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ORIGINAL ARTICLE

Retrospective Cohort Study

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

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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.

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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

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.

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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[1-4]. First described by Crohn *et al*[1] in 1932, 750000 people in the United States currently have CD. It is classified as inflammatory, penetrating, or stricturing, with or without perianal disease[5,6]. As CD became recognized as a distinct disease entity, it was observed that vitamin D deficiency was common among these patients[7,8].

Vitamin D exerts immune modulatory effects by reducing T cell mediated up-regulation of the nuclear vitamin D receptor (VDR)[9,10]. 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[11]. Further, certain VDR gene polymorphisms such as rs731236[A] (VDR) and rs732594[A] (SCUBE3) have been found to directly influence risk of CD[12]. A 2013 meta-analysis showed that carrying "Taql tt" genotype of the VDR gene is associated with increased susceptibility for CD in Europeans, while Apal "a" allele is protective. Therefore[13], 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[14,15].

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[16,17]. Studies suggest association between low vitamin D levels and increased disease activity as reflected by fecal calprotectin levels[13,18], hospitalizations as well as need for surgery in CD patients[15,19]. Conversely, vitamin D supplementation in CD may reduce chronic intestinal inflammation as reflected by CD activity index (CDAI) and C-reactive protein levels[20-22], as well as relapse frequency by as much as 50%[18].

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)[1]	IRR (95%CI)		
			Model 1	Model 2	Model 3
Overall	372/1610	23.11 (20.87, 25.58)			
Mean Vitamin D level ⩾ 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)

[1]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[14,21]. 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[22-24]. 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[25]. 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[26].

CD might itself be the root of vitamin D deficiency. Inflammatory cytokines in CD suppress renal 1-alpha hydroxylase leading to vitamin D deficiency[27,28]. 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[29]. Longer disease duration, CD disease activity and smoking status inversely correlate with serum vitamin D levels[22,30].

The Endocrine Clinical Practice Guidelines Committee recommends screening of all IBD patients especially those on corticosteroids for vitamin D status[31]. Among CD patients, serum vitamin D levels must be assessed especially for those with: elevated ESR[8], long duration of CD (> 15 years) and extended active stage of disease[32]. 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[33]. 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[34].

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[17,18]. 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.

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