Received: 1 June 2023 | Accepted: 14 January 2024

DOI: 10.1002/jpr3.12045

CASE REPORT

Gastroenterology: Inflammatory Bowel Disease

Cause or effect? Undetectable vitamin D in a patient with Crohn's disease

Julia Esswein[1] | **Maggie Vickers**[2] | **Michael Kleinman**[1] | **John Whitworth**[2] | **Mark Corkins**[2] | **S. Riley Pace**[1]

[1]Division of Internal Medicine and Pediatrics, University of Tennessee Health Sciences Center, Memphis, Tennessee, USA

[2]Division of Gastroenterology, LeBonheur Children's Hospital, Memphis, Tennessee, USA

Correspondence
Julia Esswein, 920 Madison Ave, Rm 551, Memphis, TN 38163, USA.
Email: ejulia@wustl.edu

Funding information
None

Abstract

Crohn's disease has been described as the "great mimicker" with a wide array of presentations. We describe a case of a teenager who presented with tetany and undetectable vitamin D as initial presentation of Crohn's disease. There are reports of adults in tetany due to electrolyte derangements in chronic gastrointestinal diseases secondary to malabsorption. However, the role of deficient vitamin D as it contributes to immune system dysfunction has only begun to be explored. Vitamin D is essential for calcium absorption, immune regulation, and gut epithelial barrier. This case report discusses vitamin D physiology and its potential mediation in the pathogenesis of inflammatory bowel disease.

KEYWORDS

calcium absoprtion, cathelicidin, immune system regulation, toll-like-receptors

1 | INTRODUCTION

Low vitamin D levels are commonly seen in patients with inflammatory bowel disease (IBD).[1] Low vitamin D has historically been attributed to intestinal malabsorption present in these patients, though there are developments suggesting that vitamin D may contribute to the pathophysiology of IBD, which would subsequently lead to malabsorption of electrolytes as hypothesized in this case. Current guidelines for replacement of vitamin D are based on bone mineralization needs and recognize the lack of study regarding recommendations for treating extraskeletal vitamin-D deficiencies.

1.1 | Case report

We present a 15-year-old Caucasian male with a history of abdominal migraines (reportedly well-controlled on cyproheptadine and omeprazole) who presented emergently with tetany and rhabdomyolysis. He was in his usual state of health until a few days before presentation in our emergency department with a 3-day history of diarrhea, cramps, and fever. He reported numbness and tingling in his extremities for several days, progressing to full body cramps, eventual paralysis, and inability to stand from a seated position. He was febrile to 103.2°F (39.6°C), tachycardic, and with a weight loss of 2.5 kg. Lab abnormalities included hypocalcemia, hypokalemia, hypomagnesemia, and elevated creatinine kinase (specific levels not provided in transfer paperwork). He received intravenous fluids, calcium gluconate, magnesium, and potassium chloride before transferring to our facility.

Upon arrival to our emergency department, his vital signs were unremarkable, and body mass index was 16.6 kg/m^2. Physical exam was notable for muscular pain and mild weakness. Electrocardiogram showed normal sinus rhythm. Repeat labs after treatment at the initial facility are listed in Table 1.

Electrolyte disturbances were corrected, and he was started on a regular diet. Celiac disease screen with tissue transglutamine IgA and stool PCR pathogen

TABLE 1 Initial labs on arrival to our facility, after correction by patient's local medical center.

Lab	Result	Range
Potassium	2.7 mmol/L	3.5–5
Calcium	6.4 mg/dL	8.8–10.8
Alkaline phosphatase	91 U/L	116–284
AST	106 U/L	15–40
ALT	25 U/L	11–26
Albumin	2.1 g/dL	3.5–5.4
Creatine kinase	5180 U/L	20–150
Magnesium	1.9 mg/dL	1.6–2.6
Phosphorus	3.5 mg/dL	2.9–5.4
C-reactive protein	172 mg/L	<9.0
Parathyroid hormone	177.6 pg/mL	22.0–88.0
25-(OH)D	<3.4 ng/mL	30–70

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; 25-(OH)D, 25-hydroxy vitamin D.

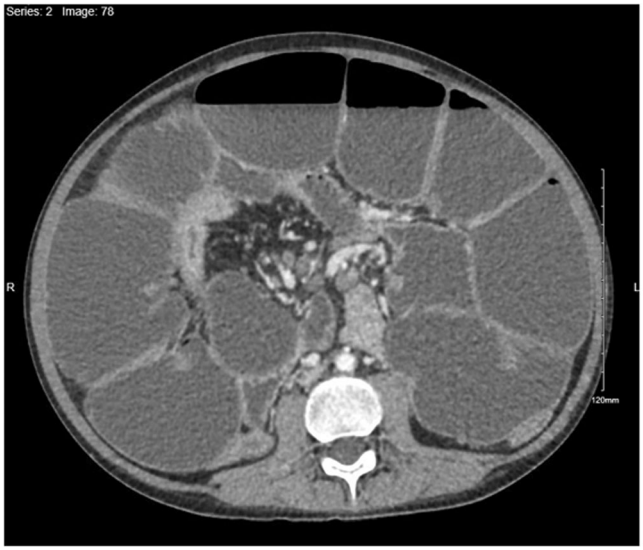

FIGURE 1 Computed tomography scan of the abdomen, showing thickening of the wall of the terminal ileum causing a partial small bowel obstruction.

panel were negative. Abdominal X-ray showed an ileus with possible partial bowel obstruction. Computed tomography scan with contrast showed inflammatory changes, thickening of the wall of and narrowing of 7 cm of terminal ileum (Figure 1), causing a partial small bowel obstruction. Gastroenterology and surgery teams were consulted.

Esophagogastroduodenoscopy and colonoscopy showed overall normal appearance with the exception of the cecum, which showed colitis with narrowed lumen and distorted landmarks preventing intubation of the ileocecal valve (Figure 2). Pathology report showed no significant histopathologic changes. However, given the clinical picture, imaging, and labs, Crohn's disease involving the terminal ileum was felt to be the most likely diagnosis. He was started on corticosteroids with subsequent improvement in symptoms. He was discharged on adalimumab. One month later, he presented with a small bowel obstruction and underwent ileocectomy with histology consistent with chronic ileocecitis with ileal fibrotic stricture. After 3 months of ergocalciferol 50,000 IU weekly, the patient's level was still low at 20.5 ng/mL. The patient is now maintained on methotrexate and folic acid due to insurance coverage but with poor compliance documented.

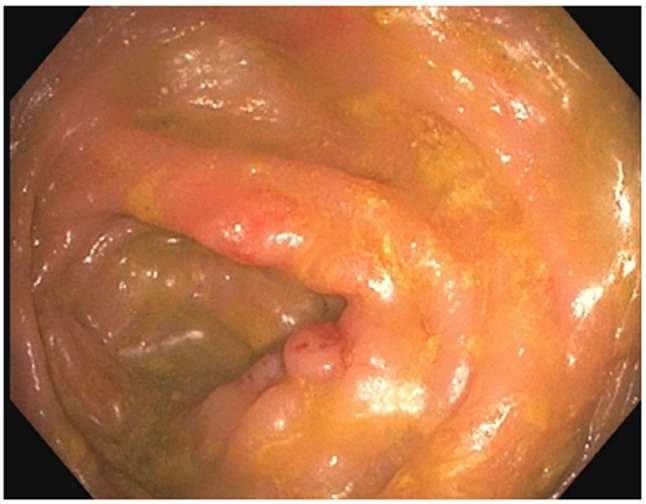

FIGURE 2 Images of edematous cecum leading to distortion of typical landmarks and preventing intubation of the terminal ileum.

2 | DISCUSSION

This patient was treated for newly diagnosed Crohn's in the setting of undetectable vitamin D and acute tetany. The majority of vitamin D is synthesized in the skin, and the portion that is ingested is taken up by enterocytes. Since this patient had no long-term gastrointestinal symptoms and limited ileal Crohn's, it is unclear why he was so deficient and why he did not improve with standard oral replacement. Whether or not vitamin D deficiency underlies the pathogenesis of IBD or is merely a result of malabsorption is a new area of study. Vitamin D is known to regulate calcium levels in the blood, but more recently, vitamin D has been shown to have some immune system effect as well.[2]

Vitamin D regulates calcium by several mechanisms. For this case, the most relevant mechanism is that vitamin D stimulates absorption of calcium in the intestine. In fact, the highest concentration of vitamin D receptors is seen in the intestinal epithelium.[3] 1,25-dihydroxyvitamin D (1,25(OH)D) binds to a nuclear

vitamin D receptor that complexes with the retinoic acid receptor.[4] This complex then activates the transcription of TRPV6, a calcium transport channel embedded into the epithelial surface, allowing calcium to be absorbed from the diet.[5]

Claudins 2 and 12—transmembrane proteins that make up tight junctions and provide a barrier from the gut lumen—have been found to respond to 1,25(OH)D signaling by significantly increasing calcium absorption.[6] Importantly, claudins 2 and 12 are found most highly concentrated in the ileum, making it the site of highest calcium absorption.[6]

An additional function of vitamin D is immune system regulation. A vitamin D receptor located in the promoter region of cathelicidin encourages the transcription of this antimicrobial peptide.[2] Cathelicidin negates circulating endotoxin from Gram-negative bacterial cells and prevents promotion of cell death in response to the death of other cells.[7,8]

Vitamin D also has some innate feedback control over the immune system. Vitamin D has been found to suppress toll-like receptor 2 (TLR2) and TLR4 on monocytes.[9] TLRs are an important component of the innate immunity cascade. Specifically, TLR2 and TLR4 are thought to be important in IBD, as TLR2 is known to recognize Gram-positive bacteria, while TLR4 is known to recognize Gram-negative bacteria.[10,11] In patients with IBD, TLR2 and TLR4 have been found to be expressed at higher-than-normal levels,[12] suggesting that this upregulation may have a role in the immune response to the disease. Therefore, if vitamin D suppresses TLR2 and TLR4, it may decrease the overall inflammatory response in the bowel.

The above evidence of immune regulation and dysregulation and maintenance of the epithelial barrier is a key component in the pathogenesis of IBD. There are additional mechanisms that are not reviewed in detail for the purposes of this report. The aforementioned research highlights the importance of continued study of vitamin D's effects and other causes of its deficiency, especially as IBD cases increase.

ACKNOWLEDGMENTS

No funding was provided for this review.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Consent to publish this case report was provided by the patient's legal guardian.

REFERENCES

1. Mouli VP, Ananthakrishnan AN. Review article: vitamin D and inflammatory bowel diseases. *Aliment Pharmacol Ther*. 2014;39(2):125-136.
2. Adams JS, Hewison M. Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. *Nat Clin Pract Endocrinol Metab*. 2008;4(2):80-90.
3. 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.
4. Raman M, Milestone AN, Walters JRF, Hart AL, Ghosh S. Vitamin D and gastrointestinal diseases: inflammatory bowel disease and colorectal cancer. *Ther Adv Gastroenterol*. 2011;4(1):49-62.
5. Kumar V. Environmental and nutritional diseases. In: Kumar V, Abbas AK, Aster JC, Deyrup AT, eds. *Robbins & Kumar Basic Pathology*. Elseveir; 2023:235-273.
6. Fujita H, Sugimoto K, Inatomi S, et al. Tight junction proteins claudin-2 and -12 are critical for vitamin D-dependent Ca^{2+} absorption between enterocytes. *Mol Biol Cell*. 2008;19(5):1912-1921.
7. Suzuki K, Murakami T, Kuwahara-Arai K, Tamura H, Hiramatsu K, Nagaoka I. Human anti-microbial cathelicidin peptide LL-37 suppresses the LPS-induced apoptosis of endothelial cells. *Int Immunol*. 2011;23(3):185-193.
8. Hu Z, Murakami T, Suzuki K, et al. Antimicrobial cathelicidin peptide LL-37 inhibits the LPS/ATP-induced pyroptosis of macrophages by dual mechanism. *PLoS One*. 2014;9(1):e85765.
9. Sadeghi K, Wessner B, Laggner U, et al. Vitamin D3 down-regulates monocyte TLR expression and triggers hyporesponsiveness to pathogen-associated molecular patterns. *Eur J Immunol*. 2006;36(2):361-370.
10. Takeuchi O, Hoshino K, Kawai T, et al. Differential roles of TLR2 and TLR4 in recognition of Gram-negative and Gram-positive bacterial cell wall components. *Immunity*. 1999;11(4):443-451.
11. Aderem A, Ulevitch RJ. Toll-like receptors in the induction of the innate immune response. *Nature*. 2000;406(6797):782-787.
12. Hausmann M, Kiessling S, Mestermann S, et al. Toll-like receptors 2 and 4 are up-regulated during intestinal inflammation. *Gastroenterology*. 2002;122(7):1987-2000.

How to cite this article: Esswein J, Vickers M, Kleinman M, Whitworth J, Corkins M, Riley Pace S. Cause or effect? Undetectable vitamin D in a patient with Crohn's disease. *JPGN Rep*. 2024;5:194-196. doi:10.1002/jpr3.12045