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

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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

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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.

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)[8,9]. The gene for VDR signals 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[11,18], hospitalizations as well as need for surgery in CD patients[19,20]. 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...
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)

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% | 41.96% |
| 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.

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: 1.38-2.42) 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 (for age, sex, 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 high levels.
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[22,26].

The Endocrine Clinical Practice Guidelines Committee recommends screening of all IBD patients especially those on corticosteroids for vitamin D status[30]. 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.

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 Klintonsky DJ. Crohn’s disease, autophagy, and the Paneth cell. N Engl J Med 2009; 360: 1785-1786 [PMID: 19369659 DOI: 10.1056/NEJMct0810347]
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: 2489585]
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.0b013e3182ba366]
8 Veit LE, Marandia 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, Lahlif 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.0b013e3182990016]
10 Bendix M, Dige A, Deleuran B, Dahlperer JF, Jørgensen SP, Bartels LE, Husted LB, Harlsorf 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 Wendt T, Dabbas B, Laperriere D, Bitton AJ, Soualihine H, Tavera-Mendoza LE, Dione S, Servant MJ, Bitton A, Seidman EG, Mader S, Behr M. Direct and indirect induction by 1,25-dihydroxyvitamin D3 of the NO2/CD215-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: 3989-3990 [PMID: 24084050 DOI: 10.3390/nu5103989]
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-hydroxyvitamin D and increased risk of cancer in patients with inflammatory bowel disease. 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, Pengle 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.0b013e3182902a09]
16 Mouli VP, Ananthakrishnan AN. Review article: vitamin D and inflammatory bowel diseases. Aliment Pharmacol Ther 2014; 39: 125-136 [PMID: 24236089 DOI: 10.1111/apt.12553]
17 Sadeghian M, Saneei P, Siasi F, Esmailizadeh 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/s10605-015-3620-1]
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, Danrup 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, Zadovnorna Y, Binion DG, Issa M. Vitamin D deficiency in patients with inflammatory bowel disease: association with disease activity and quality of life. JPN J Parenter Enteral Nutr 2011; 35: 308-316
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[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, Matsaura 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]

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