

# Relationship Between Vitamin D Deficiency and Disease Activity in Patients with Inflammatory Bowel Disease in Ahvaz, Iran

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**Background and Aims:** Previous studies have shown that vitamin D plays an important role in inflammatory bowel disease (IBD). This study was designed to investigate the relationship between vitamin D levels and disease activity in IBD patients in Ahvaz, Iran.

**Methods:** This cross-sectional study was conducted on adult IBD patients referring to the outpatient clinic of gastroenterology at Imam Khomeini Hospital in Ahvaz city, in the southwest of Iran. Each patient's disease activity defined according to Crohn's disease activity index (CDAI) in Crohn's disease (CD) and Truelove score in ulcerative colitis (UC) patients, serum 25[OH]D was measured using the radioimmunoassay method. Vitamin D deficiency was defined as concentration of <20 nmol/L.

**Results:** Studied subjects were 130 UC and 23 CD patients (62.1% females) with a mean age of  $37.5 \pm 12.35$  years. Vitamin D deficiency was present in 99 (64.7%) IBD patients. Fifty-three patients (34.6%) had active disease who, compared with patients in remission, had more frequent low vitamin D levels (80 vs 56.7%,  $P = 0.017$ ). In UC patients, disease activity was significantly associated with vitamin D deficiency ( $P = 0.035$ ), but no such relationship was observed in CD patients ( $P = 0.74$ ).

**Conclusion:** Vitamin D deficiency was significantly associated with disease activity in IBD, especially in UC patients. Therefore, careful monitoring of vitamin D deficiency in these patients is highly recommended. Prospective cohort studies are also needed to determine the role of vitamin D deficiency and its treatment in the clinical course of IBD.

**Keywords:** inflammatory bowel disease, Crohn's disease, ulcerative colitis, vitamin D deficiency, disease activity, disease severity

## Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are two major types of inflammatory bowel disease (IBD) that are identified by different clinical, endoscopic, pathological, and radiologic diagnostic methods.<sup>1</sup> In the past few years, the incidence of inflammatory bowel disease has been increasing worldwide, with the incidence of UC being higher than that of CD.<sup>2</sup> Vitamin D is a fat-soluble vitamin that is produced in the skin by a UV-dependent reaction and then hydroxylated by the kidneys and liver, and is converted to its active form, 1,25-dihydroxyvitamin D.<sup>3</sup> Vitamin D deficiency is common throughout the world and its deficiency rates ranging from 30 to 50% have been reported.<sup>4</sup> Inflammatory cytokines are one of the most important causes of the pathogenesis of inflammatory bowel disease.<sup>3,4</sup> Several studies have shown the role of vitamin D as a regulator of the immune system and its inhibitory function in

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cellular immunity and production of pro-inflammatory cytokines that play a major role in autoimmune diseases.<sup>5</sup> Vitamin D has an anti-inflammatory effect on the expression and production of several pro-inflammatory cytokines including nuclear factor Kappa-B (NF-KB), interleukin 2 (IL-2), interleukin 12 (IL-12), and interferon-gamma (IFN- $\gamma$ ).<sup>6,7</sup> In some human studies, the link between vitamin D levels and the disease severity of IBD has been shown, but it is not clear whether lack of vitamin D is the cause or consequence.<sup>8</sup> The highest prevalence of IBD has been reported to be in cold climates with low exposure to sunlight.<sup>9,10</sup> A prospective cohort study of 72,719 women (aged between 40 and 73) showed that higher predicted vitamin D status is associated with a reduced risk of CD.<sup>11</sup> In this study, we aimed to investigate the relationship between inflammatory bowel disease and its flare-up with serum levels of vitamin D.

## Methods

### Study Population

The present study is an epidemiological-analytical research performed on patients with CD or UC admitted to Imam Khomeini Hospital in Ahvaz in 2019. The inclusion criteria for patients were: willingness to participate in the study; being in the age range of 18–80 years, being diagnosed with UC or CD based on clinical records, colonoscopy, and pathology according to Lennard-Jones criteria; having no history of chronic diseases such as cancer, diabetes, renal failure; and having no history of large gastrointestinal surgery. The exclusion criteria were: consumption of vitamin D supplementation during the last 6 months, pregnancy, and lactation. The study sample size was calculated to be 153 using the G\*Power software (version 3, Universität Duesseldorf, Germany) with estimating type I error and study power of 0.5 and 0.8, respectively.

The demographic questionnaire, administered at the beginning of the study, included the patients' general information, disease information including type of disease, patient's age at the disease onset, severity of the disease, colon involvement in colonoscopy, the location of involvement, disease behavior, presence of perianal fistula, and vitamin D levels. The information needed to determine the severity of the disease and the level of vitamin D was collected according to the history and clinical course of the patients. Disease severity criteria including ESR, hemoglobin level, fever, bloody stool, bowel frequency and

colonoscopy findings were recorded for all patients. Patients were then divided into two groups according to these criteria: the first group included patients in the remission phase and the second group involved patients in the active phase of the disease or flare up. Disease severity (remission and flare up) was assessed in patients with UC based on the Truelove index criteria<sup>12</sup> while patients with CD were assessed according to CDAI criteria.<sup>13</sup> The levels of serum vitamin D3 were extracted from patients' laboratory files, and levels <20 ng/mL were considered as vitamin D deficiency.

### Ethical Considerations

The study protocol was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (approval code: AJUMS.rec.1397.908). This study was conducted according to the Declaration of Helsinki, and all participants signed written informed consents.

### Statistical Analysis

Descriptive statistical methods were used to describe the variables in order to analyze the data. Data are presented as mean  $\pm$  standard deviation (SD) or number (percentage). Chi-square and Fisher's exact test were used for comparison of categorical variables. Normal distribution of the quantitative data was assessed by the Kolmogorov–Smirnov test. Correlations between variables were determined by the Pearson correlation coefficient for numerical variables. The 95% confidence interval (CI) is reported where relevant. Multiple logistic regression analysis was used for removing the effect of confounding factors. Two-sided *P* values of <0.05 were considered statistically significant. Data analysis was performed using SPSS Version 22 (IBM Corporation).

## Results

This study was performed on IBD patients referring to Imam Khomeini Hospital in Ahvaz, Iran, and the relationship between their serum vitamin D level and disease activity was investigated. In this study, 153 patients with a mean age of  $35.12 \pm 50.37$  years, including 58 men (37.9%) and 95 women (62.1%) participated. Of these, 130 (84.97%) had ulcerative colitis and 23 (15.03%) had Crohn's disease. Fifty-three patients (34.6%) had active disease, 100 patients (65.4%) were in remission, and 99 patients (64.7%) had vitamin D deficiency. There was no significant difference in terms of age, sex, and vitamin D levels between the two groups of Crohn's disease and

ulcerative colitis ( $P>0.05$ ). Demographic data and disease characteristics of patients, colonic extension of UC, patient's age at the onset of disease, as well as location, behavior and presence of perianal fistula in CD patients are shown in Table 1. The level of serum vitamin D and its relationship with disease activity among UC and CD patients is shown in Table 2. UC patients with higher levels of serum vitamin D were in remission more than patients with lower level of serum vitamin D ( $P=0.03$ ) (Table 2). Also, UC patients with more disease severity according to Truelove score, had lower serum vitamin D ( $P=0.01$ ) levels. In UC patients, there was a significant relationship between vitamin D deficiency and disease severity ( $P=0.01$ ), but in CD patients, no significant relationship was found between vitamin D deficiency and disease severity ( $P=0.65$ ).

Colonic extension of UC was not affected by serum vitamin D level ( $P=0.84$ ) (Table 3). The results of the relationship between vitamin D status and the main variables in patients with UC and CD are shown in Table 3.

The gender-based comparison between vitamin D status and severity of the disease in CD and UC patients showed a significant relationship between vitamin D status and disease severity in women with UC ( $P=0.02$ ) (Table 4).

After using logistic regression analysis, odds ratio (OR) of patient's age and vitamin D level in UC were significantly higher in those who experienced disease flare, (Table 5) but patient's gender did not increase the odds of disease flare. In this regard, for every unit increase in vitamin D level, OR of active disease decreased to nearly 6.5%. In CD, logistic regression analysis did not show increased odds in relation to low levels of vitamin D, age and gender of patients.

## Discussion

In this study, we investigated the association of vitamin D status with disease activity in IBD patients. According to our results, more than two-thirds of our patients had vitamin D deficiency, and there was no significant difference between the prevalence of vitamin D deficiency in the two groups of UC and CD patients. Previous studies have reported various frequencies of low vitamin D levels in IBD patients ranging from 16 to 95%.<sup>5</sup> Discrepancies in the results of these studies may be attributed to different patient characteristics (eg, demographic characteristics, disease activity, and nutritional status), environmental factors, as well as a different cutoff for defining low vitamin

D levels.<sup>14</sup> The results of the present study indicated an independent association between low vitamin D level and disease severity in UC patients, but no relationship was observed in CD patients. Our findings also revealed that patients' age is an independent factor, which significantly decreased the odds of flare in UC. Moreover, in ulcerative colitis patients, there was no significant relationship between vitamin D deficiency and extension of colon involvement. In addition, in CD patients, there was no significant relationship between vitamin D deficiency and patient's age at onset, site of involvement, disease behavior, and perianal fistula. The only influencing factor was the gender of the patients. Although in men there was no significant difference between vitamin D level and severity of disease, in women this difference was significant, with vitamin D deficiency being higher in women with flare-up than remission.

Schaffler et al<sup>15</sup> found a significant inverse association between the severity of IBD, especially among UC patients with vitamin D levels, but as far as CD was concerned, there was no significant difference between high activity of the disease and low levels of vitamin D. These results are fully consistent with the findings of the present study. Similar to our results, Blanck et al<sup>16</sup> reported an association between vitamin D deficiency and increased clinical activity in UC, with active disease status being two times more frequent in vitamin D-deficient UC patients than in those with normal vitamin D levels. Also, in Torki et al,<sup>14</sup> low vitamin D level was associated with active disease status, and this association was independent of possible confounding factors. In contrast with our finding, there was no significant relationship between vitamin D deficiency and IBD in the study of Vosoughi Nia<sup>17</sup> in Mashhad, Iran. This could be due to differences in disease duration, low sample size, dietary habits, methods of measurement, history of abdominal surgery and genetic susceptibility, and other characteristics of patients, and more importantly, the geographic difference between northeast of Iran with a cold climate and short days of sunlight and southwest of Iran with hot and humid weather where our study was conducted. Some studies on CD reported that low levels of vitamin D is associated with Crohn's disease activity,<sup>18,19</sup> while others showed no such association.<sup>7,20</sup> Exploring this relationship is difficult and complex because many variables are involved in evaluating disease activity. In contrast to our findings, Jorgensen et al<sup>21</sup> found an inverse association between serum 25[OH]D and disease activity in CD patients. The reason why no

**Table 1** Basic Characteristics of Patients

Variables		UC n=130	CD n=23	P-value
Age (years)		37.68 ± 12.53	36.39 ± 11.59	0.7
Vitamin D levels, ng/mL		18.53 ± 9.55	19.3 ± 11.82	0.79
Gender, n (%)	Male	46 (35.4)	12 (52.2)	0.16
	Female	84 (64.6)	11 (47.8)	
Disease severity, n (%)	Flare-up	40 (30.8)	13 (56.5)	0.03
	Remission	90 (69.2)	10 (43.5)	
Vitamin D Status, n (%)	Normal	47 (36.2)	7 (30.4)	0.64
	Deficiency	83 (63.8)	16 (69.6)	
Colon involvement in UC patients n (%)	Proctitis	28 (21.5)	-	-
	Distal colitis & left side colitis	46 (35.4)	-	
	Pancolitis & extensive colitis	56 (43.1)	-	
CD patients' age at the onset of disease, n (%)	< 18	-	2 (8.7)	-
	18–40	-	18 (78.3)	
	> 40	-	3 (13)	
Location of involvement in CD patients, n (%)	Colitis	-	9 (39.1)	-
	Illetis	-	3 (13)	
	Illeocolitis	-	11 (47.8)	
Behavior in CD patients, n (%)	Inflammatory	-	17 (73.9)	-
	Stricture	-	4 (17.4)	
	Fistula	-	2 (8.7)	
Perianal fistula in CD patients, n (%)	No	-	16 (69.6)	-
	Yes	-	7 (30.4)	

**Abbreviations:** CD, Crohn's disease; UC, ulcerative colitis.

**Table 2** Comparison of Vitamin D Level and Status with Disease Severity

Group of Patients	Disease Severity	Vitamin D Levels, ng/mL Mean ± SD	P-value <sup>a</sup>	Vitamin D Status Normal, n (%)	Vitamin D Status Deficiency, n (%)	P-value <sup>b</sup>
UC n=130	Flare	15.63 ± 6.57	0.03	8 (20)	32 (80)	0.01
	Remission	19.82 ± 10.39		39 (43.3)	51 (56.7)	
CD n=23	Flare	19.17 ± 13.08	0.74	3 (23.1)	10 (76.9)	0.65
	Remission	19.48 ± 10.65		4 (40)	6 (10)	

**Notes:** P-value: <sup>a</sup>Comparison of vitamin D level with disease severity. P-value: <sup>b</sup>Comparison of vitamin D status with disease severity.

**Abbreviations:** CD, Crohn's disease; UC, ulcerative colitis.

relationship between vitamin D levels and disease activity in CD patients was found in our study may be due to the small number of patients. Few cohort studies have directly assessed the relationship between low vitamin D levels and the risk of IBD. In this context, a 22-year cohort evaluating the association of low vitamin D level and risk of IBD, showed a 6% reduction in the relative risk of CD with each 1 ng/mL increase in the level of vitamin D. Also, every 100 IU/day increase in vitamin D intake

was associated with a 10% reduction in the relative risk of UC.<sup>11</sup> Another cohort study on 368 UC patients showed a significant association between disease activity and serum vitamin D levels.<sup>18</sup>

Although vitamin D deficiency is common in IBD patients, it is not established yet whether it is a cause or a consequence of IBD.<sup>4</sup> In addition, there is evidence that the contribution of vitamin D deficiency to the development of IBD in genetically predisposed individuals, and that

**Table 3** Relationship Between Vitamin D Status and the Main Variables in Patients with UC and CD

Variables		Vitamin D Status		P-value
		Normal	Deficiency	
Colon involvement in UC patients, n (%) n=123	Proctitis Distal colitis & left side colitis Pancolitis & extensive colitis	9 (32.1) 18 (39.1) 20 (35.7)	19 (67.9) 28 (60.9) 36 (64.3)	0.84
CD patients' age at the onset of disease, n (%)	< 18 18–40 > 40	2 (100) 4 (22.2) 1 (33.3)	0 (0) 14 (77.8) 2 (66.7)	0.12
Location of involvement in CD patients, n (%)	Colitis Ileitis Ileocolitis	1 (11.1) 0 (0) 6 (54.5)	8 (88.9) 3 (100) 5 (45.5)	0.09
Behavior in CD patients, n (%)	Inflammatory Stricture Fistula	4 (23.5) 3 (75) 0 (0)	13 (76.5) 1 (25) 2 (100)	0.14
Perianal fistula in CD patients, n (%)	No Yes	4 (25) 3 (42.9)	12 (75) 4 (57.1)	0.62

**Abbreviations:** CD, Crohn's disease; UC, ulcerative colitis.

**Table 4** Comparison of Vitamin D Status with Gender in Patient Groups

Group of Patients		Vitamin D Status in Males, n (%)		Vitamin D Status in Females, n (%)	
		Normal	Deficiency	Normal	Deficiency
UC n=130	Flare	3 (25)	9 (75)	5 (17.2)	23 (82.1)
	Remission	15 (44.1)	19 (55.9)	24 (42.9)	32 (57.1)
	P-value	0.24		0.02	
CD n=23	Flare	3 (37.5)	5 (62.2)	0 (0)	5 (100)
	Remission	2 (50)	2 (50)	2 (33.3)	4 (66.7)
	P-value	0.99		0.45	

**Abbreviations:** CD, Crohn's disease; UC, ulcerative colitis.

**Table 5** Logistic Regression Analysis in UC

	Crude OR (CI)	P-value	Adjusted OR (CI: 95%)	P-value
Age	0.96 (0.92–0.99)	0.018	0.95 (0.92–0.99)	0.015
Sex	1.42 (0.637–3.2)	0.39	–	–
Vit. D level	0.95 (0.9–0.99)	0.023	0.94 (0.89–0.99)	0.01

**Abbreviations:** CI, confidence interval; OR, odds ratio; UC, ulcerative colitis.

vitamin D supplements have positive effects on microbiome of IBD patients. It seems that promoter of Endogenous Anti-Microbial Peptides (AMP) is modulated by vitamin D and receptors.<sup>22</sup> Our study revealed that higher levels of vitamin D will decrease relapse in UC patients ( $P$ : 0.018, 0.94), whereas lower levels of this vitamin in patients with CD do not increase the odds for disease flare.

Our study had a number of limitations. First of all, in this study vitamin D levels were not classified by patient referral season. However, a previous study showed that there was no significant association between vitamin D level and season of assessment,<sup>14</sup> and Ahvaz city has a warm climate and it is warm and sunny for three seasons of the year. The study was conducted in a single outpatient

clinic with a limited number of patients presenting with active disease. Also, we were not able to assess inflammatory markers in patients who could provide better data on disease activity. In addition, the nutritional status of patients was not evaluated. Vitamin D is either synthesized by sunlight in the skin, or supplied by supplements and foods containing vitamin D. However, since few foods contain sufficient amounts of vitamin D,<sup>9</sup> the participants' diet may have been low in vitamin D, and since consumers of vitamin D supplements were not included in the study, it can be concluded that oral intake did not have a significant effect on vitamin D levels of the subjects.

In summary, there was a significant vitamin D deficiency in our IBD patients (two-thirty). Vitamin D deficiency was significantly associated with active disease status and independent of potential confounding factors such as patient age and disease characteristics (colonic involvement in UC patients; disease behavior, location, age at the onset of disease, and perianal fistula in CD patients). Although the relationship between vitamin D levels and disease activity in UC patients was well documented, no association was found between vitamin D status and Crohn's disease severity. Colonic extension of UC patients and age at disease onset, behavior, location and perianal fistula in CD patients were not affected by serum vitamin D level. In conclusion, these findings indicate that vitamin D status can be a marker of high disease activity in IBD patients, especially ulcerative colitis. A more comprehensive evaluation of inflammatory markers, including intestinal reliable markers, is required to better investigate the role of vitamin D in IBD activity. Due to the high prevalence of vitamin D deficiency in IBD patients, appropriate vitamin D screening as well as adequate vitamin D supplementation may be helpful.

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## Disclosure

The authors report no conflicts of interest in this work.

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