# Vitamin D and Its Role in Ulcerative Colitis

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**Background:** Inflammatory bowel disease includes ulcerative colitis and Crohn's disease. Immunomodulatory effects of vitamin D have been linked with autoimmune diseases such as inflammatory bowel disease. Procalcitonin as a marker of inflammation, has been proposed for bacterial infections.
**Objectives:** The aim of our study was to investigate the relationship between serum level of vitamin D and procalcitonin with activity of ulcerative colitis disease.
**Patients and Methods:** In this cross-sectional study, 96 patients referred to the Gastroenterology Clinic of Baqiyatallah hospital in 2013, were analyzed. Thirty-two patients had active and 32 patients had silent ulcerative colitis or were in the remission phase of the disease. Thirty-two age- and sex-matched healthy controls were studied. The diagnosis of ulcerative colitis was previously established on the basis of clinical symptoms and colonoscopic demonstration.
**Results:** Our sample comprised of 32 patients with active and 32 patients with silent ulcerative colitis, and 32 age- and sex-matched healthy controls. The frequency of vitamin D deficiency was significantly higher in patients with active and silent ulcerative colitis when compared to healthy controls (75% and 65.6% versus 59.4%, respectively; P = 0.04). We found no significant difference in the serum level of procalcitonin among the groups. This study showed that the serum levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in patients with active ulcerative colitis were higher than the two other groups.
**Conclusions:** Our results showed that vitamin D deficiency is more common in patients with ulcerative colitis. Laboratory findings confirmed the rise of ESR and CRP.

*Keywords:* Cholecalciferol; Procalcitonin; Colitis, Ulcerative

## 1. Background

1.25-dihydroxyvitamin $D_3$ [1.25 $(OH)_2D_3$] is an active form of vitamin $D_3$. In addition to its classic role in calcium homeostasis, it can be involved in immunoregulatory mechanisms (1, 2). A major source of vitamin D is its manufacture through a photolysis reaction in the skin. Dietary intake of vitamin D is obscure because there are only a few foods naturally rich in vitamin D.

The effects on the immune system are performed by the vitamin D receptor, present in immunological cells, such as monocytes. Vitamin D receptor is constitutively present in normal human monocytes and in malignant lymphocytes (3).

Furthermore, 1.25 $(OH)_2D_3$ is a form of vitamin D that binds to the vitamin D receptor and inhibits T lymphocyte proliferation and lymphokine production (4). This inhibitory effect through the blockage of antigen presentation could inhibits experimental autoimmunity (5-8). There is evidence that shows a link between vitamin D availability and the prevalence of inflammatory bowel disease (IBD) (9) while, vitamin D deficiency is common in patients with inflammatory bowel disease (10).

The two forms of inflammatory bowel disease include Crohn's disease and ulcerative colitis. They are chronic diseases characterized by improper responses to luminal bacteria in susceptible patients (11). Increased levels of inflammation mediators and immune system cells (macrophages, neutrophils, and lymphocytes) have been found in the intestinal mucosa and submucosa of patients with inflammatory bowel disease (12, 13).

Ulcerative colitis, affecting the mucosa of the colon and the rectum, is characterized by remission and flare-up and is concomitant with the immune system (14). It has been showed that defective T-lymphocyte proliferative response is responsible for ulcerative colitis (15). Reduced proliferative responses to IL-4 may also be involved in ulcerative colitis (16).

The 1.25 $(OH)_2D_3$ is known to be a modulator of immunocompetent cell activity and seems to regulate early events of antigen presentation by inhibiting T lymphocyte activity and interfering with IL-2 production. Furthermore, treatment with 1.25 $(OH)_2D_3$ results in the suppression of inflammatory bowel disease symptoms (17).

Iran is a country with high prevalence of vitamin D deficiency yet there are a few studies on diseases such as inflammatory bowel disease and their association with vitamin D and procalcitonin levels (18, 19).

## 2. Objectives

The aim of our study was to investigate the relationship between serum levels of vitamin D and procalcitonin, and activity of ulcerative colitis disease.

## 3. Patients and Methods

In this cross-sectional study, after receiving the ethics approval and patient informed consents, 96 patients referred to the gastroenterology clinic of Baqiyatallah hospital in 2013, were selected by random sampling. Thirty-two patients had active and 32 patients had silent ulcerative colitis or were in the remission phase of the disease. An individual with active disease is considered as someone with flare up clinical symptoms of disease; while an in individual with silent disease the clinical symptoms of disease have subsided. Thirty-two age- and sex-matched healthy controls were studied. The diagnosis of ulcerative colitis was previously established on the basis of clinical symptoms and by endoscopic, colonoscopic and histological demonstration. Demographic data, clinical examination, medical history, symptoms and laboratory findings were recorded. Serum procalcitonin was measured using the chromatography method and was quantitatively recorded (nanograms per milliliter). Serum procalcitonin levels of more than 2 ng/mL, indicated higher severity of disease. Patients were excluded if they were pregnant or if they had any of the following complications, hypercalcemia, Paget's disease, metabolic bone disease, osteoporosis and osteomalacia, renal failure, liver failure, malignancy, hyperparathyroidism, hypoparathyroidism, colectomy history, impaired fat absorption, sarcoidosis, tuberculosis or other mycobacterial infections.

Data were analyzed using the statistical package for social sciences (SPSS) version 16 (SPSS Inc. Chicago, IL) for windows. Normally distributed variables (approved by one-sample Kolmogorov-Smirnov test) were compared using independent sample t-test between groups and paired sample t-test within groups. Chi-square test was also used to compare categorical variables in the two groups. For assessing simultaneous effect of variables, logistic regression was used. A p value of less than 0.05 was considered statistically significant.

## 4. Results

From the total of 96 studied patients with a mean age of $32.14 \pm 6.6$ years, there was no significant difference among the groups of patients (P = 0.296) (Table 1). From the total of 44 males and 52 females, 13 males and 19 females had the active form of the disease. There was no significant difference among the groups (P = 0.74) (Table 1).

Table 2 shows serum levels of vitamin D in different patients. Serum vitamin D levels were not significantly different amongst different groups of patients (P = 0.45). Table 2 shows vitamin D deficiency. The difference was statistically significant (P = 0.04). There was no significant difference in the serum level of procalcitonin among the different groups (P = 0.09) (Table 2). Serum qualitative levels of C-reactive protein (CRP) were significantly different amongst different groups (P = 0.000). Table 2 shows the qualitative values of CRP in different groups.

Serum levels of CRP in patients with active disease were significantly higher than the other two groups (21.48 $\pm$ 27.72 IU vs. 1.87 $\pm$ 3.26 IU and 1.5 $\pm$ 3.4 IU). Quantitative levels of CRP among the groups showed no significant difference (P = 0.012).

Serum levels of erythrocyte sedimentation rate (ESR) in patients with active disease were significantly higher than patients with silent disease and the control group (P = 0.001). Blood sugar levels were significantly different between groups (P = 0.003) (Table 2). Table 2 shows the mean numbers of white blood cells. The mean numbers of white blood cells in patients with active disease were significantly higher than the other groups (P = 0.000). The mean hemoglobin level among the three groups was significantly different (P = 0.001) (Table 2). Table 2 demonstrates mean number of blood platelets in patients with active disease, silent disease and the control group. The mean platelet count was significantly different among the three groups of patients (P = 0.002). Mean serum calcium levels were significantly different (P = 0.003) (Table 2). Mean serum phosphate level in patients with active disease was significantly lower than in patients with silent disease and the control group (P = 0.037).

Table 3 shows the pathological lesion location in colonoscopy. There was a significant difference in the distribution of pathological lesion location in colonoscopy (P = 0.001). Most patients with active disease (96.8) had the severe form of disease and 3.2% had moderate severity, while most patients with silent disease (52.4%) had moderate severity and 47.6% had mild severity. Disease severity was significantly different between the groups (P = 0.000).

**Table 1.** Demographic Data of Patients [a]

| Demographic Data | Group | | | P Value |
| --- | --- | --- | --- | --- |
| | Active | Silent | Control | |
| **Age, y** | $33.53 \pm 6.1$ | $30.96 \pm 6.2$ | $31.93 \pm 7.4$ | 0.296 |
| **Gender** | | | | |
| Male | 13 | 15 | 16 | 0.74 |
| Female | 19 | 17 | 16 | 0.74 |

[a] Values are presented as No. or mean ± SD.

**Table 2.** The Laboratory Findings of Patients in Each Group [a,b]

| Laboratory Findings | Groups | | | P Value |
|---|---|---|---|---|
| | **Active (N = 30)** | **Silent (N = 32)** | **Control (N = 32)** | |
| **Vit D3, IU** | 14.32 ± 7.46 | 16.45 ± 9.4 | 17.59 ± 13.6 | 0.45 |
| **Vit D3 deficiency** | 24 (75) | 21 (65.6) | 19 (59.4) | 0.04 |
| **ESR, IU** | 35.25 ± 29.72 | 8.68 ± 3.59 | 7.75 ± 3.49 | 0.001 |
| **CRP, IU** | | | | 0.012 |
| 1 + | 6 (20) | 0 (0) | 2 (6.2) | |
| 2 + | 8 (26.7) | 0 (0) | 0 (0) | |
| 3 + | 4 (13.3) | 0 (0) | 0 (0) | |
| **WBC, (× 1000/mm)** | 9.02 ± 3.48 | 6.95 ± 1.77 | 6.49 ± 1.41 | 0 |
| **Procalcitonin, IU** | 0.13 ± 0.07 | 0.1 ± 0.05 | 0.144 ± 0.10 | 0.09 |
| **Blood sugar. mg/dL** | 110.73 ± 30.74 | 100.06 ± 15.66 | 83.1 ± 16.23 | 0.003 |
| **Hemoglobin, mg/dL** | 12.05 ± 2.21 | 14.73 ± 2.16 | 13.86 ± 1.06 | 0.001 |
| **Platelets, ×1000/mm** | 335.29 ± 181.56 | 270.95 ± 76.253 | 219.78 ± 31.65 | 0.002 |
| **Calcium, IU** | 7.98 ± 1.56 | 9.15 ± 0.309 | 9.34 ± 4.389 | 0.003 |
| **Phosphate, IU** | 3.59 ± 0.653 | 3.78 ± 0.379 | 3.97 ± 0.637 | 0.037 |

[a] Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; and WBC, White blood cells.
[b] Values are presented as No. (%) or mean ± SD.

**Table 3.** Location of Pathological Lesion in Groups [a]

| Pathological Lesion Location | Groups | | Total (N = 62) |
|---|---|---|---|
| | **Active Disease (N = 30)** | **Silent Disease (N = 32)** | |
| **Recto-sigmoid** | 5 (16.7) | 0 (0) | 5 (8.1) |
| **Left colon** | 14 (46.7) | 11 (34.4) | 25 (40.3) |
| **Transverse colon** | 4 (13.3) | 0 (0) | 4 (6.5) |
| **Pan colitis** | 7 (23.3) | 21 (65.6) | 28 (45.2) |

[a] Values are presented as No. (%).

## 5. Discussion

We found that vitamin D deficiency in patients with active disease was more than the other groups, and this difference between the groups was statistically significant. Furthermore, inflammatory markers like CRP and ESR in patients with active disease were also significantly higher than the two other groups.

We also concluded that procalcitonin levels in the three groups were almost identical and there was no significant difference between the three groups. Some studies on the relationship between inflammatory disease and procalcitonin levels have reported that the level of this marker increases during acute inflammation (20, 21).

Blood sugar levels, number of blood platelets and the mean numbers of white blood cells were significantly higher in patients with active disease than other groups, yet they had lower hemoglobin and lower serum calcium level. Mean serum phosphate level in patients with active disease was significantly lower than patients with silent disease and the control group.

In terms of pathological lesion and disease severity, in most patients with active disease the left colon was involved and they had the severe form of disease while in the silent group pan colitis was common with moderate severity.

The Vitamin D Receptor (VDR) is a ligand inducible transcription factor, present in immunological cells, such as monocytes and activated lymphocytes. This receptor has been shown to be a vital regulator of many autoimmune diseases including IBD (22).

Iran is a country with high prevalence of vitamin D deficiency yet there are only a few studies on inflammatory bowel disease and its association with vitamin D and procalcitonin levels (18). Most previous research studied IBD in general yet we evaluated ulcerative colitis specifically. One of the limitations and problems of this study was change in the disease process.

Joseph et al. reported that Indian patients with Crohn's disease had significantly lower levels of vitamin D compared with the control group, and patients with more active disease, had lower serum levels of vitamin D (23).

These results were approved by Gilman et al. from Ireland (24) and Blanck and Aberra (25). In our study serum levels of vitamin D in patients with active disease was significantly lower than patients with silent disease and the control group.

According to the study of Raman et al. (26) from Canada, vitamin D can be effective on inflammatory bowel disease activity. Our results were in line with the study of Raman et al. (26), regarding the effect of vitamin D on activity of inflammatory bowel disease. Our study was more specific for UC patients. These results were confirmed by the study of Ardizzone et al. (27) from Italy, which showed the immunomodulatory role of vitamin D in autoimmune diseases, and its effect on the immune system.

Naderi et al. (28), in their study from Iran, concluded that vitamin D receptors were more common on the leukocytes of patients with inflammatory bowel disease, which could explain the association of vitamin D and the disease. This effect was demonstrated in our study.

Ulitsky et al. (29) in a study done in the USA reported that vitamin D deficiency is more prevalent in patients with inflammatory bowel disease at the time of activation of the disease, and has lower levels when compared to the other stages of the disease. Our patients with active disease also had lower levels of vitamin D.

In conclusion, vitamin D deficiency is more common in patients with ulcerative colitis, thus we can introduce vitamin D as an immunomodulator. Procalcitonin in some studies, has been associated with inflammatory disease yet this association was not confirmed in current study. Vitamin D supplements can be recommended for these patients and serum levels of CRP and ESR can be a marker for predicting the onset and recurrence of ulcerative colitis, and included in the diagnostic protocol. Finally further studies with a larger sample size are suggested to confirm the results of this study.

## Authors' Contributions

All authors contributed equally in this project.

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