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*Original Article*

# Serum Vitamin D Level in Inflammatory Bowel Disease (IBD) and it's Association with IBD Activity

Miah MSA[1], *Chowdhury MFK[2], Islam S[3], Newaz AAS[4], Akter D[5], Saha T[6], Akhter MT[7], Adikhary D[8], Saha KP[9], Razib KO[10], Ghosh CK[11]

**Abstract**

*Vitamin D influences innate immunity, which is believed to be the imbalance of it involved in the pathogenesis of Inflammatory Bowel Disease (IBD). Evidence exists on the association between vitamin D deficiency and inflammatory bowel disease (IBD). To assess the serum vitamin D concentration in patients with inflammatory bowel disease and to study the relationship of vitamin D level with disease activity in the patients with inflammatory bowel disease. This case-control study was carried out in the department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (BSMMU). Total 40 IBD cases, diagnosed on clinical background and 40 apparently healthy control group of similar age and sex were taken. Blood samples were collected and serum vitamin D level was measured with Chemiluminescent Microparticle Immunoassay (CMIA) method in Biochemistry laboratory of BSMMU. The result were analyzed by statistical package for social sciences (SPSS) version 22. Vitamin D deficiency and insufficiency were defined as serum concentration of ≤20 ng/ml and 21–29 ng/ml respectively. Disease activity were evaluated using the Harvey Bradshaw Index for Crohn's Disease, Truelove and Witt's Index for Ulcerative colitis. The vitamin D levels were correlated with disease activity in IBD patients comparing with control group. Mean (±SD) serum vitamin D levels were 16.27 ± 5.16 ng/ml in IBD group and 24.25 ± 6.69 in controls (p <0.001). Almost all (97 %) of IBD patients had low serum vitamin D in comparison to controls; more than three-fourth (77.5%) of the patients of IBD exhibited deficiency (<20 ng/ml), one-fifth (20%) had insufficiency (21-29 ng/ml) of serum vitamin D, whereas in the controls 30% had deficiency, 42.5% had insufficiency, and 27.5% had sufficient serum vitamin D. There was highly significant inverse correlation between vitamin D level and disease activity in IBD patients. The study showed that IBD patients had significantly lower serum vitamin D levels in comparison to controls. Serum vitamin D concentration is inversely correlated with disease activity in IBD patients. The study suggests that inadequate vitamin D level, along with other factors, probably contributes to the development of active disease in patients with IBD.*

***Keywords:*** *Serum Vitamin D Level, IBD, crohn's disease, ulcerative colitis*

1. Dr. Md. Shah Alam Miah, Assistant Registrar, Sheikh Russel National Gastroliver Institute & Hospital, Mohakhali, Dhaka.
2. *Dr. Md. Fazlul Karim Chowdhury, Assistant Professor, Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University. #01716330906. chanchal4234@gmail.com
3. Dr. Susmita Islam, Assistant Professor, Department of gastroenterology, BSMMU.
4. Dr. Abdullah Al Shah Newaz, Assistant Professor, Department of gastroenterology, BSMMU.
5. Dr. Dilruba Akter, Assistant Registrar, SRNGIH, Mohakhali, Dhaka.
6. Dr. Tanmoy Saha, Medical Officer, SRNGIH, Mohakhali, Dhaka.
7. Dr. Md. Tuhin Akhter, Registrar, SRNGIH, Mohakhali, Dhaka.
8. Dr. Debprosad Adikhary, Registrar (Medicine), Satkira Medical College Hospital, Satkira.
9. Dr. Kirshna Pada Saha, Assistant Professor, Department of Colorectal Surgery , BSMMU.
10. Dr. Kh. Olinor Razib, Medical Officer, Dept. of Neurosurgery, BSMMU.
11. Prof. Dr. Chanchal Kumar Ghosh, Professor Department of gastroenterology, BSMMU.

*For correspondence

## INTRODUCTION

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD) is a chronic idiopathic inflammatory disorder of the gastrointestinal tract with a typically relapsing and remitting course[27,46]. Crohn's disease (CD) is a chronic inflammatory disorder that may involve any part of the alimentary tract from mouth to anus, with a propensity for the distal small intestine and proximal large bowel.[10]

UC is a chronic, relapsing disease characterized by diffuse mucosal inflammation of the colon.[44] It is thought to be caused by an inappropriate inflammatory response to the gut contents in genetically predisposed individuals.[1]

UC almost invariably involves the rectum and it may extend proximally in a continuous pattern to affect part of the colon or the entire colon. Clinical manifestations of active disease include bloody diarrhea (with or without mucus), urgency, tenesmus, abdominal pain, weight loss, fever, and malaise. Acute complications such as severe bleeding and toxic megacolon may occur, which can lead to perforation. There is an increased risk of colorectal cancer in UC patients. Risk factors include long duration of disease, extensive colonic involvement, severe inflammation and epithelial dysplasia, and childhood onset disease.[17]

Environmental factors such as smoking, medications such as non-steroidal anti-inflammatory drugs, stress and

psychological factors such as depression, nutritional factors and even air pollution increase risk of IBD.[2,3,4,5,50,65]

Another environmental factor involved in the patho-physiology of IBD is vitamin D deficiency.[47] Vitamin D is a major regulator of calcium and phosphorus metabolism and key in maintaining bone health.[50] There is evidence that vitamin D plays a role in immune regulation.[50] Vitamin D receptors are expressed by immune cells, including antigen presenting cells, natural killer cells, B and T lymphocytes (Yap *et al.,* 2015).

Vitamin-D inhibit proliferation of T-helper cells and secretion of IL-2, IFN-γ and IL-5, while increasing production of IL-4 by Th2 cells. Thus, vitamin D seems to modulate T-cell differentiation, driving cells towards the Th2 phenotype and inhibiting Th1development.[48]

Recent studies support the role of vitamin D in the pathogenesis, clinical course, and also the potential treatment of autoimmune diseases such as multiple sclerosis[51], systemic lupus erythematous.[40] and IBD.[51] Vitamin D regulates epithelial cell integrity[12,20,48] and its deficiency leads to intestinal barrier dysfunction, mucosal damage, and susceptibility to infectious agents (Kong *et al.,* 2008, Assa *et al.,* 2014). It also affects the mucosal and systemic immune system activities, generally with regulatory and anti-inflammatory properties.[667] There is also evidence on the role of vitamin D on the gut microbiome, which is implicated in the pathogenesis and clinical course of IBD.[12,20,48] Accordingly, it is possible that vitamin D affects the severity of inflammation and disease course in IBD patients.[50]

## MATERIALS AND METHODS

This case control was carried out in the department of Gastroenterology, BSMMU, from November 2017 to February 2019. Adult patients with IBD diagnosed on the basis of compatible history, clinical features, laboratory findings and endoscopy with histopathology were enrolled in study group. Equal number of age-sex matched apparently healthy individuals selected from employees of the university or post graduate students those who voluntarily agreed and fulfilled the eligibility criteria was included as controls. We excluded patients with pregnancy, history of gastrointestinal surgery, female patients on hormonal contraception, chronic kidney disease, diabetes mellitus, history of hypoparathyroidism, metastatic bone disease or other malignancies and patients taking vitamin D supplements that can be associated with vitamin D deficiency. Total eighty (80) participants, 40 were apparently healthy control and 40 patient fulfilling the inclusion criteria of inflammatory bowel disease (IBD), who were admitted or came for follow-up in IBD clinic in the Department of Gastroenterology at BSMMU were enrolled. Demographic and clinical characteristics were recorded. According to Harvey Bradshaw Index (HBI) for Disease Activity of Crohn's Disease patients were classified as Mild disease (5-7), Moderate disease (8-16), Severe disease (>16). Ulcerative colitis patients are classified as mild, moderate, severe by Truelove and Witts' severity index. Blood samples were purposively collected for serum Vitamin D in active disease group and age- gender matched healthy controls. Serum vitamin 25 (OH) D concentrations was measured with Architect ci 4100 using the Chemiluminescent microparticle immunoassay* (CMIA) method In the Biochemistry Department of BSMMU.

Data were analyzed using SPSS version 22.0 software. Descriptive statics like frequency and corresponding percentage for qualitative data, mean and standard deviation for quantitative data were calculated. While the data presented on categorical scale were compared between groups using Chi-square (x2). The data presented on continuous scale were compared between groups with the help of unpaired t-Test. Quantitative data in three groups were compared by one way ANOVA test. P values of < 0.05 was considered significance.

## RESULTS

From November 2017 to February 2019 with 40 patients with diagnosis of crohn's disease or ulcerative colitis were consecutively enrolled as cases and 40 apparently healthy adult individuals as controls. Twenty of the IBD patients had CD and 20 had UC. Mean age of IBD patients was 32.10 ± 9.99 years and 32.63 ± 10 years of control group and age range was 18 - 60 years in both groups.

Table I states the distribution of the age in case and control groups; among the IBD patients 33 (82.5%) were in age group 17 -40 years and 7 (17.5%) were >40 years, whereas in the control 32 (80.0%) were in age group 17 -40 years and 8 (20.0%) were >40 years.

**Table-I: Distribution of the age in case and control (n=80)**

| Age (years) | Case (n=40) | Control (n=40) | P value |
|---|---|---|---|
| 17 - 40 | 33 (82.5) | 32 (80.0) | |
| >40 | 7 (17.5) | 8 (20.0) | |
| Mean±SD | 32.10 ± 9.99 | 32.63 ± 10.00 | 0.815 |

Unpaired t test was done to measure the level of significance

Table II shows the distribution of the sex in case and control groups; among the IBD patients 25 (62.5%) were males and 15 (37.5%) were females, whereas in the control 25 (62.5%) were males and 15 (37. 5%) were females.

**Table-II: Distribution of the sex in case and control groups (n=80)**

| Gender | Case (n=40) | Control (n=40) | p-value |
|---|---|---|---|
| Male | 25 (62.5) | 25 (62.5) | 1.000 |
| Female | 15 (37.5) | 15 (37.5) | |

Chi-square test was done to measure the level of significance

Table III states the distribution of vitamin D level both in case and control groups; In IBD patients 31 (77.5%) had deficiency, 8 (20%) had insufficiency, and 1 (2.5%) had sufficiency of serum vitamin D level, whereas in the control group, 12 (30%) had deficiency, 17 (42.5 %) had insufficiency, and 11 (27.5%) sufficiency in serum vitamin D level. IBD patients had significantly lower mean serum level of vitamin D as compared to the control group (16.27± 5.16 vs. 24.25 ±6.69) respectively and P value <0.001).

**Table- III: Distribution of vitamin D level in case and control groups (n=80)**

| Vitamin D | Case (n=40) | Control (n=40) | p-value |
|---|---|---|---|
| ≤20 (Vit-D deficiency) | 31 (77.5) | 12 (30.0) | 21-29 |
| (Vit-D insufficiency) | 8 (20.0) | 17 (42.5) | |
| >29-100 (Sufficient Vit-D) | 1 (2.5) | 11 (27.5) | <0.001 |
| Mean±SD | 16.27±5.16 | 24.25±6.69 | |

Unpaired t test was done to measure the level of significance

Table IV contains the distribution of the duration of illness of the IBD patients; here duration of illness of 24 (60%) patients were > 4 weeks (established case), 16 (40%) were ≤ 4 weeks (new case) duration.

**Table -IV: Duration of illness of the IBD Patients (n=40)**

| Duration of illness (months) | Frequency (n) | Percentage (%) |
|---|---|---|
| ≤4 weeks | 16 | 40.0 |
| >4 weeks | 24 | 60.0 |
| Mean±SD (years) | 2.45 ±3.73 (0.08 - 20) | |

Table V shows the distribution of type of IBD and its severity. Here both Cron's disease and ulcerative colitis was equal in number (50%).

**Table -V : Type of IBD and its severity (n=40)**

| Severity of disease | Crohn's disease (n=20) | Ulcerative colitis (n=20) | Total |
|---|---|---|---|
| Mild | 4 (20.0) | 5 (25.0) | 9 (22.5) |
| Moderate | 6 (30.0) | 5 (25.0) | 11 (27.5) |
| Severe | 10 (50.0) | 10 (50.0) | 20 (50.0) |

Table VI shows the comparison of lab parameters between Crohn's disease and Ulcerative colitis. No significant difference of vitamin D level, Hb%, ESR and CRP were found between Crohn's disease and Ulcerative colitis patients (15.50 ± 4.26 vs 17.05 ± 5.94, p=0.349), (11.25 ± 2.84 vs 11.65 ± 2.66, p=0.649), (26.80 ± 17.01 vs 43.00 ± 30.64, p=0.046) and (26.85 ± 37.18 vs 24.10 ± 34.70, p=0.810) respectively.

**Table- VI: Comparison of lab parameters between Crohn's disease and Ulcerative colitis (n=40)**

| | Crohn's disease (n=20) | Ulcerative colitis (n=20) | p-value |
|---|---|---|---|
| 25(OH)D level | 15.50±4.26 | 17.05±5.94 | 0.349 |
| Hb% | 11.25±2.84 | 11.65±2.66 | 0.649 |
| ESR | 26.80±17.01 | 43.00±30.64 | 0.046 |
| CRP | 26.85±37.18 | 24.10±34.70 | 0.810 |

Unpaired t test was done to measure the level of significance

Table VII shows the 25(OH)D level according to severity of IBD; as Crohn's Disease activity increased, the level of serum vitamin D decreased (21.0 ±1.41 , 17.17±22.93, 12.30±2.50) reciprocally and P value <0.001. Also as the disease activity of Ulcerative colitis increased, the level of Vitamin D decreased (25.0 ±3.08, 17.40±1.67, 12.90± 3.84) reciprocally and P value <0.001.

**Table -VII: 25(OH)D level according to severity of IBD (n=40)**

| Type of IBD | Mild (n=20) | Moderate (n=20) | Severe | Total |
|---|---|---|---|---|
| Crohn's disease (n=20) | 21.00 ± 1.41 | 17.17 ± 2.93 | 12.30 ± 2.50 | <0.001 |
| Ulcerative colitis (n=20) | 25.00 ± 3.08 | 7.40 ± 11.67 | 12.90 ± 3.84 | <0.001 |
| Total | 23.22 ± 3.15 | 17.27 ± 2.33 | 12.60 ± 3.17 | <0.001 |

ANOVA test was done to measure the level of significance

Table VIII shows the 25(OH)D level according to duration of IBD; here, no difference of Vitamin D was found between newly diagnosed patients with established cases both in CD group (17.33 ± 4.12 ng/mL vs 14.00 ± 3.92, p value 0.081) and UC group (16.57 ± 5.96 vs 17.30 ± 6.15, p value 0.80) .

**Table- VIII: 25(OH)D level according to duration of IBD (n=40)**

| Type of IBD | < 1 months (n=20) | ≥ 1 months (n=20) | Total |
|---|---|---|---|
| Crohn's disease (n=20) | | | |
| <20 | 8 (88.9) | 10 (90.9) | |
| 21 - 29 | 1 (11.1) | 1 (9.1) | |
| Mean±SD | 17.33 ± 4.12 | 14.00 ± 3.92 | 0.081 |
| Ulcerative colitis (n=20) | | | |
| <20 | 5 (71.4) | 9 (69.2) | |
| 21 - 29 | 2 (28.6) | 3 (23.1) | |
| 30 - 100 | 0 (0.0) | 1 (7.7) | |
| Mean±SD | 16.57 ± 5.96 | 17.30 ± 6.15 | 0.800 |

Unpaired t test was done to measure the level of significance

Table IX illustrate the distribution of serum Vitamin D level among IBD and controls by age; here in male 10 (40%) had insufficiency, 9(36%) had sufficiency and 6(24%) had deficiency of serum vitamin D level. IBD patients had significantly lower serum vitamin D level as compared to the control group (16.27± 5.16 vs. 24.25 ± 6.69, P value <0.001). The difference was significant.

[In IBD patients 13(86.66%) had deficiency, 1(6.66%) had insufficiency and 1(6.66%) had sufficiency of serum vitamin D level].

**Table-IX: Distribution of IBD and controls by age (n=80)**

| Age | Deficiency (≤20) | Insufficiency (21 – 29) | Sufficiency (>29) | p-value |
|---|---|---|---|---|
| IBD | | | | |
| 17 – 40 | 26 (81.3) | 6 (85.7) | 1 (100.0) | 0.862 |
| >40 | 6 (18.8) | 1 (14.3) | 0 (0.0) | |
| Control | | | | |
| 17 – 40 | 8 (66.7) | 16 (94.1) | 8 (72.7) | 0.148 |
| >40 | 4 (33.3) | 1 (5.9) | 3 (27.3) | |

Chi-square test was done to measure the level of significance

Table X states the distribution of serum Vitamin D level among IBD and controls by sex; in male 19 (76%) had deficiency, 6(24%) had insufficiency of serum vitamin D level. In the healthy control females, 7 (46.66%) had insufficiency, 6(40%) had deficiency and 2 (13.33%) had insufficiency in serum vitamin D level.

**Table-X: Distribution of IBD and controls by gender (n=80)**

| Gender | Deficiency (≤20) | Insufficiency (21 – 29) | Sufficiency (>29) | p-value |
|---|---|---|---|---|
| IBD | | | | |
| Male | 19 (59.4) | 6 (85.7) | 0 (0.0) | 0.182 |
| Female | 13 (40.6) | 1 (14.3) | 1 (100.0) | |
| Control | | | | |
| Male | 6 (50.0) | 10 (58.8) | 9 (81.8) | 0.266 |
| Female | 6 (50.0) | 7 (41.2) | 2 (18.2) | |

Table XI illustrate the distribution of Crohn's disease severity and Vitamin D status; in Crohn's disease patients, half 10 (50%) had severe disease activity (>16), followed by 6 (30%) moderate disease activity (8-16) and 4 (20%) mild disease activity (5-7).

**Table-XI: Distribution of Crohn's disease severity and Vitamin D status (n=20)**

| Level of 25 (OH)D | Mild (n=4) | Moderate (n=6) | Severe (n=10) | Total |
|---|---|---|---|---|
| <20 | 2 (50.0) | 6 (100.0) | 10 (100.0) | |
| 21 - 29 | 2 (50.0) | 0 (0.0) | 0 (0.0) | |
| Mean±SD | 21.00±1.41 | 17.17±2.93 | 12.30±2.50 | <0.001 |

ANOVA test was done to measure the level of significance

Table XII illustrate the distribution of ulcerative colitis severity and Vitamin D status; in ulcerative colitis patients, half 10 (50%) had severe disease activity, followed by 5(25%) moderate disease activity and 5 (25%) mild disease activity.

**Table-XII: Distribution of Ulcerative colitis severity and Vitamin D status (n=20)**

| Level of 25 (OH)D | Mild (n=5) | Moderate (n=5) | Severe (n=10) | Total |
|---|---|---|---|---|
| <20 | 0 (0.0) | 5 (100.0) | 9 (90.0) | |
| 21 - 29 | 4 (80.0) | 0 (0.0) | 1 (10.0) | |
| 30 - 100 | 1 (20.0) | 0 (0.0) | 0 (0.0) | |
| Mean±SD | 25.00±3.08 | 17.40±1.67 | 12.90±3.84 | <0.001 |

ANOVA test was done to measure the level of significance

Table XIII shows the distribution of IBD by ESR and vitamin D; there were statistically significant association between vitamin D levels and erythrocyte sedimentation rate (36.31 ± 27.63 vs 26.29 ± 15.70 vs 50.00 ± 0.00 , p value <0.001).

**Table-XIII: Distribution of IBD by ESR and vitamin D (n=40)**

| ESR | Deficiency (≤20) (n=32) | Insufficiency (21 - 29) (n=7) | Sufficiency (>29) (n=1) | p-value |
|---|---|---|---|---|
| >30 | 15 (46.9) | 2 (28.6) | 1 (100.0) | |
| ≤30 | 17 (53.1) | 5 (71.4) | 0 (0.0) | |
| Total | 36.31±27.63 | 26.29±15.70 | 50.00±0.00 | <0.001 |

ANOVA test was done to measure the level of significance

Table XIV shows the distribution of IBD by CPR and vitamin D; there were statistically significant association between vitamin D levels and serum C-reactive protein (27.88 ± 35.28 vs 18.00 ± 39.73 vs 1.00 ± 0.00, p vale <0.001).

**Table-XIV: Distribution of IBD by CRP and vitamin D (n=40)**

| CRP | Deficiency (≤20) (n=32) | Insufficiency (21 - 29) (n=7) | Sufficiency (>29) (n=1) | p-value |
|---|---|---|---|---|
| >6 | 26 (81.3) | 2 (28.6) | 0 (0.0) | |
| ≤6 | 6 (18.8) | 5 (71.4) | 1 (100.0) | |
| Total | 27.88±35.28 | 18.00±39.73 | 1.00±0.00 | <0.001 |

ANOVA test was done to measure the level of significance

## DISCUSSION

In recent years, vitamin D has attracted a significant amount of scientific attention (Bruyn et al., 2013). Along with function of regulating the phosphocalcic metabolism, growing evidence point its anti-inflammatory, anti-proliferative and anti-apoptotic functions.[63] It is estimated that as many as one billion people worldwide suffer from vitamin D deficiency or insufficiency and this was shown to be prevalent across all age groups, genders, and geographic regions.[19,31,32] So, it is important to emphasize that vitamin D deficiency is a current public health issue that has been increasing, including in healthy individuals of all ages in developed and developing countries.

The present case-control study was carried out with the aim to determine the prevalence of vitamin D concentration in Inflammatory Bowel Disease and to compare them with that of apparently healthy controls and correlate with disease activity of IBD patients.[28]

The present study included forty inflammatory bowel disease (IBD) patients (15 females and 25 males) and forty (age and sex matched) healthy control participants**.** In this study we have seen significantly lower mean serum vitamin D levels in IBD patients compared to controls, (16.27±5.16 ng/ml) vs (24.25±6.69 ng/ml) respectively with p value<0.001. These finding are consistent with research finding of[21] who reported mean vitamin D levels in IBD patients was 24±10 ng/ml and in controls 31±13 ng/ml. The difference was significant, $p$<0.05.

When IBD patients and control subjects were classified according to Vitamin D status, among 40 IBD cases, 39 cases (97.5%) had low vitamin D concentration (<30 ng/ml); only one case (2.5%) had sufficient vitamin D concentration (≥30 ng/ml). Out of 39 low vitamin D patients, 31 cases (77.5%) were deficient (≤20 ng/ml) and 8 cases (20.0%) were insufficient (21-29 ng/ml). Among 40 control subjects, 29 participants (72.5%) were found to be low vitamin D (<30ng/ml) while in 11 participants (27.5%) vitamin D level were sufficient .This means that vitamin D deficiency is more prevalent in IBD patients than control subjects.

In the present study, however 1 out of 40 IBD patients and 11 out of 40 control subjects had sufficient vitamin D concentration. This was also similar with result of with results of [63,22] who confirmed lower levels of vitamin D among IBD patients as compared to the controls. The result of this study, however dissimilar with results of Ko *et al.*,(2019) who found that there was no significant difference in vitamin D levels between groups. This may be due to demographics, physical activity, and nutritional status.

In our study no difference was found in the prevalence of low vitamin D between CD and UC patients. This agrees with the results of study by.[39,22] However this study result do not agree with the result of[43] They reported that mean 25(OH)D levels were lower in CD patients compared with UC patients.

In the present study, as regard to age, there was no significant difference between IBD patients with different vitamin D status (Vitamin D deficiency and Vitamin D insufficiency). This finding is similiar with the finding of.[56] However, the results of this present study did not agree with results of[62] who reported younger patient were more Vitamin D deficient.

In our study there was no significant difference between IBD patients with different vitamin D status (vitamin D deficiency and vitamin D insufficiency) as regard to gender with p value = 0.182. Our observations are consistent with the findings of Hassan *et al.*,(2013) . However, the results of our study did not agree with results of[39,68] who reported the prevalence of low vitamin D was higher in males.

In the present study there was no significant difference between vitamin D level and disease duration (new case vs established case, p value 0.081). This however, did not agrees with the result of study by[63] who reported more vitamin D deficiency in patients with longer disease duration and[21] who reported newly diagnosed IBD patients had lower Vitamin D levels than established cases.

In our study there was a significant difference between different vitamin D status (vitamin D deficiency and insufficiency) as regard to HBI in Crohn's disease and Truelove and Witt's severity in Ulcerative colitis. It was also found that vitamin D correlated inversely with IBD disease activity. These findings are similar with study by[68] who also reported the association between higher disease activity and lower vitamin D levels.[9] reported vitamin D levels decreased with increased disease activity in ulcerative colitis patients.[9,21,38] reported significant correlation between vitamin D levels and crohn's disease activity but no significant correlation with ulcerative colitis disease activity. However[22] reported that serum vitamin D levels are not affected by disease severity in IBD patients (both UC and CD patients).

## CONCLUSION

In this case-control study, we observed that average serum vitamin D concentration of IBD patients were significantly low in comparison to controls. In our study, vitamin D concentration inversely correlated with disease activity and not significantly correlated with age and disease duration. The study suggests that inadequate vitamin D level, along with other factors, probably contributes to the development of active disease in patients with IBD.

### Limitation

Only a small number of IBD patients and controls were enrolled. The participants were from one centre, so result can't be generalized to reference population. Dietary intake of vitamin D, nutritional status of study participants not studied. Seasonal variation, time spent in sunlight were not studied.

### Recommendation

Further large scale studies should be considered to strengthen the study and establish the relationship of vitamin D levels with IBD along with other cofounders.

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