

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2017 April 14; 23(14): 2453-2634



**EDITORIAL**

- 2453 Noninvasive molecular analysis of *Helicobacter pylori*: Is it time for tailored first-line therapy?

*Ierardi E, Giorgio F, Iannone A, Losurdo G, Principi M, Barone M, Pisani A, Di Leo A*

**REVIEW**

- 2459 Pathogenesis and clinical spectrum of primary sclerosing cholangitis

*Gidwaney NG, Pawa S, Das KM*

- 2470 Biliary tract cancer stem cells - translational options and challenges

*Mayr C, Ocker M, Ritter M, Pichler M, Neureiter D, Kiesslich T*

**MINIREVIEWS**

- 2483 Potential role of nutraceutical compounds in inflammatory bowel disease

*Larussa T, Imeneo M, Luzzza F*

- 2493 Unusual gastric tumors and tumor-like lesions: Radiological with pathological correlation and literature review

*Lin YM, Chiu NC, Li AFY, Liu CA, Chou YH, Chiou YY*

- 2505 New progress in roles of nitric oxide during hepatic ischemia reperfusion injury

*Zhang YQ, Ding N, Zeng YF, Xiang YY, Yang MW, Hong FF, Yang SL*

**ORIGINAL ARTICLE****Basic Study**

- 2511 Berberine displays antitumor activity in esophageal cancer cells *in vitro*

*Jiang SX, Qi B, Yao WJ, Gu CW, Wei XF, Zhao Y, Liu YZ, Zhao BS*

**Case Control Study**

- 2519 Clinical utility of the platelet-lymphocyte ratio as a predictor of postoperative complications after radical gastrectomy for clinical T2-4 gastric cancer

*Inaoka K, Kanda M, Uda H, Tanaka Y, Tanaka C, Kobayashi D, Takami H, Iwata N, Hayashi M, Niwa Y, Yamada S, Fujii T, Sugimoto H, Murotani K, Fujiwara M, Kodera Y*

- 2527 Colors of vegetables and fruits and the risks of colorectal cancer

*Lee J, Shin A, Oh JH, Kim J*

**Retrospective Cohort Study**

- 2539 Impact of vitamin D on the hospitalization rate of Crohn's disease patients seen at a tertiary care center  
*Venkata KVR, Arora SS, Xie FL, Malik TA*

- 2545 Barcelona clinic liver cancer nomogram and others staging/scoring systems in a French hepatocellular carcinoma cohort  
*Adhoute X, Pénaranda G, Raoul JL, Edeline J, Blanc JF, Pol B, Campanile M, Perrier H, Bayle O, Monnet O, Beaurain P, Muller C, Castellani P, Le Treut YP, Bronowicki JP, Bourlière M*

**Retrospective Study**

- 2556 Laparoscopic approach to suspected T1 and T2 gallbladder carcinoma  
*Ome Y, Hashida K, Yokota M, Nagahisa Y, Okabe M, Kawamoto K*
- 2566 Clinical characteristics of peptic ulcer perforation in Korea  
*Yang YJ, Bang CS, Shin SP, Park TY, Suk KT, Baik GH, Kim DJ*
- 2575 Effects of omeprazole in improving concurrent chemoradiotherapy efficacy in rectal cancer  
*Zhang JL, Liu M, Yang Q, Lin SY, Shan HB, Wang HY, Xu GL*

**Clinical Trials Study**

- 2585 *PIK3CA* gene mutations in Northwest Chinese esophageal squamous cell carcinoma  
*Liu SY, Chen W, Chughtai EA, Qiao Z, Jiang JT, Li SM, Zhang W, Zhang J*
- 2592 Endothelial progenitor cells in peripheral blood may serve as a biological marker to predict severe acute pancreatitis  
*Ha XQ, Song YJ, Zhao HB, Ta WW, Gao HW, Feng QS, Dong JZ, Deng ZY, Fan HY, Peng JH, Yang ZH, Zhao Y*
- 2601 Comparative study of ROR2 and WNT5a expression in squamous/adenosquamous carcinoma and adenocarcinoma of the gallbladder  
*Wu ZC, Xiong L, Wang LX, Miao XY, Liu ZR, Li DQ, Zou Q, Liu KJ, Zhao H, Yang ZL*

**Observational Study**

- 2613 Serum omentin and vaspin levels in cirrhotic patients with and without portal vein thrombosis  
*Kukla M, Waluga M, Żorniak M, Berdowska A, Wosiewicz P, Sawczyn T, Buldak RJ, Ochman M, Ziora K, Krzemiński T, Hartleb M*
- 2625 Upper gastrointestinal cancer burden in Hebei Province, China: A population-based study  
*Li DJ, Liang D, Song GH, Li YW, Wen DG, Jin J, He YT*

**ABOUT COVER**

Editorial board member of *World Journal of Gastroenterology*, Vicente Lorenzo-Zuniga, MD, PhD, Associate Professor, Chief Doctor, Staff Physician, Endoscopy Unit, Department of Gastroenterology, Hospital Universitari Germans Trias i Pujol/CIBERehd, Badalona 08916, Spain

**AIMS AND SCOPE**

*World Journal of Gastroenterology* (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7<sup>th</sup>, 14<sup>th</sup>, 21<sup>st</sup>, and 28<sup>th</sup> each month. The *WJG* Editorial Board consists of 1375 experts in gastroenterology and hepatology from 68 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

**INDEXING/ABSTRACTING**

*World Journal of Gastroenterology* (*WJG*) is now indexed in Current Contents<sup>®</sup>/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch<sup>®</sup>), Journal Citation Reports<sup>®</sup>, Index Medicus, MEDLINE, PubMed, PubMed Central, Digital Object Identifier, and Directory of Open Access Journals. The 2015 edition of Journal Citation Reports<sup>®</sup> released by Thomson Reuters (ISI) cites the 2015 impact factor for *WJG* as 2.787 (5-year impact factor: 2.848), ranking *WJG* as 38 among 78 journals in gastroenterology and hepatology (quartile in category Q2).

**FLYLEAF**

**I-IX Editorial Board**

**EDITORS FOR THIS ISSUE**

**Responsible Assistant Editor:** Xiang Li  
**Responsible Electronic Editor:** Cai-Hong Wang  
**Proofing Editor-in-Chief:** Lian-Sheng Ma

**Responsible Science Editor:** Yuan Qi  
**Proofing Editorial Office Director:** Jin-Lei Wang

**NAME OF JOURNAL**  
*World Journal of Gastroenterology*

**ISSN**  
ISSN 1007-9327 (print)  
ISSN 2219-2840 (online)

**LAUNCH DATE**  
October 1, 1995

**FREQUENCY**  
Weekly

**EDITORS-IN-CHIEF**  
**Damian Garcia-Olmo, MD, PhD, Doctor, Professor, Surgeon**, Department of Surgery, Universidad Autonoma de Madrid; Department of General Surgery, Fundacion Jimenez Diaz University Hospital, Madrid 28040, Spain

**Stephen C Strom, PhD, Professor**, Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet, Stockholm 141-86, Sweden

**Andrzej S Tarnawski, MD, PhD, DSc (Med), Professor of Medicine, Chief Gastroenterology**, VA Long Beach Health Care System, University of California, Irvine, CA, 5901 E. Seventh Str., Long Beach,

CA 90822, United States

**EDITORIAL BOARD MEMBERS**  
All editorial board members resources online at <http://www.wjgnet.com/1007-9327/editorialboard.htm>

**EDITORIAL OFFICE**  
Jin-Lei Wang, Director  
Yuan Qi, Vice Director  
Ze-Mao Gong, Vice Director  
*World Journal of Gastroenterology*  
Baishideng Publishing Group Inc  
8226 Regency Drive,  
Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

**PUBLISHER**  
Baishideng Publishing Group Inc  
8226 Regency Drive,  
Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>

<http://www.wjgnet.com>

**PUBLICATION DATE**  
April 14, 2017

**COPYRIGHT**  
© 2017 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

**SPECIAL STATEMENT**  
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

**INSTRUCTIONS TO AUTHORS**  
Full instructions are available online at <http://www.wjgnet.com/bpg/gerinfo/204>

**ONLINE SUBMISSION**  
<http://www.f6publishing.com>

## Retrospective Cohort Study

# Impact of vitamin D on the hospitalization rate of Crohn's disease patients seen at a tertiary care center

Krishna VR Venkata, Sumant S Arora, Feng-Long Xie, Talha A Malik

Krishna VR Venkata, Sumant S Arora, Department of Internal Medicine, University of Alabama at Birmingham Montgomery Health Center, Montgomery, AL 36116, United States

Feng-Long Xie, Talha A Malik, Department of Medicine-Gastroenterology, University of Alabama at Birmingham, Birmingham, AL 35294, United States

**Author contributions:** Venkata KVR, Arora SS and Malik TA conceptualized the study hypothesis, design and methodology; Venkata KVR and Arora SS collected data by retrospective chart review; Xie FL performed the statistical analysis; With regard to manuscript write up, Venkata KVR compiled the methods and results section, while Arora SS and Malik TA wrote the introduction and discussion section and all authors proof read for final manuscript edits.

**Institutional review board statement:** The study was reviewed and approved by the University Of Alabama Office Of Institutional Review Board.

**Informed consent statement:** Informed consent waiver was given by the IRB as the study is chart review.

**Conflict-of-interest statement:** The authors declare that they have no conflicts of interest.

**Data sharing statement:** No additional data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Correspondence to:** Krishna VR Venkata, MD, Department of Internal Medicine, University of Alabama at Birmingham Montgomery Health Center, 2055 E. South Blvd, Suite 200,

Montgomery, AL 36116, United States. [klakshmi@uabmc.edu](mailto:klakshmi@uabmc.edu)  
Telephone: +1-713-8150946

Received: November 10, 2016

Peer-review started: November 13, 2016

First decision: December 19, 2016

Revised: March 7, 2017

Accepted: March 15, 2017

Article in press: March 15, 2017

Published online: April 14, 2017

## Abstract

### AIM

To study the association between vitamin D level and hospitalization rate in Crohn's disease (CD) patients.

### METHODS

We designed a retrospective cohort study using adult patients (> 19 years) with CD followed for at least one year at our inflammatory bowel disease center. Vitamin D levels were divided into: low mean vitamin D level (< 30 ng/mL) vs appropriate mean vitamin D level (30-100 ng/mL). Generalized Poisson Regression Models (GPR) for Rate Data were used to estimate partially adjusted and fully adjusted incidence rate ratios (IRR) of hospitalization among CD patients. We also examined IRRs for vitamin D level as a continuous variable.

### RESULTS

Of the 880 CD patients, 196 patients with vitamin D level during the observation period were included. Partially adjusted model demonstrated that CD patients with a low mean vitamin D level were almost twice more likely to be admitted (IRR = 1.76, 95%CI: 1.38-2.24) compared to those with an appropriate vitamin D level. The fully adjusted model confirmed this association (IRR = 1.44, 95%CI: 1.11-1.87). Partially adjusted model with vitamin D level as a continuous variable demonstrated,



higher mean vitamin D level was associated with a 3% lower likelihood of admission with every unit (ng/mL) rise in mean vitamin D level (IRR = 0.97, 95%CI: 0.96-0.98). The fully adjusted model confirmed this association (IRR = 0.98, 95%CI: 0.97-0.99).

### CONCLUSION

Normal or adequate vitamin D stores may be protective in the clinical course of CD. However, this role needs to be further characterized and understood.

**Key words:** Crohn's disease; Vitamin D; Vitamin D deficiency; Hospitalization rate; Inflammatory bowel disease

© **The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Growing body of epidemiological evidence supports a key role of vitamin D deficiency not just in inflammatory bowel disease development but also on Crohn's disease (CD) severity. Our study sought to test the hypothesis that adequate vitamin D levels have a protective role in the clinical course of CD in terms of a decreased likelihood of hospitalization. Our results are clinically important as they suggest potentially worse outcomes in CD patients with low vitamin D levels as reflected by a numerically increased rate of hospitalization in this group.

Venkata KVR, Arora SS, Xie FL, Malik TA. Impact of vitamin D on the hospitalization rate of Crohn's disease patients seen at a tertiary care center. *World J Gastroenterol* 2017; 23(14): 2539-2544 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i14/2539.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i14.2539>

## INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder characterized by transmural inflammation (all layers from mucosa to serosa) that may discontinuously involve any part of the alimentary tract<sup>[1-4]</sup>. First described by Crohn *et al*<sup>[1]</sup> in 1932, 750000 people in the United States currently have CD. It is classified as inflammatory, penetrating, or stricturing, with or without perianal disease<sup>[5,6]</sup>. As CD became recognized as a distinct disease entity, it was observed that vitamin D deficiency was common among these patients<sup>[7,8]</sup>.

Vitamin D exerts immune modulatory effects by reducing T cell mediated up-regulation of the nuclear vitamin D receptor (VDR)<sup>[9,10]</sup>. The gene for VDR signals through enhancer segments in the *NOD2* gene, thereby inducing NF-kappaB transcription factor function. This in turn stimulates gene encoding antimicrobial peptide defensin beta2 (DEFB2/HBD2). However, this sequential activation is absent in macrophages of CD patients

thus favoring intestinal inflammation<sup>[11]</sup>. Further, certain VDR gene polymorphisms such as rs731236[A] (VDR) and rs732594[A] (SCUBE3) have been found to directly influence risk of CD<sup>[12]</sup>. A 2013 meta-analysis showed that carrying "TaqI tt" genotype of the VDR gene is associated with increased susceptibility for CD in Europeans, while Apal "a" allele is protective. Therefore<sup>[13]</sup>, vitamin D is believed to play an integral role in immune pathogenesis of CD and may help reduce CD-related hospitalizations, disease severity, need for surgery, and colon cancer incidence<sup>[14,15]</sup>.

Growing body of epidemiological evidence supports a key role of vitamin D deficiency not just in inflammatory bowel disease (IBD) development but also on CD severity<sup>[16,17]</sup>. Studies suggest association between low vitamin D levels and increased disease activity as reflected by fecal calprotectin levels<sup>[13,18]</sup>, hospitalizations as well as need for surgery in CD patients<sup>[15,19]</sup>. Conversely, vitamin D supplementation in CD may reduce chronic intestinal inflammation as reflected by CD activity index (CDAI) and C-reactive protein levels<sup>[20-22]</sup>, as well as relapse frequency by as much as 50%<sup>[18]</sup>.

University of Alabama at Birmingham (UAB) is the only tertiary care IBD referral center in the state of Alabama that provides health care by dedicated sub-specialists in a large hospital with sophisticated intensive care facilities after referral from primary care and smaller hospitals. IBD center has facilities available for both inpatient and outpatient management of patients with CD and its complications and so it is a unique setting to study the effect of various covariates such as vitamin D levels on outcomes in CD. Our study sought to test the hypothesis that adequate vitamin D levels have a protective role in the clinical course of CD in terms of a decreased likelihood of hospitalization.

## MATERIALS AND METHODS

**Study design, patient population, and selection criteria**  
We conducted a retrospective cohort study to look at vitamin D levels and CD outcomes. For this study, we analyzed data from 880 CD patients seen at our tertiary care IBD center from 2000 to 2014 and followed for at least one year. Subjects were included in the analysis if they were older than 19 years and had vitamin D levels available. Other included variables were duration of disease, race, sex, smoking status, use of steroids, biological agents, thiopurines or methotrexate and hospitalization rate. The University of Alabama's Office of Institutional Review Board (IRB) approved the study and it was deemed compliant with the Helsinki declaration.

### Data collection and variable definitions

Data were collected by means of retrospective chart review, specifically per Electronic medical record (EMR) documentation and laboratory results. Data collected at the time of first observation

**Table 1** Characteristics of Crohn's disease patients by mean vitamin D level

	Mean < 30 (n = 115)	Mean ≥ 30 (n = 81)
Age, (mean ± SD, yr)	45.50 (15.07)	54.26 (17.63)
DoD	17.83 (11.77)	22.58 (14.50)
Race		
Caucasian	66.96%	87.65%
African-American	31.30%	12.35%
Others	1.74%	0.00%
Female	61.74%	71.6%
BMI		
Low (< 18.5)	11.30%	8.64%
Normal (18.5-24.9)	40.00%	41.98%
Over Weight (25-29.9)	20.00%	27.16%
Obese (≥ 30)	28.70%	22.22%
Smoking	26.96	11.11
Steroids	51.30	45.68
Immune modulators	84.35%	76.54%
Biologicals	61.74%	51.85%
Thiopurines	61.74%	51.85%
Methotrexate	20.87	13.58

DoD: Duration of disease; BMI: Body mass index.

included age, race, sex, duration of CD and vitamin D levels. Participants were followed through the last observation at our IBD center for CD-related hospitalizations. We also collected data on body mass index (BMI), smoking history, medication history for steroid use, traditional and biological immune modulator use. Steroid use was defined as exposure to oral or parenteral corticosteroids for at least six weeks during observation. Thiopurine use was defined as use of azathiopurine or 6-mercaptopurine for at least four weeks during the period of observation. Methotrexate (MTX) use was defined as use of MTX for at least four weeks during the period of observation. Biologic use was defined as use of any biologic agent for at least four weeks during the period of observation. A CD-related hospitalization was defined as any hospital admission for a complication of CD, including infections, fistula, strictures, abscess or exacerbations. 25-Hydroxy vitamin D concentration was measured by Immunoassay method. Adequate vitamin D level was 30-100 ng/mL, while vitamin D level < 30 ng/mL was considered low. We used 30ng/ml as threshold as it is the laboratory reference value for normal lower limit of vitamin D levels in our hospital.

### Statistical analysis

After calculating summary statistics, we performed univariate analyses to examine the incidence rates of CD related hospitalizations among CD patients based on vitamin D levels. We then built Generalized Poisson Regression Models for rate data to estimate partially adjusted (for age, sex, race and duration of disease) as well as fully adjusted (additionally for BMI, smoking, steroid use, traditional and biological immune modulator use) incidence rate ratios (IRR)

of hospitalization among CD patients with low mean vitamin D levels (< 30 ng/mL) vs those with adequate mean vitamin D levels (30-100 ng/mL) during the entire follow up (observation) period.

For each patient, the period of observation was defined as the time in years between the first and the last documented encounter at our tertiary care IBD center during the years 2000 through 2014. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute Inc., Cary, NC). Statistical tests were two-sided with a significance level  $\alpha < 0.05$ .

## RESULTS

Vitamin D levels were measured in 196 of 880 CD patients seen at our institute during the observation period and were included in this study. Of these, 115 patients had a low mean vitamin D level and 81 had an appropriate vitamin D level (Table 1). Among CD patients, incidence rate of hospitalization for a CD related exacerbation was 30.18 per 100 person-years with low mean vitamin D level vs 14.19 per 100 person-years with an appropriate mean vitamin D level (Table 2). GPR Model for Rate Data that was partially adjusted demonstrated that CD patients with a low mean vitamin D level were 1.76 times more likely to be admitted during the observation period (IRR = 1.76, 95%CI: 1.38-2.24) compared to those with an appropriate vitamin D level. The fully adjusted (adjusted for age, sex, duration of CD, smoking, BMI and CD therapy) model confirmed this clinically and statistically significant association (IRR = 1.44, 95%CI: 1.11-1.87) (Table 2).

Partially adjusted (adjusted for age, sex, race, duration of disease) GPR Model for Rate Data with vitamin D level as a continuous variable, demonstrated that higher mean vitamin D level was associated with a lower likelihood of admission with every unit (ng/mL) rise in mean vitamin D level associated with a 3% lower risk of admission during the observation period (IRR = 0.97, 95%CI: 0.96-0.98). The fully adjusted model confirmed this clinically and statistically significant association (IRR = 0.98, 95%CI: 0.97-0.99).

## DISCUSSION

We demonstrated that CD patients with a low mean vitamin D level (< 30 ng/mL) were almost 1.5 times more likely to be admitted (IRR = 1.44, 95%CI: 1.11-1.87) compared to those with an appropriate vitamin D level. Overall, the likelihood of CD-related hospitalization decreased by about 3% with every unit (ng/mL) rise in mean vitamin D level. Our findings could have a few plausible interpretations: (1) Vitamin D may serve as a surrogate marker of CD severity in terms of general ill-state, CD activity or exacerbations meriting hospitalization and the need for surgery; (2) CD patients may be more likely to be admitted if they have low vitamin D levels compared to those with

**Table 2** Crude, partially adjusted, fully adjusted rate ratios for Crohn's disease- related hospitalization

	CD-related number of hospitalizations/total person years	Hospitalization rate (95%CI) <sup>1</sup>	IRR (95%CI)		
			Model 1	Model 2	Model 3
Overall	372/1610	23.11 (20.87, 25.58)			
Mean Vitamin D level $\geq$ 30 mg/dL	101/712	14.19 (11.67, 17.24)	1 (reference)	1 (reference)	1 (reference)
Mean Vitamin D level < 30 mg/dL	271/898	30.18 (26.79, 33.99)	2.13(1.69, 2.67)	1.76 (1.38, 2.24)	1.44 (1.11, 1.87)

<sup>1</sup>Per 100 person-year. Model 1 is unadjusted; Model 2 is partially adjusted for age, sex, race, duration of disease; Model 3 is fully adjusted for age, sex, race, duration of disease, BMI, smoking, steroids, traditional and biological, immune modulators, thiopurines, methotrexate. CD: Crohn's disease; BMI: Body mass index.

adequate vitamin D levels, despite same degree of CD activity.

Of note, our study results are in agreement with prior studies that normal or adequate vitamin D stores may play a protective role in the clinical course of CD<sup>[14,21]</sup>. Furthermore, when adjusted for covariates including age, sex, race, duration of disease, BMI, smoking, steroid use, traditional and biological immune modulator use; the disparity in CD-related hospitalization rate remained significant among the two vitamin D groups. This striking difference in observed admission rates indeed warrants further investigation to further characterize and understand the role of vitamin D in CD.

Several factors have been shown to predict vitamin D deficiency in CD. These include: insufficient sunlight exposure, malnutrition, impaired conversion of vitamin D to metabolite (*i.e.*, 25-hydroxycholecalciferol), accelerated breakdown, heightened excretion, and gene mutations affecting vitamin D hydroxylation and transport<sup>[22-24]</sup>. Besides, a notable seasonal variation has been observed in CD in form of a winter decline in vitamin D levels and rise in bone turnover markers such as serum parathyroid hormone, osteocalcin, bone-specific alkaline phosphatase and urinary N-telopeptides of type 1 collagen<sup>[25]</sup>. Meanwhile, non-Caucasian ethnicity, adequate sun exposure and avoidance of tanning beds have been found to be associated with sufficient vitamin D levels in CD<sup>[26]</sup>.

CD might itself be the root of vitamin D deficiency. Inflammatory cytokines in CD suppress renal 1- $\alpha$  hydroxylase leading to vitamin D deficiency<sup>[27,28]</sup>. Furthermore, CD is associated with altered T cell response to gut microflora. Emerging evidence from animal studies has linked vitamin D deficiency to T cell self-reactivity and loss of immune tolerance to self-structures<sup>[29]</sup>. Longer disease duration, CD disease activity and smoking status inversely correlate with serum vitamin D levels<sup>[22,30]</sup>.

The Endocrine Clinical Practice Guidelines Committee recommends screening of all IBD patients especially those on corticosteroids for vitamin D status<sup>[31]</sup>. Among CD patients, serum vitamin D levels must be assessed especially for those with: elevated ESR<sup>[8]</sup>, long duration of CD (> 15 years) and extended active stage of disease<sup>[32]</sup>. Between the two vitamin D subtypes, the active form of vitamin D (*i.e.*, 25-hydroxycholecalciferol)

has more marked beneficial effect on CD activity as reflected by decrease in C-reactive protein levels<sup>[33]</sup>. Further, oral active vitamin D is better absorbed even in presence of distal small-bowel resection in CD, and should therefore be preferred to cholecalciferol, especially in CD patients with severe short-bowel syndrome<sup>[34]</sup>.

Among potential limitations of our study, the following are noteworthy. We accounted for CD-related hospitalizations exclusively within our institution. Furthermore, we studied a small proportion of CD patients seen at our institution, *i.e.*, those with vitamin D levels drawn. This could have potentially led to selection bias. Retrospective observational study design and the use of EMR for data extraction are additional limitations. Due to this limitation, we couldn't accurately assess the various causes associated with vitamin D deficiency in our patient population. Although vitamin D levels fluctuate in various seasons possibly due to difference in day light sun exposure, we did not differentiate vitamin D levels according to the season, as we assumed that state of Alabama has adequate day light sun exposure throughout the year relative to the North-eastern and Mid-western United states. We calculated mean values for vitamin D levels collected throughout our observation period. This would balance variation in vitamin D levels around the year when represented as a normal distribution.

In regard to whether our study's conclusions are generalizable to all CD patients, one should bear in mind that the segment of CD patients seen at our tertiary care IBD referral center represents those with a more severe disease phenotype. This may explain the significantly higher overall CD hospitalization rate within our study population. Our findings are in general applicable and relevant to CD patients with moderate to severe disease compared to those with mild CD.

While previous papers have studied the association between vitamin D and clinical disease activity in CD, our study is unique as it examines the association between Vitamin D levels and Crohns related hospitalization rates<sup>[17,18]</sup>. This association merits further investigation because vitamin D is a modifiable risk factor. Vitamin D level may serve as a potential therapeutic and a health maintenance target to improve quality of life and reduce complications in CD. Further studies need to be done to assess if



interventions to raise Vitamin D level will decrease hospitalization rates. Also future research on this topic should consider looking at the association between vitamin D levels and other markers of disease outcome in Crohn's such as need for surgery and the frequency and duration of corticosteroid use as well as mean disease activity parameters through observation.

## COMMENTS

### Background

As Crohn's disease (CD) became recognized as a distinct disease entity, it was observed that vitamin D deficiency was common among these patients. Vitamin D is believed to play an integral role in immune pathogenesis of CD and may help reduce CD-related hospitalizations, disease severity, need for surgery, and colon cancer incidence. Growing body of epidemiological evidence supports a key role of vitamin D deficiency not just in inflammatory bowel disease development but also on CD severity. This study sought to test the hypothesis that adequate vitamin D levels have a protective role in the clinical course of CD in terms of a decreased likelihood of hospitalization.

### Research frontiers

Recent meta-analysis and other studies showed association between vitamin D and CD. The authors provide support to hypothesis with this paper, reporting decreased likelihood of hospitalization in CD patients with adequate vitamin D level.

### Innovations and breakthroughs

This paper shows that low vitamin D levels are associated with potentially worse outcomes in CD patients as reflected by a numerically increased rate of hospitalization in this group.

### Applications

Patients with low vitamin D levels are associated with increased hospitalization rate but further studies needs to be done to assess if intervention to raise vitamin D levels will decrease hospitalization rates.

### Terminology

A CD-related hospitalization was defined as any hospital admission for a complication of CD, including infections, fistula, strictures, abscess or exacerbations.

### Peer-review

This is a well-written manuscript on impact of adequate levels of Vit-D on hospitalization rates in patients with CD. The study is observational, based on retrospective chart review.

## REFERENCES

- 1 Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis: a pathologic and clinical entity. 1932. *Mt Sinai J Med* 2000; **67**: 263-268 [PMID: 10828911]
- 2 Klionsky DJ. Crohn's disease, autophagy, and the Paneth cell. *N Engl J Med* 2009; **360**: 1785-1786 [PMID: 19369659 DOI: 10.1056/NEJMcibr0810347]
- 3 Turk N, Turk Z. Prevalent hypovitaminosis D in Crohn's disease correlates highly with mediators of osteoimmunology. *Clin Invest Med* 2014; **37**: 21382 [PMID: 24895985]
- 4 Sands BE, Siegel CA. Crohn's Disease. In: Feldman M, Friedman LS, Brandt LJ, editors. *Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management*. Philadelphia, PA: Saunders/Elsevier, 2016: 1990-2022
- 5 Schwartz DA, Pemberton JH, Sandborn WJ. Diagnosis and treatment of perianal fistulas in Crohn disease. *Ann Intern Med* 2001; **135**: 906-918 [PMID: 11712881]
- 6 Lichtenstein GR, Hanauer SB, Sandborn WJ. Management of Crohn's disease in adults. *Am J Gastroenterol* 2009; **104**: 465-83; quiz 464, 484 [PMID: 19174807 DOI: 10.1038/ajg.2008.168]
- 7 Palmer MT, Weaver CT. Linking vitamin d deficiency to inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19**: 2245-2256 [PMID: 23591600 DOI: 10.1097/MIB.0b013e31828a3b6f]
- 8 Veit LE, Maranda L, Fong J, Nwosu BU. The vitamin D status in inflammatory bowel disease. *PLoS One* 2014; **9**: e101583 [PMID: 24992465 DOI: 10.1371/journal.pone.0101583]
- 9 Ham M, Longhi MS, Lahiff C, Cheifetz A, Robson S, Moss AC. Vitamin D levels in adults with Crohn's disease are responsive to disease activity and treatment. *Inflamm Bowel Dis* 2014; **20**: 856-860 [PMID: 24681654 DOI: 10.1097/MIB.0000000000000016]
- 10 Bendix M, Dige A, Deleuran B, Dahlerup JF, Jørgensen SP, Bartels LE, Husted LB, Harsløf T, Langdahl B, Agnholt J. Flow cytometry detection of vitamin D receptor changes during vitamin D treatment in Crohn's disease. *Clin Exp Immunol* 2015; **181**: 19-28 [PMID: 25707738 DOI: 10.1111/cei.12613]
- 11 Wang TT, Dabbas B, Laperriere D, Bitton AJ, Soualhine H, Tavera-Mendoza LE, Dionne S, Servant MJ, Bitton A, Seidman EG, Mader S, Behr MA, White JH. Direct and indirect induction by 1,25-dihydroxyvitamin D3 of the NOD2/CARD15-defensin beta2 innate immune pathway defective in Crohn disease. *J Biol Chem* 2010; **285**: 2227-2231 [PMID: 19948723 DOI: 10.1074/jbc.C109.071225]
- 12 Carvalho AY, Bishop KS, Han DY, Ellett S, Jesuthasan A, Lam WJ, Ferguson LR. The role of Vitamin D level and related single nucleotide polymorphisms in Crohn's disease. *Nutrients* 2013; **5**: 3898-3909 [PMID: 24084050 DOI: 10.3390/nu5103898]
- 13 Xue LN, Xu KQ, Zhang W, Wang Q, Wu J, Wang XY. Associations between vitamin D receptor polymorphisms and susceptibility to ulcerative colitis and Crohn's disease: a meta-analysis. *Inflamm Bowel Dis* 2013; **19**: 54-60 [PMID: 22467262 DOI: 10.1002/ibd.22966]
- 14 Ananthakrishnan AN, Cheng SC, Cai T, Cagan A, Gainer VS, Szolovits P, Shaw SY, Churchill S, Karlson EW, Murphy SN, Kohane I, Liao KP. Association between reduced plasma 25-hydroxy vitamin D and increased risk of cancer in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2014; **12**: 821-827 [PMID: 24161349 DOI: 10.1016/j.cgh.2013.10.011]
- 15 Ananthakrishnan AN, Cagan A, Gainer VS, Cai T, Cheng SC, Savova G, Chen P, Szolovits P, Xia Z, De Jager PL, Shaw SY, Churchill S, Karlson EW, Kohane I, Plenge RM, Murphy SN, Liao KP. Normalization of plasma 25-hydroxy vitamin D is associated with reduced risk of surgery in Crohn's disease. *Inflamm Bowel Dis* 2013; **19**: 1921-1927 [PMID: 23751398 DOI: 10.1097/MIB.0b013e3182902ad9]
- 16 Mouli VP, Ananthakrishnan AN. Review article: vitamin D and inflammatory bowel diseases. *Aliment Pharmacol Ther* 2014; **39**: 125-136 [PMID: 24236989 DOI: 10.1111/apt.12553]
- 17 Sadeghian M, Saneai P, Siassi F, Esmailzadeh A. Vitamin D status in relation to Crohn's disease: Meta-analysis of observational studies. *Nutrition* 2016; **32**: 505-514 [PMID: 26837598 DOI: 10.1016/j.nut.2015.11.008]
- 18 Raftery T, Merrick M, Healy M, Mahmud N, O'Morain C, Smith S, McNamara D, O'Sullivan M. Vitamin D Status Is Associated with Intestinal Inflammation as Measured by Fecal Calprotectin in Crohn's Disease in Clinical Remission. *Dig Dis Sci* 2015; **60**: 2427-2435 [PMID: 25757449 DOI: 10.1007/s10620-015-3620-1]
- 19 Nicholson I, Dalzell AM, El-Matary W. Vitamin D as a therapy for colitis: a systematic review. *J Crohns Colitis* 2012; **6**: 405-411 [PMID: 22398085 DOI: 10.1016/j.crohns.2012.01.007]
- 20 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**: e407-e413 [PMID: 23403039 DOI: 10.1016/j.crohns.2013.01.012]
- 21 Ulitsky A, Ananthakrishnan AN, Naik A, Skaros S, Zadornova Y, Binion DG, Issa M. Vitamin D deficiency in patients with inflammatory bowel disease: association with disease activity and quality of life. *JPEN J Parenter Enteral Nutr* 2011; **35**: 308-316

- [PMID: 21527593 DOI: 10.1177/0148607110381267]
- 22 **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**: 182-188 [PMID: 22325172 DOI: 10.1016/j.crohns.2011.08.002]
  - 23 **Rafferty T**, O'Sullivan M. Optimal vitamin D levels in Crohn's disease: a review. *Proc Nutr Soc* 2015; **74**: 56-66 [PMID: 25497215 DOI: 10.1017/S0029665114001591]
  - 24 **Siffledeen JS**, Siminoski K, Steinhart H, Greenberg G, Fedorak RN. The frequency of vitamin D deficiency in adults with Crohn's disease. *Can J Gastroenterol* 2003; **17**: 473-478 [PMID: 12945007]
  - 25 **McCarthy D**, Duggan P, O'Brien M, Kiely M, McCarthy J, Shanahan F, Cashman KD. Seasonality of vitamin D status and bone turnover in patients with Crohn's disease. *Aliment Pharmacol Ther* 2005; **21**: 1073-1083 [PMID: 15854168 DOI: 10.1111/j.1365-2036.2005.02446.x]
  - 26 **de Bruyn JR**, van Heeckeren R, Ponsioen CY, van den Brink GR, Löwenberg M, Bredenoord AJ, Frijstein G, D'Haens GR. Vitamin D deficiency in Crohn's disease and healthy controls: a prospective case-control study in the Netherlands. *J Crohns Colitis* 2014; **8**: 1267-1273 [PMID: 24666975 DOI: 10.1016/j.crohns.2014.03.004]
  - 27 **Kelly P**, Suibhne TN, O'Morain C, O'Sullivan M. Vitamin D status and cytokine levels in patients with Crohn's disease. *Int J Vitam Nutr Res* 2011; **81**: 205-210 [PMID: 22237768 DOI: 10.1024/0300-9831/a000066]
  - 28 **Prosnitz AR**, Leonard MB, Shults J, Zemel BS, Hollis BW, Denson LA, Baldassano RN, Cohen AB, Thayu M. Changes in vitamin D and parathyroid hormone metabolism in incident pediatric Crohn's disease. *Inflamm Bowel Dis* 2013; **19**: 45-53 [PMID: 22488969 DOI: 10.1002/ibd.22969]
  - 29 **Basson A**. Vitamin D and Crohn's disease in the adult patient: a review. *JPEN J Parenter Enteral Nutr* 2014; **38**: 438-458 [PMID: 24154811 DOI: 10.1177/0148607113506013]
  - 30 **Joseph AJ**, George B, Pulimood AB, Seshadri MS, Chacko A. 25 (OH) vitamin D level in Crohn's disease: association with sun exposure & disease activity. *Indian J Med Res* 2009; **130**: 133-137 [PMID: 19797809]
  - 31 **Holick MF**, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011; **96**: 1911-1930 [PMID: 21646368 DOI: 10.1210/jc.2011-0385]
  - 32 **Tajika M**, Matsuura A, Nakamura T, Suzuki T, Sawaki A, Kato T, Hara K, Ookubo K, Yamao K, Kato M, Muto Y. Risk factors for vitamin D deficiency in patients with Crohn's disease. *J Gastroenterol* 2004; **39**: 527-533 [PMID: 15235869 DOI: 10.1007/s00535-003-1338-x]
  - 33 **Miheller P**, Muzes G, Hritz I, Lakatos G, Pregun I, Lakatos PL, Herszényi L, Tulassay Z. Comparison of the effects of 1,25 dihydroxyvitamin D and 25 hydroxyvitamin D on bone pathology and disease activity in Crohn's disease patients. *Inflamm Bowel Dis* 2009; **15**: 1656-1662 [PMID: 19408329 DOI: 10.1002/ibd.20947]
  - 34 **Leichtmann GA**, Bengoa JM, Bolt MJ, Sitrin MD. Intestinal absorption of cholecalciferol and 25-hydroxycholecalciferol in patients with both Crohn's disease and intestinal resection. *Am J Clin Nutr* 1991; **54**: 548-552 [PMID: 1652198]

**P- Reviewer:** Gupta C, Mihara H, Wejman J **S- Editor:** Ma YJ

**L- Editor:** A **E- Editor:** Wang CH





Published by **Baishideng Publishing Group Inc**  
8226 Regency Drive, Pleasanton, CA 94588, USA  
Telephone: +1-925-223-8242  
Fax: +1-925-223-8243  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>



ISSN 1007-9327

