, 50 in vitamin D deficiency and 54 in no vitamin D deficiency groups.

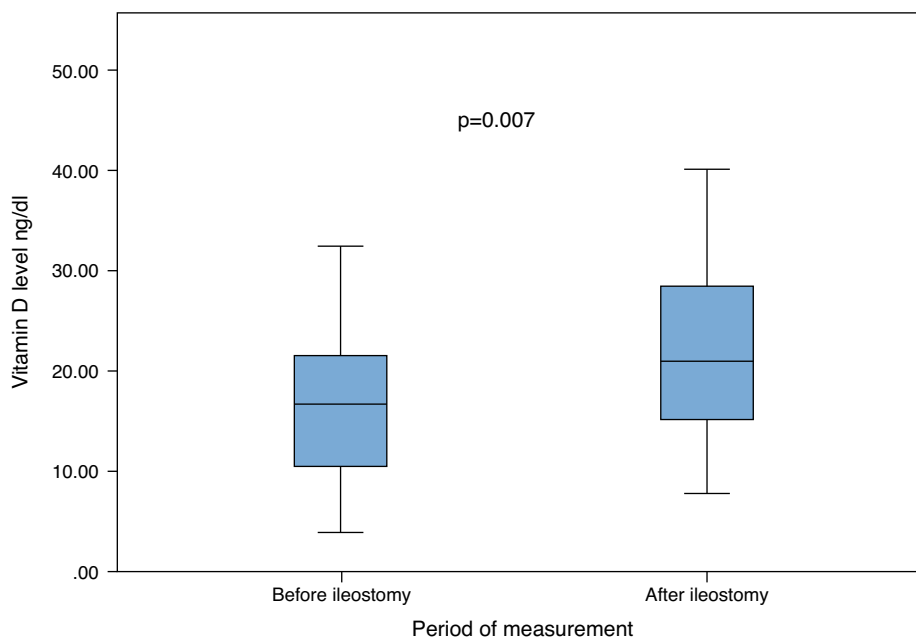


Fig. 1 – Box plot distribution of vitamin D levels before and after ileostomy (N = 26).

non-steroidal anti-inflammatory drugs (NSAID), between the study and control groups (Table 1).

Multivariate analysis of risk factors for vitamin D deficiency

Low Hb, low phosphorus level and shorter duration of IBD diagnosis were significantly associated with vitamin D deficiency in the univariate analysis and thus were included in the multivariable analysis. When the effect of these variables was analyzed together in the logistic regression, low Hb (odds ratio [OR]: 1.32, 95% confidence interval [CI]: 1.08-1.60, $p=0.006$) and low phosphorus (OR: 1.83, 95% CI: 1.16-2.89, $p=0.009$) remained independently associated with vitamin D deficiency (Table 2).

Discussion

In this study, we found that the low vitamin D levels (vitamin D deficiency or insufficiency) were common in IBD patients with ileostomy, with a frequency of 82.1% (92/112). Surprisingly, vitamin D status improved after ileostomy, when compared with pre-ileostomy status, based on the data in 26 patients with sequential measurements of serum vitamin D level.

Vitamin D deficiency was found to be associated with anemia ($p=0.009$), suggesting that there may be a link between vitamin D deficiency and anemia in these patients. In the 33 patients who had available data for anemia type identification, ACD was more prevalent in patients with vitamin D deficiency than controls (66.7% vs. 33.3%), although this finding did not reach statistical significance ($p=0.204$). There was no association between vitamin D deficiency and ileum inflammation on ileoscopy ($p=0.155$).

Low vitamin D levels are common in patients with IBD in general.⁷ Up to 63% of patients with CD have vitamin D deficiency [39], while in patients with UC vitamin D deficiency has been shown to occur in 45% of the cases.⁷ In both CD and UC, severity of disease was found to be associated with vitamin D deficiency.^{13,14} Since vitamin D has been shown to have anti-inflammatory properties, its lower level may predispose to greater inflammation and disease activity in both CD and UC, creating a vicious circle.^{15,16} Our study showed that the creation of an ileostomy may help boost the level of serum vitamin D, presumably due to the bypass or resection of the diseased bowel downstream.

The cause of vitamin D deficiency in IBD patients appears to be multifactorial, including decreased sun exposure¹⁷ and decreased dietary vitamin D intake due to the disease.¹⁸ In patients with CD, additional culprits are vitamin D

Table 2 – Multivariate analysis of risk factors associated with vitamin D deficiency in IBD patients with ileostomy.

Variables	OR	CI	p-value
Low phosphorus	1.83	1.16-2.89	0.009
Low hemoglobin	1.32	1.08-1.60	0.006
Years from IBD diagnosis	1.04	1.00-1.07	0.051

OR, odds ratio; CI, confidence interval.

malabsorption and protein losing enteropathy causing loss of vitamin D binding protein.¹⁹ Terminal ileum resection in patients CD has also been proposed as a contributor to vitamin D deficiency due to decreased enterohepatic circulation of bile acids.²⁰

Surgical approach in patients with IBD such as end ileostomy imposes additional metabolic consequences to an already burdened population. In IBD patients with ileostomy, our group has previously shown a high prevalence of low bone mineral density, further complicated by increased risk of fractures.²¹ There may be an increased risk of vitamin B12 deficiency in these patients, although this seems to be more common when significant amounts of ileum are resected.²² In addition, there is an increased fecal excretion of cholesterol and bile acids in patients with ileostomy, which has been shown to improve cholesterol profile in these patients, while it may further impair bile acid enterocirculation.²³ The association between vitamin D deficiency and anemia, on the other hand, has not been established in this population.

To our knowledge, this is the first study evaluating vitamin D deficiency and its risk factors in IBD patients with ileostomy. Kennedy et al.²⁴ studied calcium metabolism in 49 patients with ileostomy and mentioned that the levels of vitamin D in these patients varied from 21.4 ± 9.5 nmol/L in the winter to 46.4 ± 19.2 nmol/L in the summer. However, risk factors for vitamin D deficiency were not evaluated. In the present study, vitamin D deficiency was common in IBD patients submitted to ileostomy. The exact etiopathogenesis for vitamin D deficiency in IBD patients with ileostomy is unknown. We postulate that it may be related to altered intestinal transit time and ileal resection in this population. Some IBD patients with ileostomy may have extensive inflammation or strictures, which leads to stasis of fecal content in the small bowel and bacterial overgrowth.²⁵ In turn, bacterial overgrowth causes deconjugation of bile acids and decreases the absorption of fat soluble vitamins such as vitamin D.²⁶ Ileostomy with ileal resection in CD may lead to impaired bile acid enterohepatic circulation. In patients with ileal CD, lower vitamin D levels seem to be more common.²⁰

To better understand the exact burden that ileostomy poses toward vitamin D deficiency, we compared the levels of vitamin D before and after ileostomy in 26 patients with available data. Surprisingly, the mean level of vitamin D was significantly lower before ileostomy than after ileostomy. These findings may be a consequence of better disease control or less inflammation leading to nutritional improvement in IBD patients after ileostomy. In addition, after surgery these patients may have improved oral intake and increased quality of life with more outdoor activity.

Interestingly, we found a significant association between low vitamin D and Hb in both univariable and multivariate analyses. This finding, along with the similar one reported in patients with ileal pouch-anal anastomosis (IPAA),²⁷ prompted our hypothesis that the link between vitamin D deficiency and anemia is not a coincidence. This association has not yet been studied in IBD patients without ileostomy or IPAA. A total of 37 patients had available laboratory data to further categorize the subtype of anemia into ACD, IDA or mixed pattern. ACD was the most common type of anemia in the cohort, occurring in 21 patients (66.6%). Although ACD occurred more

frequently in patients with vitamin D deficiency, this did not reach statistical significance (75.0% vs. 46.2%, $p = 0.204$), probably due to the small sample size.

The association of vitamin D deficiency with anemia has been demonstrated in patients with and without chronic kidney disease.^{28,29} In the elderly, vitamin D deficiency seems to be associated with ACD, but not with other types of anemia, pointing toward a possible role of vitamin D in inflammation suppression.²⁸ Vitamin D deficiency was significantly associated with a high hepcidin level, a pro-inflammatory mediator and a player in iron metabolism. Hepcidin may play a role in ACD in CD.³⁰ We therefore attempted to connect the dots. We postulate that vitamin D deficiency is linked to anemia in IBD patients, specifically ACD, through the inflammation-hepcidin axis. Whether vitamin D deficiency contributes to increased inflammation leading to ACD or whether both vitamin D deficiency and anemia are a common end of a chronic inflammatory state is unknown. Prospective, longitudinal studies are needed to further sort out the association or causal relationship.

Although the presence of inflammation in the ileum diagnosed by ileoscopy could potentially be predisposed to low vitamin D levels by further impairing absorption of bile acids and vitamin D through the inflamed mucosa, this was not confirmed in by our study. This may indicate that the most important factor for vitamin D deficiency in these patients is disruption of the anatomy. Similar findings of low vitamin D levels in IBD patients with IPAA without correlation with inflammation on endoscopy or histology have been described in the literature.²⁷ Alternatively, this may imply that conditions such as ileostomy and IPAA cause a reset of the immunostat, interfering with nutrition and metabolism.

There are several clinical implications of the findings in this study. Vitamin D deficiency is common in patients with ileostomy and vitamin D levels should be routinely measured in these patients. In addition, we suggest that Hb levels should be checked when vitamin D deficiency is encountered and *vice versa*. In addition, there may be a role for vitamin D supplementation through immunomodulation in the treatment of ACD in this patient population, warranting future studies for confirmation.

This study has limitations. First, the sample size may limit the power of the study, particularly the analysis of anemia. Second, the rate of vitamin D deficiency may reflect greater disease severity of the IBD patient population in our tertiary center and may not represent the IBD population in general, resulting in referral bias. Because this is a retrospective study, data on levels of vitamin D and anemia before and after the ileostomy were lacking in some patients, as checking of vitamin D before ileostomy has not been a part of routine clinical practice. Further studies confirming the association of vitamin D deficiency with anemia subtypes in IBD patients independent of surgical status may be of interest. In addition, it may be interesting to compare different doses of vitamin D supplementation in patients with ileostomy in the future to establish if vitamin D supplementation can ameliorate not only the vitamin D deficiency but also anemia in IBD patients with ileostomy.

In conclusion, vitamin D deficiency is common in IBD patients with ileostomy irrespective of inflammation on

endoscopy or histology and is associated with anemia. Patients with IBD and anemia should be routinely screened for vitamin D deficiency and *vice versa*. Vitamin D deficiency may play a role in ACD.

Conflicts of interest

The authors declare no conflicts of interest.

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