**Name of journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO: 30022**

**Manuscript Type:****ORIGINAL ARTICLE**

***Retrospective study***

**Predictors of vitamin D deficiency in inflammatory bowel disease and health: A** **Mississippi perspective**

Pallav *et al.* Predictors of vitamin D deficiency

Kumar Pallav, Daniel Riche, Warren L May, Patrick Sanchez, Nitin K Gupta

**Kumar Pallav, Patrick Sanchez, Nitin K Gupta,** Division of Digestive Diseases, University of Mississippi Medical Center, Jackson, MS 39216, United States

**Daniel Riche, Warren L May,** Department of Pharmacy Practice, University of Mississippi Medical Center, Jackson, MS 39216, United States

**Author contributions:** Pallav K designed research, acquired data and wrote the manuscript; Gupta N, Riche D designed research, critically reviewed the manuscript; Sanchez P acquired data and assisted with manuscript preparation; May WL designed research, analyzed data.

**Institutional review board statement:** This study was reviewed and approved by the institutional review board of University of Mississippi Medical Center.

**Informed consent statement:** Informed consent was not obtained for this retrospective chart review.

**Conflict-of-interest** **statement:** None of the authors have any disclosures relevant to this article

**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:** Unsolicited manuscript

**Correspondence to: Kumar Pallav, MBBS, Assistant Professor,** Division of Digestive Diseases, University of Mississippi Medical Center, 2500 N State Street, Jackson, MS 39216, United States. drkumarpallav@yahoo.com

**Telephone:** +1-601-9844540

**Fax:** +1-601-9844538

**Received:** September 4, 2016

**Peer-review started:** September 6, 2016

**First decision:** October 11, 2016

**Revised:** December 5, 2016

**Accepted:** December 21, 2016

**Article in press:**

**Published online:**

**Abstract**

***AIM***

To identify the predictors of vitamin D deficiency in patients with and without inflammatory bowel disease (IBD).

***METHODS***

Patients with ulcerative colitis (UC) or Crohn’s disease (CD) related diagnostic codes who received medical care at University of Mississippi Medical Center (UMMC) between July 2012 and 2015 were identified. After thorough chart review, we identified patients with biopsy proven IBD who had also been tested for serum 25-hydroxyvitamin D [25(OH)D] concentration. We compared these patients to a previously studied cohort of healthy controls who also had vitamin D concentration checked. Logistic regression analysis was performed to determine the association between vitamin d deficiency and UC, CD, race, age, gender and body mass index (BMI).

***RESULTS***

We identified 237 patients with confirmed IBD. Of these, only 211 had a serum 25(OH)D concentrations available in the medical record. The group of healthy controls consisted of 98 individuals with available serum 25(OH)D concentration. 43% of IBD patients were African American (AA). Patients with CD were more likely to have vitamin D concentration checked. Bivariate analysis showed that AA (51% *vs* 21%, *P =* 0.00001), subjects with BMI >30 kg/m2 (39% *vs* 23% *P =* 0.01) and CD (40% *vs* 26%, *P =* 0.04) were more likely to be vitamin D deficient than vitamin D sufficient. Those with Age > 65 were more likely to be vitamin D sufficient (46% *vs* 15%, *P =* 0.04). Multiple regression showed that only BMI > 30 kg/m2 and AA race are associated with vitamin D deficiency.

***CONCLUSION***

BMI > 30 kg/m2 and AA race are predictive of vitamin D deficiency. Gender, age and diagnosis of IBD are not predictive of vitamin D deficiency.

**Key words:** Vitamin D deficiency; Inflammatory bowel disease; Body mass index; Ulcerative colitis; Crohn’s disease; African American

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The studies evaluating the relationship between vitamin D deficiency and inflammatory bowel disease (IBD) have shown heterogeneity perhaps due to multiple overlapping risk factors that need to be accounted for. We performed a retrospective study to identify the risk factors for vitamin D deficiency in a population with a large African American component. Using logistic regression analysis we studied the effect of diagnosis, race, age, gender and body mass index (BMI) on prevalence of vitamin D deficiency. In subjects with and without IBD, BMI > 30 kg/m2 and African American race are predictive of vitamin D deficiency. Gender, age and diagnosis of IBD were not predictive of vitamin D deficiency in our population.

Pallav K, Riche D, May WL, Sanchez P, Gupta NK. Predictors of vitamin D deficiency in inflammatory bowel disease and health: A Mississippi perspective. *World J Gastroenterol* 2016; In press

**INTRODUCTION**

Crohn’s disease (CD) and ulcerative colitis (UC) are chronic idiopathic conditions of the gastrointestinal tract that manifest as inflammationwith distinct, yet often overlapping clinical features[1]. The Etiology of IBD is thought to reflect innate and adaptive immune-mediated responses to luminal bacterial antigens leading to enhanced intestinal permeability and dysregulated intestinal immunity[1-3]. There has been an increasing interest in the regulatory effects of vitamin D on the immune system in IBD and colorectal cancer[4,5]. Numerous studies have demonstrated a link between low serum 25-hydroxyvitamin D [25(OH)D] concentrations and IBD in both CD[6-10] and UC patients[10,11]. Vitamin D deficiency may predispose IBD patients to a higher disease activity[6], suboptimal response to treatment[12], and higher incidence of surgery and hospitalization[13]. On the other hand, IBD patients may be at an increased risk for low serum 25(OH)D concentrations due to one or more of the following: Insufficient dietary intake and inadequate sun exposure[14,15]; malabsorption of dietary and biliary vitamin D and its metabolites[16];faulty conversion of vitamin D to active metabolic forms; failure to conserve an adequate functional pool of vitamin D[17] and loss of protein-bound 25hydroxy vitamin D[18] due to a protein losing enteropathy[19].

Studies aimed at delineating this complex relationship are confounded by factors such as age, BMI, and race leading to inconsistent conclusions[18,20-25]. Furthermore, African Americans (AA) are understudied in most of the IBD literature, and data representing this population is scarce[26]. According to the 2011 U.S. Census Bureau, 40% of Mississippians are AA[27] thereby presenting a unique opportunity to study this population.

We aim to determine the vitamin D status in an understudied cohort consisting of IBD and non-IBD patients and Investigate the association between serum 25(OH)D concentrations and IBD diagnosis (UC and CD). In addition, this study aimed to investigate risk factors for vitamin D deficiency namely race, gender, age, and BMI; as well as to compare vitamin D status with that of healthy controls.

**MATERIALS AND METHODS**

This retrospective study was conducted at University of Mississippi Medical Center (UMMC), which is a tertiary care center and the only academic medical institution in the state of Mississippi. Over half a million patient encounters are reported every year. While UMMC caters to both high and low acuity patients, being a referral center more patients tend to be sicker. There are no reports for who sees most of the IBD patients in the state but we see over 500 patients annually. We get patients through word of mouth and community referrals. Less than 15% of the patients are uninsured and the majority has either public or private insurance. All patient visits are in the main campus in Jackson. Patients were identified using various diagnosis codes for UC, CD and IBD. Electronic medical records for all patients with IBD associated diagnostic codes seen between July 2012 and July 2015 were reviewed. Demographic, biometric, and clinical information was collected through review of electronic medical records. A standard document was used to collect the information however a pilot study was not conducted. Diagnosis of IBD was based on endoscopic, clinical and histologic data. IBD Patients with available plasma 25(OH)D concentration were included in this study. We excluded patients with history of malignancy. The control group consisted of patients without IBD or any active systemic disease that presented to UMMC and had plasma 25(OH)D concentrations obtained during routine follow up.

***Vitamin D status assessment***

* All vitamin D concentrations were assessed using The ARCHITECT 25-OH vitamin D assay (Abbott diagnostics, Germany). There is no absolute consensus on Vitamin D deficiency and sufficiency. Vitamin D was operationalized into clinically meaningful categories for analysis. Plasma 25(OH) D concentrations < 20 ng/mL (50 nmol/L) indicate vitamin D deficiency. Plasma 25(OH) D concentrations between 21 and 29 ng/mL (52.5 and 72.5 nmol/L) represent vitamin D insufficiency while concentrations > 30 ng/mL (75 nmol/L) represent vitamin D sufficiency[22,28,29].
* ***Statistical analysis***

A biomedical statistician performed statistical analysis. We used a generalized logistic regression model to estimate odds ratio (OR). The generalized logistic regression extends the traditional model and in this instance, our outcome of interest was ordinal and has three levels for vitamin D: Deficient, Insufficient and Sufficient.

Comparisons of the distributions for demographic characteristics were made with Pearson’s chi-square statistic. Higher than expected Pearson’s residual (*i.e*., |Z|> 2.0) was considered evidence of departure from independence. We considered *P <* 0.05 evidence of statistical significance.

Data were reported as frequencies and proportions for the marginal distributions of the categorical variables and proportions for the joint distributions of the cross-classification tables. The institutional review board at UMMC approved this study.

**RESULTS**

Two hundred and thirty seven IBD patients (139 CD, 98 UC) and 98 controls were identified. Amongst the IBD patients, 211 had 25(OH)D concentration checked on 257 occasions. Those with CD were more likely to have a 25(OH)D concentration measured in our facility. Also those tested for vitamin D concentration tended to be slightly older. Otherwise there were no major differences between IBD patients with and without measured 25(OH)D concentration (Table 1).

Of 309 patients included in final analysis, 98 (31.7%) were controls, 129 (41.7%) were CD patients and 82 (26.5%) were UC patients. Compared to IBD patients, the controls had higher mean age and female preponderance. IBD patients were more likely to be AA and had lower mean body mass index (BMI) (Table 2)

Demographics of the study population as a whole are shown in Table 3. Overall, there was a 2:1 female-to-male ratio. 115(61.2%) of the subjects were White (61.2%), 91 (39.6%) were African Americans and 5 (1.9%) were of other races. BMI was categorized into normal, overweight, and obese, with similar proportion of individuals in each category.

Vitamin D as the outcome is also presented in Table 3 and divided into clinically meaningful categories. The marginal distribution of vitamin D given in the first row of Table 3 indicates that the sample is approximately evenly distributed with about one-third in each category.

***Bivariate analysis***

Table 3 gives the results of a chi-square contingency table analysis to determine the association of vitamin D with each of the demographic variables.

Disease status (CD *vs* UC *vs* Control) and plasma vitamin D concentrations were significantly associated (*P =* 0.04). The proportion of controls with sufficient vitamin D was higher as compared to the other two groups. For the CD group, there were many more with deficient vitamin D than expected and fewer with sufficient vitamin D than expected.

 Age and vitamin D were significantly associated (*P =* 0.0256). The Pearson’s residuals indicated that the youngest age group (less than 35), had a higher proportion with deficient vitamin D than expected and a lower proportion of sufficient vitamin D than expected. The opposite was true for the age greater than 65 group where the proportion of those with deficient vitamin D was lower than expected, while the proportion in the sufficient group was higher than expected.

Race and vitamin D were significantly associated (*P <* 0.0001). The proportion of African Americans with deficient vitamin D was much higher than expected and the proportion with sufficient vitamin D was much lower than expected. Whites and others showed the opposite trend with lower than expected proportions with deficient vitamin D and higher than expected proportions with sufficient vitamin D.

Gender was not significantly associated with vitamin D sufficiency (*P =* 0.6).

BMI and vitamin D were significantly associated (*P =* 0.0110). For BMI < 25 kg/m2, the proportion of sufficient vitamin D subjects was higher than expected. Subjects with BMI > 30 kg/m2 had a higher proportion with deficient vitamin D than expected and a lower proportion with sufficient vitamin D than expected.

For all demographic variables, the insufficient group did not appear to differ significantly from the marginal of approximately one-third. The differences were in the sufficient and deficient vitamin D concentrations for diagnosis, Age, race and BMI.

 Of the four factors that appeared to be associated with plasma vitamin D concentrations, BMI is the only modifiable risk factor. Therefore, we investigated the potential for confounding factors for the relationship of BMI with vitamin D by statistically testing the associations between BMI and non-modifiable risk factors: age, race and gender. (Table 4)

BMI was associated with diagnosis (*P =* 0.0048), age (*P =* 0.0055) and gender (*P* value=0.0017). BMI was not significantly associated with race (Table 4).

***Distribution of vitamin D across stratified levels of BMI and diagnosis***

**BMI < 25:** Those < 35 years old are more likely to have vitamin D deficiency. Curiously, the 50-64 year age group is less likely to exhibit vitamin D deficiency compared to the other groups. The CD patients are more likely to have deficient vitamin D than the other groups. There is a significant association between diagnosis and vitamin D only in the BMI < 25 kg/m2 group (*P =* 0.0026) (Table 5).

**BMI 25-30 kg/m2:** No association was found in the BMI 25-30 kg/m2 group (*P =* 0.389) (Table 5).

**BMI > 30 kg/m2:** The BMI >30 kg/m2 group is the most homogeneous, and there is no statistical evidence of an association (*P =* 0.88).

That is, the BMI > 30 kg/m2 group is more likely to be vitamin D deficient, but there is no further evidence of a relationship between diagnosis and vitamin D once BMI > 30 kg/m2 is considered. On the other hand, the BMI < 25 kg/m2 group is more likely to have sufficient vitamin D, but the presence of CD may alter the effect on vitamin D. We find this group stands out as being vitamin D deficient compared to the others (Table 5).

***Seasonal variation in vitamin D concentrations***

We compared mean vitamin D concentrations in traditional summer *vs* winter months and while the summertime vitamin D concentrations were marginally higher (26.9 *vs* 23.1, *P =* 0.064), which is not statistically significant. Admittedly, it was close enough to consider adding into the regression analysis, however this p-value is only using a partial dataset (based on seasonal analysis many patients are excluded) - therefore not included into the regression analysis.

***Regression model***

We also investigated a cumulative logistic regression model that included age and race as covariates and the nine BMI categories. We did not include gender since it was not significantly associated with outcome or predictor. The model found race remained significant (*P <* 0.0001), age was borderline significant (*P =* 0.0715), and there were significant differences between the nine BMI groups. To adjust for the multiple testing, we considered the proportions different only if *P <* 0.002, a conservative Bonferroni approach. Differences identified were the same as the stratified analysis in Table 6.

***Reduced model***

We performed a manual backward elimination procedure to reduce the model. For the procedure, we retained variables with *P <* 0.10. The reduced model includes race, BMI and diagnosis only. Table 6 gives the results of the analyses, both full and reduced model for comparison. The results are similar for both models; therefore, we interpret the odds ratios from the final model, only.

Although there was no significant effect for diagnosis at the *P <* 0.05 level, we did find a global difference (*P =* 0.085) and retained it in the model. Using a simple confidence interval for the odds ratio, the odds of deficiency compared to sufficiency are higher for the CD group compared to controls [odds ratio (OR) = 2.22; 95%CI: 1.07-4.63]. There was also a similar result for insufficiency compared to sufficiency comparing CD to controls (OR = 2.16; 95%CI: 1.07-4.63).

 Race was a significant predictor of vitamin D concentrations based on the global test (*P <* 0.0001). Whites are about one-fourth less likely than African Americans to exhibit deficiency compared to sufficiency (OR = 0.23; 95%CI: 0.12-0.43). No other results are significant and the sample size is very small for the “Other” group, leading to loss of power.

Finally, BMI was a significant predictor of vitamin D concentrations based on a significant global test (*P =* 0.003). Using the normal weight group as a reference (*i.e.,* 25-30 kg/m2), we estimated odds ratios for underweight and overweight. Although there were no significant effects for underweight, there was a significant effect for the overweight (BMI > 30 kg/m2) group. The overweight group is much more likely to develop vitamin D deficiency (OR = 2.61; 95%CI 1.26-5.42), as well as insufficiency compared to sufficiency (OR=2.27; 95%CI: 1.07-4.63).

**DISCUSSION**

Ergocalciferol (Vitamin D2), the predominant circulating and storage form of vitamin D[30] and cholecalciferol (Vitamin D3) are obtained from diet or supplementation. Vitamin D3 is alsoformed in the skin *via* ultraviolet B (UVB) light exposure[31]. There are accumulating epidemiological, clinical, and basic data that support an immune-modulatory role for vitamin D in IBD[20]. On the other hand, IBD patients may be at a higher risk for vitamin D deficiency, thereby making this relationship a bidirectional one.

Bivariate analysis identified the following risk factors for vitamin D deficiency: (1) Crohn’s disease; (2) BMI > 30 kg/m2; (3) Age < 35 years; and (4) African American race. However, regression analysis showed that only African American race and BMI > 30 kg/m2 were significantly associated with vitamin D deficiency. While CD and vitamin D deficiency showed correlation, the relationship was not statistically significant likely due to insufficient numbers (*P* = 0.085). Similar findings have also been reported previously[14,32].

The prevalence of Obesity is increasing in the United States. According to the most recent obesity prevalence survey conducted by the Centers for Disease Control (CDC), greater than 35.1% US adults and 35.5% of adults in Mississippi fall in the BMI > 35 kg/m2 category[33]. This is a potentially modifiable risk factor and may affect disease severity in IBD patients due to a pro-inflammatory effect[34] and through sequestration and/or volumetric dilution of vitamin D by adipose tissue[18,32]. Recently, Vimaleswaran *et al*[25] performed a bidirectional mendelian randomization analysis providing evidence for the role of obesity as a causal risk factor for the development of vitamin D deficiency.

Melanin in skin absorbs UVB light slowing the absorption and conversion of Vitamin D3[35]. Therefore, African Americans are considered to be at increased risk for Vitamin D deficiency[36]. If vitamin D deficiency is a cause of IBD, then it could be theorized that African Americans would be at enhanced risk for IBD as well. Traditionally, African American risk for IBD is considered to be lower, not higher. This may in part be reflective of under-diagnosis within this population[26]. We found that race was a significant predictor of vitamin D concentrations based on the global test (*P <* 0.0001) with African American patients having a higher proportion of deficiency, while Whites and other races were four times less likely to have vitamin D deficiency.

Traditionally increasing age has been linked to vitamin D deficiency. This is related to multiple factors including: decreased metabolic activity of aging skin[23], reduced muscle mass that normally serves as a reservoir of vitamin D[30] and decreased sun exposure associated with residing in assisted living facilities[21].

Contrary to traditional belief, our initial analysis suggested that older age is protective against vitamin D deficiency (*P* = 0.0256). Future prospective studies are needed to help delineate the role of dietary, environmental and socio-economic factors that contribute to these findings.

While we feel that our study is well conducted and methodologically sound, we do recognize certain limitations. Our study is retrospective and data regarding all factors that affect vitamin D concentrations including: detailed dietary records, unreported supplement use, and cumulative sun exposure were not available for analysis. In many patients we struggled to find exact dates of symptom onset, history regarding smoking and alcohol use, objective assessment of symptoms including mayo clinical score or CDAI. Based on these issues we did not collect data regarding disease severity/need for surgery/complications/exact medication use etc. We do believe that the lack of this data does not undermine the validity of the presented data. This study includes patients from a single center and results may not be applicable to a different geographic area. Some of our findings may have achieved significance if we had studied a larger number of individuals. Despite these limitations, we are confident that this analysis accurately assesses the characteristics of vitamin D deficiency in a previously understudied population.

In summary, we hereby present data from a unique population in which disease state and diagnosis is significantly affected by dietary and socioeconomic status. Specifically, we show that BMI > 30 kg/m2 and African American race are associated with vitamin D deficiency in IBD and non-IBD patients. Future studies aimed at better understanding these differences may lead to improved disease outcomes.

**COMMENTS**

***Background***

The diagnosis and management of inflammatory bowel disease has made remarkable progress over the past decade. Both diagnostic as well as therapeutic paradigms are being constantly evaluated and improved. Despite the improved ability to identify and treat inflammatory bowel disease (IBD), it remains a significant source of morbidity and financial burden. The current treatment of IBD is also fraught with severe complications and adverse events. Therefore identification of preventable risk factors and development of risk-free novel agents is imperative to the progress of this field. In the recent past vitamin D has come to limelight for its immune modulating properties and has attracted the attention of IBD researchers worldwide, on one hand vitamin D deficiency is thought to play a role in pathogenesis of IBD and on the other hand it may be a consequence of IBD. There is significant disagreement amongst studies evaluating the relationship between IBD and vitamin D deficiency. This is at least partly due to confounding by factors that may affect both plasma vitamin D concentration and IBD. These factors may include age, race, gender, sex and body mass index (BMI). Additionally such data is quite sparse on African American patients. The population in Mississippi is unique in having a high percentage of African Americans as well as obese subjects. In this study we identified that a BMI > 30 and African American race are independent risk factors for vitamin D deficiency.

***Research frontiers***

The association between vitamin D deficiency and pathogenesis of IBD is under investigation. Prior studies have significant disagreement. Better identification of confounding factors can help streamline future research and obtain concordant results. A more precise understanding of this relationship may lead to novel insights in to prevention and management**.**

***Innovations and breakthrough***

In this study the authors studied multiple possible risk factors for vitamin D deficiency in patients with and without IBD. The authors applied multiple regression to establish that BMI > 30 and African American race are associated with vitamin D deficiency in those with and without IBD. The authors also confirmed that age and gender did not significantly effect serum 25(OH)D concentrations in the studied population. This study confirms the findings of a large bi-directional Mendelian analysis. However literature is lacking in such data in African American patients and that makes our population unique.

***Applications***

This study suggests that in future studies assessing the role of vitamin D deficiency in development of IBD as well as that of vitamin D in management of IBD should take into account the effects of race and BMI.

***Terminology***

IBD or inflammatory bowel disease is a group of conditions of the small and large bowel characterized by chronic inflammation and a remitting and relapsing course. Crohn’s disease and ulcerative colitis are the two main forms of inflammatory bowel disease. While the mechanism of tissue destruction is autoimmune the exact etiology of these conditions is unknown. Over the past decade significant research has lead to better understanding and treatment options for these conditions however these treatments are associated with significant adverse events with average efficacy. The role of preventable risk factors such as vitamin D deficiency and obesity is currently under investigation.

***Peer-review***

This is a well-written paper addressing the relevant scientific question; predictors of vitamin D deficiency in especially African American IBD patients. BMI > 30 and race and not diagnosis are found as predictors for vitamin D insufficiency, which is interesting and relevant to clinic practise. However, the authors did not include disease activity, which is shown to be associated to vitamin D deficiency and could be a confounder of the authors’ results. The authors should address the limitation in the discussion if disease activity data is not available.

**REFERENCES**

1 **Bernstein CN**, Fried M, Krabshuis JH, Cohen H, Eliakim R, Fedail S, Gearry R, Goh KL, Hamid S, Khan AG, LeMair AW, Malfertheiner Q, Rey JF, Sood A, Steinwurz F, Thomsen OO, Thomson A, Watermeyer G. World Gastroenterology Organization Practice Guidelines for the diagnosis and management of IBD in 2010. *Inflamm Bowel Dis* 2010; **16**: 112-124 [PMID: 19653289 DOI: 10.1002/ibd.21048]

2 **Ardizzone S**, Cassinotti A, Trabattoni D, Manzionna G, Rainone V, Bevilacqua M, Massari A, Manes G, Maconi G, Clerici M, Bianchi Porro G. [Immunomodulatory effects of 1,25-dihydroxyvitamin D3 on TH1/TH2 cytokines in inflammatory bowel disease: an in vitro study.](https://www.ncbi.nlm.nih.gov/pubmed/19309553) *Int J Immunopathol Pharmacol* 2009; **22**: 63-71 [PMID: 19309553]

3 **van Lierop PP**, Samsom JN, Escher JC, Nieuwenhuis EE. Role of the innate immune system in the pathogenesis of inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2009; **48**: 142-151 [PMID: 19179875 DOI: 10.1097/MPG.0b013e3181821964]

4 **Raman M**, Milestone AN, Walters JR, Hart AL, Ghosh S. Vitamin D and gastrointestinal diseases: inflammatory bowel disease and colorectal cancer. *Therap Adv Gastroenterol* 2011; **4**: 49-62 [PMID: 21317994 DOI: 10.1177/1756283X10377820]

5 **Krishnan AV**, Feldman D. Mechanisms of the anti-cancer and anti-inflammatory actions of vitamin D. *Annu Rev Pharmacol Toxicol* 2011; **51**: 311-336 [PMID: 20936945 DOI: 10.1146/annurev-pharmtox-010510-100611]

6 **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**: 3085-3091 [PMID: 26031421 DOI: 10.1007/s10620-015-3727-4]

7 **Cantorna MT**. Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease. *Prog Biophys Mol Biol* 2006; **92**: 60-64 [PMID: 16563470 DOI: 10.1016/j.pbiomolbio.2006.02.020]

8 **Loftus EV**, Sandborn WJ. Epidemiology of inflammatory bowel disease. *Gastroenterol Clin North Am* 2002; **31**: 1-20 [PMID: 12122726]

9 **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]

10 **Souza HN**, Lora FL, Kulak CA, Mañas NC, Amarante HM, Borba VZ. [Low levels of 25-hydroxyvitamin D (25OHD) in patients with inflammatory bowel disease and its correlation with bone mineral density]. *Arq Bras Endocrinol Metabol* 2008; **52**: 684-691 [PMID: 18604382]

11 **Blanck S**, Aberra F. Vitamin d deficiency is associated with ulcerative colitis disease activity. *Dig Dis Sci* 2013; **58**: 1698-1702 [PMID: 23334382 DOI: 10.1007/s10620-012-2531-7]

12 **Zator ZA**, Cantu SM, Konijeti GG, Nguyen DD, Sauk J, Yajnik V, Ananthakrishnan AN. Pretreatment 25-hydroxyvitamin D levels and durability of anti-tumor necrosis factor-α therapy in inflammatory bowel diseases. *JPEN J Parenter Enteral Nutr* 2014; **38**: 385-391 [PMID: 24088707 DOI: 10.1177/0148607113504002]

13 **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]

14 **Joseph AJ**, George B, Pulimood AB, Seshadri MS, Chacko A. 25 (OH) vitamin D level in Crohn's disease: association with sun exposure & amp; disease activity. *Indian J Med Res* 2009; **130**: 133-137 [PMID: 19797809]

15 **Vogelsang H**, Klamert M, Resch H, Ferenci P. Dietary vitamin D intake in patients with Crohn's disease. *Wien Klin Wochenschr* 1995; **107**: 578-581 [PMID: 7502502]

16 **Farraye FA**, Nimitphong H, Stucchi A, Dendrinos K, Boulanger AB, Vijjeswarapu A, Tanennbaum A, Biancuzzo R, Chen TC, Holick MF. Use of a novel vitamin D bioavailability test demonstrates that vitamin D absorption is decreased in patients with quiescent Crohn's disease. *Inflamm Bowel Dis* 2011; **17**: 2116-2121 [PMID: 21910173 DOI: 10.1002/ibd.21595]

17 **Compston JE**, Creamer B. Plasma levels and intestinal absorption of 25-hydroxyvitamin D in patients with small bowel resection. *Gut* 1977; **18**: 171-175 [PMID: 856674]

18 **Drincic AT**, Armas LA, Van Diest EE, Heaney RP. Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity. *Obesity (Silver Spring)* 2012; **20**: 1444-1448 [PMID: 22262154 DOI: 10.1038/oby.2011.404]

19 **Beeken WL**, Busch HJ, Sylwester DL. Intestinal protein loss in Crohn's disease. *Gastroenterology* 1972; **62**: 207-215 [PMID: 4637981]

20 **Garg M**, Lubel JS, Sparrow MP, Holt SG, Gibson PR. Review article: vitamin D and inflammatory bowel disease--established concepts and future directions. *Aliment Pharmacol Ther* 2012; **36**: 324-344 [PMID: 22686333 DOI: 10.1111/j.1365-2036.2012.05181.x]

21 **Gloth FM**, Gundberg CM, Hollis BW, Haddad JG, Tobin JD. Vitamin D deficiency in homebound elderly persons. *JAMA* 1995; **274**: 1683-1686 [PMID: 7474272]

22 **Holick MF**. Vitamin D deficiency. *N Engl J Med* 2007; **357**: 266-281 [PMID: 17634462]

23 **Holick MF**, Matsuoka LY, Wortsman J. Age, vitamin D, and solar ultraviolet. *Lancet* 1989; **2**: 1104-1105 [PMID: 2572832]

24 **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]

25 **Vimaleswaran KS**, Berry DJ, Lu C, Tikkanen E, Pilz S, Hiraki LT, Cooper JD, Dastani Z, Li R, Houston DK, Wood AR, Michaëlsson K, Vandenput L, Zgaga L, Yerges-Armstrong LM, McCarthy MI, Dupuis J, Kaakinen M, Kleber ME, Jameson K, Arden N, Raitakari O, Viikari J, Lohman KK, Ferrucci L, Melhus H, Ingelsson E, Byberg L, Lind L, Lorentzon M, Salomaa V, Campbell H, Dunlop M, Mitchell BD, Herzig KH, Pouta A, Hartikainen AL, Streeten EA, Theodoratou E, Jula A, Wareham NJ, Ohlsson C, Frayling TM, Kritchevsky SB, Spector TD, Richards JB, Lehtimäki T, Ouwehand WH, Kraft P, Cooper C, März W, Power C, Loos RJ, Wang TJ, Järvelin MR, Whittaker JC, Hingorani AD, Hyppönen E. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. *PLoS Med* 2013; **10**: e1001383 [PMID: 23393431 DOI: 10.1371/journal.pmed.1001383]

26 **Veluswamy H**, Suryawala K, Sheth A, Wells S, Salvatierra E, Cromer W, Chaitanya GV, Painter A, Patel M, Manas K, Zwank E, Boktor M, Baig K, Datti B, Mathis MJ, Minagar A, Jordan PA, Alexander JS. African-American inflammatory bowel disease in a Southern U.S. health center. *BMC Gastroenterol* 2010; **10**: 104 [PMID: 20828408 DOI: 10.1186/1471-230X-10-104]

27 **National Center for Health Statistics (US).** Health, United States, 2014: With Special Feature on Adults Aged 55–64. Hyattsville (MD): National Center for Health Statistics (US); 2015 May. Report No.: 2015-1232 [PMID: 26086064]

28 **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]

29 **Rosen CJ**. Clinical practice. Vitamin D insufficiency. *N Engl J Med* 2011; **364**: 248-254 [PMID: 21247315 DOI: 10.1056/NEJMcp1009570]

30 **Mawer EB**, Backhouse J, Holman CA, Lumb GA, Stanbury SW. The distribution and storage of vitamin D and its metabolites in human tissues. *Clin Sci* 1972; **43**: 413-431 [PMID: 4342673]

31 **Fritsche J**, Mondal K, Ehrnsperger A, Andreesen R, Kreutz M. Regulation of 25-hydroxyvitamin D3-1 alpha-hydroxylase and production of 1 alpha,25-dihydroxyvitamin D3 by human dendritic cells. *Blood* 2003; **102**: 3314-3316 [PMID: 12855575]

32 **Jahnsen J**, Falch JA, Mowinckel P, Aadland E. Vitamin D status, parathyroid hormone and bone mineral density in patients with inflammatory bowel disease. *Scand J Gastroenterol* 2002; **37**: 192-199 [PMID: 11843057]

33 **Centers for disease control and prevention (CDC).** Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory 2014 (cited 2015-9-25). Available from: URL: http://www.cdc.gov/obesity/data/prevalence-maps.html

34 **Karmiris K**, Koutroubakis IE, Kouroumalis EA. The emerging role of adipocytokines as inflammatory mediators in inflammatory bowel disease. *Inflamm Bowel Dis* 2005; **11**: 847-855 [PMID: 16116320]

35 **Looker AC**, Dawson-Hughes B, Calvo MS, Gunter EW, Sahyoun NR. Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulations from NHANES III. *Bone* 2002; **30**: 771-777 [PMID: 11996918]

36 **Weisberg P**, Scanlon KS, Li R, Cogswell ME. Nutritional rickets among children in the United States: review of cases reported between 1986 and 2003. *Am J Clin Nutr* 2004; **80**: 1697S-1705S [PMID: 15585790]

**P-Reviewer:** Basson AR, Bendix M, Lakatos PL, Massironi S **S-Editor:** Yu J

**L-Editor:** **E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** United States

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C, C

Grade D (Fair): D

Grade E (Poor): 0

**Table 1 Comparison between inflammatory bowel disease patients with and without available vitamin D concentration *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **IBD Patients without available vitamin D concentration*****n =* 26** | **IBD patients with available Vitamin D concentration*****n* = 211** | ***P* value** |
| CD | 10 (38.5) | 129 (61.1) | 0.034 |
| Age (yr), median (IQR) | 32 (26) | 41 (25) | 0.03 |
| Female | 12 (46.2) | 125 (59.2) | 0.213 |
| AA | 11 (42.3) | 91 (43.1) | 0.391 |
| BMI (kg/m2), median (IQR) | 25.6 (9.9) | 29.3 (7.5) | 0.179 |
| Patients on Vitamin D supplementation | 2 (8.33) | 36 (17.06) | 0.271 |

CD: Crohn’s disease; AA: African American; BMI: Body mass index.

**Table 2 Comparison between inflammatory bowel disease and non-** **inflammatory bowel disease patients** ***n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Controls*****n* = 98** | **IBD Patients*****n*= 211** | ***P* value** |
| Patients with vitamin D deficiency | 56 (57.1) | 143 (61.6) | .0694 |
| Age at vitamin D testing (yr), median (IQR) | 60.5 (14.5) | 41 (25) | <0.0001 |
| Female | 86(87.8) | 125 (59.2) | <0.0001 |
| AA | 23 (23.9) | 91 (43.1) | 0.0009 |
| BMI (kg/m2), median (IQR) | 29.3 (7.5) | 27 (8.9) | 0.0438 |
| Patients receiving vitamin D supplementation | Not available | 37 (17.5) | Not Applicable |

AA: African American; BMI: Body mass index.

**Table 3 Distribution of vitamin D concentration across various diagnosis, demographics (age, race, gender) and body mass index (modifiable risk factor), *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Vitamin D** |  |
|  |  | **Deficient** | **Insufficient** | **Sufficient** | ***P* value** |
|  |  |  |  |  |  |
| Total  | 309 | 100 | 99 | 110 |  |
|  |  | (32.4) | (32.0) | (35.6) |  |
|  |  |  |  |  |  |
| Diagnosis  |  |  |  |  |  |
| Controls  | 98 (31.7) | 27.6% | 29.6% | **42.8%** | 0.0407 |
| CD  | 129 (41.7) | **40.3%** | 33.3% | **26.4%** |  |
| UC  | 82 (26.5) | 25.6% | 32.9% | 41.5% |  |
|  |  |  |  |  |  |
| Age (yr) |  |  |  |  |  |
| < 35 | 72 (23.3) | 38.9% | 34.7% | 26.4% | 0.0415 |
| 35-49 | 73 (23.6) | 34.2% | 28.8% | 37.0% |  |
| 50-64  | 99 (32.0) | 37.4% | 28.3% | 34.3% |  |
| > 65  | 65 (21.0) | **15.4%** | 38.5% | **46.2%** |  |
|  |  |  |  |  |  |
| Race |  |  |  |  |  |
| White  | 189 (61.2) | **21.7%** | 34.4% | **43.9%** | < 0.0001 |
| AA  | 114 (36.9) | **50.9%** | 28.1% | **21.0%** |  |
| Other  | 6 (1.9) | 16.7% | 33.3% | **50.0%** |  |
|  |  |  |  |  |  |
| Gender |  |  |  |  |  |
| Female | 211 (68.3) | 33.7% | 32.2% | 34.1% | 0.6857 |
| Male  | 98 (31.7) | 29.6% | 31.6% | 38.8% |  |
|  |  |  |  |  |  |
| BMI (kg/m2) |  |  |  |  |  |
| Less than 25  | 97 (31.4) | 29.9% | 25.8% | **44.3%** | 0.0110 |
| 25-30  | 102 (33.0) | 27.5% | 31.4% | 41.2% |  |
| More than 30  | 110 (35.6) | **39.1%** | 38.2% | **22.7%** |  |

CD: Crohn’s disease; AA: African American; BMI: Body mass index; UC: Ulcerative colitis.

**Table 4 Associations of body mass index with diagnosis and demographic variables**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  |  |
|  | ***n* (%)** | **BMI < 25 kg/m2** | **BMI 25-30 kg/m2** | **BMI > 30 kg/m2** | ***P* value** |
|  |  |  |  |  |  |
| Total  | 309 | 97 | 102 | 110 |  |
|  |  | (31.4) | (33.0) | (35.6) |  |
|  |  |  |  |  |  |
| Diagnosis  |  |  |  |  |  |
| Controls | 98 (31.7) | **20.4%** | 34.7% | **44.9%** | 0.0048 |
| CD  | 129 (41.7) | **42.6%** | 29.5% | **27.9%** |  |
| UC  | 82 (26.5) | 26.8% | 36.6% | 36.6% |  |
|  |  |  |  |  |  |
| Age (yr) |  |  |  |  |  |
| < 35  | 72 (23.3) | **52.8%** | 29.2% | **18.1%** | 0.0007 |
| 35-49  | 73 (23.6) | 26.0% | 30.1% | 43.8% |  |
| 50-64 | 99 (32.0) | **23.2%** | 37.4% | 39.4% |  |
| > 65  | 65 (21.0) | 26.2% | 33.9% | 40.0% |  |
|  |  |  |  |  |  |
| Race  |  |  |  |  |  |
| White  | 189 (61.2) | 28.6% | 36.5% | 34.9% | 0.5253 |
| AA  | 114 (36.9) | 36.0% | 27.2% | 36.8% |  |
| Other  | 6 (1.9) | 33.3% | 33.3% | 33.3% |  |
|  |  |  |  |  |  |
| Gender  |  |  |  |  |  |
| Female | 211 (68.3) | **27.5%** | 30.3% | **42.2%** | 0.0017 |
| Male  | 98 (31.7) | **39.8%** | 38.8% | **21.4%** |  |
|  |  |  |  |  |  |

CD: Crohn’s disease; AA: African American; BMI: Body mass index; UC: Ulcerative colitis.

**Table 5 Distribution of vitamin D concentration across stratified levels of body mass index and diagnosis**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  |  |
|  | ***n* (%)** | **Vitamin D deficient** | **Vitamin D insufficient** | **Vitamin D sufficient** | ***P* value** |
|  |  |  |  |  |  |
| **BMI < 25 (kg/m2)** |
| Total  | 97 | 29 | 25 | 43 |  |
|  |  | (29.9) | (25.8) | (44.3) |  |
|  |  |  |  |  |  |
| Diagnosis |  |  |  |  |  |
| Controls  | 20 (20.6) | 15.0% | 15.0% | **70.0%** | 0.0026 |
| CD  | 55 (56.7) | **43.6%** | 27.3% | **29.1%** |  |
| UC  | 22 (22.7) | **9.1%** | 31.8% | **59.1%** |  |
| **BMI = 25-30 (kg/m2)** |
| Total  | 102 | 28 | 32 | 42 |  |
|  |  | (27.5%) | (31.4%) | (41.2%) |  |
| Diagnosis  |  |  |  |  |  |
| Controls  | 34 (33.3) | 26.5% | 26.5% | 47.1% | 0.3894 |
| CD  | 38 (37.3) | 34.2% | 36.8% | **29.0%** |  |
| UC  | 30 (29.4) | 20.0% | 30.0% | 50.0% |  |
| **BMI > 30 (kg/m2)** |
| Total  | 110 | 43 | 42 | 25 |  |
|  |  | (39.1%) | (38.2%) | (22.7%) |  |
|  |  |  |  |  |  |
| Diagnosis  |  |  |  |  |  |
| Controls  | 44 (40.0) | 34.1% | 38.6% | 27.3% | 0.8823 |
| CD | 36 (32.7) | 41.7% | 38.9% | 19.4% |  |
| UC  | 30 (27.3) | 43.3% | 36.7% | 20.0% |  |

CD: Crohn’s disease; AA: African American; BMI: Body mass index; UC: Ulcerative colitis.

**Table 6 Results of multivariate modelling with age, race, gender, body mass index and diagnosis as predictors of deficient, insufficient and sufficient vitamin D**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Full model** |  | **Reduced model** |  |
|  | **OR****(95%CI),****deficient *vs* sufficient** | **OR****(95%CI),****insufficient *vs* sufficient** | **Global*****P* value (full)** | **OR****(95%CI)****Deficient *vs* sufficient** | **OR****(95%CI),****insufficient *vs* sufficient** | **Global*****P* value****(reduced)** |
| Diagnosis |  |  | 0.1482 |  |  | 0.0852 |
|  Controls | Ref. | Ref. |  | Ref. | Ref. |  |
|  CD | 1.71(0.74, 3.94) | 2.11(0.95, 4.69) |  | 2.22(1.07, 4.63) | 2.16(1.07, 4.36) |  |
|  UC | 0.73(0.30, 1.76) | 1.13(0.50, 2.53) |  | 0.92(0.42, 2.02) | 1.20(0.59, 2.48) |  |
|  |  |  |  |  |  |  |
| Gender |  |  | 0.9584 |  |  |  |
|  Female | Ref. | Ref. |  |  |  |  |
|  Male | 0.90(0.46, 1.79) | 0.95(0.50, 1.81) |  |  |  |  |
|  |  |  |  |  |  |  |
| Age (yr) |  |  | 0.1578 |  |  |  |
|  < 35 | 3.62(1.18, 11.12) | 1.47(0.56, 3.83) |  |  |  |  |
|  35-49 | 1.90(0.68, 5.30) | 0.68(0.28, 1.63) |  |  |  |  |
|  50-64 | 2.61(1.04, 6.58) | 0.86(0.40, 1.86) |  |  |  |  |
|  65+ | Ref. | Ref. |  |  |  |  |
|  |  |  |  |  |  |  |
| Race |  |  | 0.00061 |  |  | < 0.00011 |
| AA | Ref. | Ref. |  | Ref. | Ref. |  |
| White  | 0.251(0.13, 0.48) | 0.67(0.34, 1.29) |  | 0.231(0.12, 0.43) | 0.64(0.33, 1.22) |  |
| Other | 0.30(0.03, 3.38) | 0.68(0.09, 4.89) |  | 0.18(0.02, 1.95) | 0.57(0.08, 3.96) |  |
|  |  |  |  |  |  |  |
| BMI (kg/m2) |  |  | 0.00171 |  |  | 0.00301 |
|  < 25 | 0.68(0.32, 1.43) | 0.57(0.28, 1.17) |  | 0.71(0.34, 1.48) | 0.63(0.31, 1.26) |  |
|  25-30 | Ref. | Ref. |  | Ref. | Ref. |  |
|  > 30 | 2.711(1.28, 5.73) | 2.361(1.17, 4.75) |  | 2.611(1.26, 5.42) | 2.271(1.14, 4.52) |  |

1Statistically significant. CD: Crohn’s disease; AA: African American; BMI: Body mass index; UC: Ulcerative colitis.