INTRODUCTION

Inflammatory bowel disease (IBD), including UC and CD, is a gastrointestinal disorder with a chronic and recurrent inflammatory process that requires lifelong treatment. IBD is highly prevalent in developed countries, such as North America and Europe, and affects up to 0.5% of the general population. Despite previous low incidence rates, Asia has experienced a meaningful increase in IBD incidence over the last 20 years, whereas Europe is experiencing a stagnation or decline.

Patients with IBD may have a variety of symptoms, such as diarrhea with blood and mucus, abdominal pain, and fatigue, that reduce the quality of life. There is much interest in the nutritional status of patients with IBD, and efforts are needed to improve nutritional status.

Vitamin D deficiency is more common in patients with IBD than in the general population. The incidence of vitamin D deficiency in IBD patients ranges from 16% to 95%, and is known to frequently occur in CD than in UC.

Many factors can contribute to vitamin D deficiency, such as malabsorption, reduced exposure to sunlight, lack of physical activity, reduced dietary and vitamin D intake, and smoking. The most stable form of measurement of vitamin D in serum is 25-hydroxyvitamin D (25-OH vitamin D), and its level reflects the vitamin D provided by sun exposure, dietary intake, supplementation, and storage.

Several epidemiological studies have found a significant inverse relationship between vitamin D level and the develop-
opment of IBD. Although the effects of vitamin D supple-
mentation on the outcome of the disease and the timing of
proper vitamin D supply are not yet clear, several studies
suggest that vitamin D plays an important role in the course
of IBD. This study aimed to determine the correlation between
serum vitamin D level and disease activity in patients with
IBD.

METHODS

1. Patients
Our study was performed in the gastroenterology clinic of
Inje University Seoul Paik Hospital for patients diagnosed
with UC or CD from January 2000 to December 2017. The
diagnosis of UC or CD was made based on the diagnostic
guideline suggested by the IBD study group of the Korean
Association for the Study of Intestinal Disease. The medi-
cal records of the enrolled patients were retrospectively
analyzed, including demographic, laboratory, endoscopic,
radiological, pathological, and other clinical data. Patients
were excluded if they had no data of serum vitamin D level
or had comorbidities affecting serum vitamin D levels (i.e.,
renal failure, liver disease, lactation, pregnancy, medications,
such as vitamin D supplements and anticonvulsants). The
80 of normal control group was selected based on age and
sex among those had normal colonoscopy finding and se-
rum vitamin D level was measured during health checkup in
2017 at Seoul Paik Hospital of Inje University. Among them,
63.8% (51/80) were men, with a mean age of 40.4±13.6 years
(range, 29–73 years). The study was conducted after the ap-
proval of the Ethics Committee of Seoul Paik Hospital of Inje
University (IRB File No. 2017-12-007). Informed consent was
waived.

2. Measurements
Patients’ characteristics including disease duration, location
and behavior, IBD-related surgeries, and medical history
were obtained from the clinical records. Physical examina-
tions were performed, and height and weight were mea-
sured on single calibrated scales. Hemoglobin, white blood
cell counts (WBC), CRP, ESR, albumin, and cholesterol levels
were also measured as indicators of inflammation and dis-
ease severity on the same day vitamin D level was measured.
Medication history has been checked for cumulative drugs
used since the disease was diagnosed.

Vitamin D status was obtained through measurement of
serum 25-OH vitamin D level by using a fully automated
immunoassay (ADVIA Centaur XP, Siemens, Munich, Ger-
many) because it was considered as the best measurement
of an individual’s vitamin D status.

3. Definitions of Disease Activity and Vitamin D
Deficiency
The primary outcome was the association of vitamin D
deficiency with IBD disease activity. Disease activity was as-
essed using the partial Mayo score and Harvey-Bradshaw
index (HBI) for UC and CD, respectively. The partial Mayo
score includes reported stool frequency, presence of rectal
bleeding, and a global assessment of the physician. The HBI
includes general well-being, number of liquid stools per day,
abdominal pain, abdominal mass, and complications. For
UC, a partial Mayo score of 2 or higher was defined as active
disease. In CD, an HBI score of <4 was defined as clinical re-
mission, and a score of 4 or higher was defined as active dis-
ease. The patients were classified based on their serum
25-OH vitamin D levels. Vitamin D deficiency was defined as
vitamin D level of <20 ng/mL.

4. Statistical Analysis
Data were analyzed using the SPSS software version 24.0
(IBM Corp., Armonk, NY, USA). Consecutive variables were
summarized using mean and standard deviation, and cat-
ergorical variables were represented by the corresponding
numbers and ratios. We used independent sample t-test to
compare quantitative data. Correlations between variables
were verified by the Fisher exact test. Binary logistic regres-
sion, for disease activity and vitamin D level, was adjusted
considering independent variables, such as age, sex, BMI,
smoking, disease duration, and laboratory variables (serum
vitamin D, hemoglobin, WBC, ESR, CRP, and albumin). A P-
value <0.05 was considered statistically significant.

RESULTS

1. Baseline Characteristics
We enrolled 87 patients with IBD in this study (UC, 45; CD,
42). Among them, 65.5% were men, with a mean age of
44.9±15.1 years (range, 18–75 years). The mean duration of
the disease was 4.7±4.8 years (range, 0.1–17.1 years). 5-ASA,
prednisolone, immunomodulators, and anti-TNF therapy
were administered in 98.9%, 56.3%, 56.3% and 32.2% of pa-
tients, respectively. Five patients (5.7%) underwent small
bowel resection and colectomy for complications, such as ste-
nosis, recurrent hemorrhage, and abscess. Table 1 shows the
demographic data and clinical characteristics of the patients.
2. Vitamin D Levels

Vitamin D deficiency (<20 ng/mL) was found in 73.6% of patients with IBD (UC, 73.3%; CD, 73.8%). Patients with IBD showed a lower mean of vitamin D level (16.3±9.0 ng/mL) than the healthy control group (20.4±7.0 ng/mL), with no statistically significant difference (P=0.136) (Fig. 1).

The mean vitamin D level in patients with CD was lower than that in those with UC, which was not statistically significant (15.4±8.2 ng/mL vs. 17.1±9.7 ng/mL, P=0.640) (Fig. 1).

In the univariate analysis, the age of patients in the vitamin D deficiency group was significantly younger (41.3±15.8 years) than that of those in the normal group (52.6±10.6 years) (P=0.011), but sex, BMI, duration of disease, disease location, drug use, and surgery were not significantly associated with serum vitamin D level. Also, the presence of anemia, leukocytosis, higher ESR and CRP levels, and lower albumin and total cholesterol levels were not significantly associated with vitamin D levels. Meanwhile, in the binary logistic regression analysis, age and disease activity were independently associated with vitamin D levels and the odds ratios were 0.96 (P=0.023; 95% CI, 0.92–0.99) and 5.06 (P=0.044; 95% CI, 1.04–7.59) (Table 2).

Table 1. Demographic Data and Clinical Characteristics of 87 Patients with IBD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>UC (n=45)</th>
<th>CD (n=42)</th>
<th>All patients (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>48.5±13.7</td>
<td>40.9±15.6</td>
<td>44.9±15.1</td>
</tr>
<tr>
<td>Male</td>
<td>28 (62.2)</td>
<td>29 (69.0)</td>
<td>57 (65.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.6±3.4</td>
<td>21.5±4.5</td>
<td>22.1±4.0</td>
</tr>
<tr>
<td>Smoker</td>
<td>7 (15.6)</td>
<td>7 (16.7)</td>
<td>14 (16.1)</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>6.4±5.7</td>
<td>2.9±2.4</td>
<td>4.7±4.8</td>
</tr>
<tr>
<td>Disease location for UC</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Proctitis</td>
<td>15 (33.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Left-sided colitis</td>
<td>9 (20.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Extensive colitis</td>
<td>21 (46.7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Disease location for CD</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ileal</td>
<td>11 (26.2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Colonic</td>
<td>8 (19.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ileocolonic</td>
<td>23 (54.8)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-ASA</td>
<td>45 (100)</td>
<td>41 (97.6)</td>
<td>86 (98.9)</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>25 (55.6)</td>
<td>24 (57.1)</td>
<td>49 (56.3)</td>
</tr>
<tr>
<td>Immunomodulators (AZA/MTX/6-MP)</td>
<td>23 (51.1)</td>
<td>26 (61.9)</td>
<td>49 (56.3)</td>
</tr>
<tr>
<td>Anti-TNF (infliximab/adalimumab)</td>
<td>11 (24.4)</td>
<td>17 (40.5)</td>
<td>28 (32.2)</td>
</tr>
<tr>
<td>IBD-related surgery</td>
<td>2 (4.4)</td>
<td>3 (7.1)</td>
<td>5 (5.7)</td>
</tr>
<tr>
<td>Mean 25-OH vitamin D (ng/mL)</td>
<td>17.1±9.7</td>
<td>15.4±8.2</td>
<td>16.3±9.0</td>
</tr>
<tr>
<td>Vitamin D deficiency (&lt;20 ng/mL)</td>
<td>33 (73.3)</td>
<td>31 (73.8)</td>
<td>64 (73.6)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.5±2.3</td>
<td>13.9±1.5</td>
<td>13.7±1.9</td>
</tr>
<tr>
<td>WBC (x10⁶ cells/μL)</td>
<td>7.4±2.8</td>
<td>6.7±2.8</td>
<td>7.0±2.8</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>21.6±23.9</td>
<td>27.7±23.8</td>
<td>24.6±23.9</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.9±2.5</td>
<td>0.4±0.5</td>
<td>0.7±1.9</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.3±0.4</td>
<td>4.3±0.6</td>
<td>4.3±0.5</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>181.3±35.0</td>
<td>173.6±43.0</td>
<td>177.6±39.0</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD or number (%).
5-ASA, 5-aminosalicylic acid; AZA, azathioprine; MTX, methotrexate; 6-MP, 6-mercaptopurine; TNF, tumor necrosis factor; 25-OH vitamin D, 25-hydroxyvitamin D; WBC, white blood cells.
3. Vitamin D and Disease Activity
Among the enrolled patients with IBD, 27 (31.0%) and 60 patients (69.0%) had active disease and were in remission, respectively. Compared with patients in remission, those with active disease had more frequent use of steroid and immunomodulators (74.1 vs. 48.3%, \( P=0.035 \)), as well as biological therapy (55.6 vs. 21.7%, \( P=0.003 \)), lower serum vitamin D level (11.4±6.3 ng/mL vs. 18.1±9.2 ng/mL, \( P=0.012 \)), and more frequent vitamin D deficiency (95.8% vs. 65.1%, \( P=0.003 \)) in the univariate analysis. With regard to serological biomarkers, patients with active disease were found to have higher WBC count, ESR, and CRP levels than those who were in clinical remission. However, in the binary logistic regression analysis, only low levels of vitamin D were independently associated with disease activity, with an odds ratio of 0.91 (\( P=0.028; 95\% \text{ CI}, 0.84–0.99 \)).

On subgroup analysis, only patients with CD with active disease had lower serum vitamin D level (9.6±2.9 ng/mL vs. 18.3±8.5 ng/mL, \( P=0.001 \)) and more frequent vitamin D deficiency (100% vs. 60.7%, \( P=0.007 \)) than patients in clinical remission, which was statistically significant (Table 3).

Disease activity was inversely correlated with vitamin D deficiency in patients with CD (\( P=0.007 \)). However, no correlation was observed in patients with UC (\( P=0.134 \)) (Fig. 2).

DISCUSSION
The sources of vitamin D are the synthesis of the skin through sunlight and the intake of food or supplement containing vitamin D. Although the main cause is still unclear, patients with IBD have a higher incidence of vitamin D deficiency than the general population.23 In this study, we identified the same results as several previous studies that reported a higher vitamin D deficiency incidence in IBD. The incidence of vitamin D deficiency in patients with IBD

### Table 2. Multivariate Analysis of Vitamin D Status and Selected Variables in IBD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal (≥20 ng/mL) (n=23)</th>
<th>Deficiency (&lt;20 ng/mL) (n=64)</th>
<th>OR (95% CI)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>52.6±10.6</td>
<td>41.3±15.8</td>
<td>0.96 (0.92–0.99)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Male sex</td>
<td>14 (60.9)</td>
<td>43 (67.2)</td>
<td>0.75 (0.19–3.01)</td>
<td>0.680</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.8±3.4</td>
<td>21.8±4.2</td>
<td>1.03 (0.86–1.24)</td>
<td>0.727</td>
</tr>
<tr>
<td>Smoking</td>
<td>7 (30.4)</td>
<td>7 (10.9)</td>
<td>2.15 (0.30–5.04)</td>
<td>0.441</td>
</tr>
<tr>
<td>Active disease</td>
<td>2 (8.7)</td>
<td>26 (40.6)</td>
<td>5.06 (1.04–7.59)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>5.4±5.4</td>
<td>4.5±4.5</td>
<td>0.99 (0.86–1.15)</td>
<td>0.971</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.9±1.8</td>
<td>13.6±2.0</td>
<td>0.93 (0.63–1.35)</td>
<td>0.688</td>
</tr>
<tr>
<td>WBC (x10⁶ cells/µL)</td>
<td>6.4±2.4</td>
<td>7.3±2.9</td>
<td>1.00 (1.00–1.00)</td>
<td>0.828</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>21.7±19.3</td>
<td>25.6±25.4</td>
<td>0.99 (0.95–1.02)</td>
<td>0.454</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.3±0.5</td>
<td>0.8±2.1</td>
<td>2.38 (0.42–3.5)</td>
<td>0.327</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.3±0.3</td>
<td>4.3±0.5</td>
<td>0.98 (0.14–6.8)</td>
<td>0.986</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>181.7±27.0</td>
<td>176.1±42.6</td>
<td>1.00 (0.99–1.02)</td>
<td>0.985</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD or number (%).

4 UC (n=12) and CD (n=11).

5 UC (n=33) and CD (n=31).

5-ASA, 5-aminosalicylic acid; AZA, azathioprine; MTX, methotrexate; 6-MP, 6-mercaptopurine; TNF, tumor necrosis factor.
in our study (73.6%) was relatively higher than that reported in a previous retrospective American study (49.8%), but lower than that in the recent study conducted in Korea (89.2%). These results are consistent with previous findings that Asian people tended to have a higher incidence of vitamin D deficiency than Caucasians. In addition, differences in research results may be due to other criteria for defining low vitamin D levels and environmental factors, and patient characteristics such as demographics, physical activity, and nutritional status. In our study, we considered...
albumin and cholesterol levels as indicators of nutritional status and investigated the association with vitamin D deficiency. However, we could not find a significant relationship between albumin and cholesterol level and vitamin D level, so we assumed that vitamin D deficiency was not caused by malnutrition.

There are several causes for vitamin D deficiency. Some studies show that lack of exposure to sunlight can be an important cause of vitamin D deficiency in patients with IBD, particularly from northern climates. They demonstrated that an association was found between winter season and vitamin D deficiency due to low sunlight and ultraviolet-B exposure. Inadequate physical activity in patients with chronic illness, known as another risk factor associated with vitamin D deficiency. In addition, bowel resection is found to be associated with vitamin D deficiency owing to the discontinuation of the enterohepatic circulation in the terminal ileum, interrupting the absorption of fat-soluble vitamins, such as vitamin D. However, those studies have not persistently investigated the effect of bowel resection on vitamin D deficiency, and our results also did not find a significant correlation between bowel resection and vitamin D deficiency (P=0.319). In addition, vitamin D levels and location of IBD lesions are not significantly related in this study (P=0.463).

Few reports have evaluated the effect of vitamin D supplementation on the clinical course of IBD in clinical trials. A recent American study investigating 138 patients showed that patients who did not receive vitamin D supplementation had lower levels of vitamin D and more frequent use of the health care system. In some other studies, inflammatory activity of CD has been found to be associated with vitamin D deficiency. Some researchers claimed that low vitamin D levels are associated with active disease, whereas others do not. Finding this association is complicated because of the many variables in assessing disease activity.

In contrast, studies on disease activity in UC and vitamin D deficiency are insufficient, with conflicting results. Although our study and a Romanian study observed that no association was found between vitamin D deficiency and disease activity, an American study of 34 patients with UC showed that they were associated. In addition, in a recent cohort study of 368 patients with UC, patients with normal vitamin D levels had significantly lower disease activity, but no association was found between systemic markers of inflammation and vitamin D levels. This study found an inverse correlation between low vitamin D levels and disease activity in patients with CD. We observed that patients with CD with low vitamin D levels had significantly higher disease activity measured by HBI. However, such association was not observed in patients with UC. These results were consistent with a large retrospective study of 200 outpatients with IBD at a Norwegian research institution (UC, 78; CD, 122).

Other variables, particularly ESR, CRP, and albumin levels, were associated with clinical disease activity, but no significant association was found between serum vitamin D status and inflammatory markers (ESR, CRP, and leukocytes) in our study. These results can be supported by the theory that serum vitamin D levels can reflect local inflammation in tissues rather than systemic inflammation, but further studies are needed to clarify the relationship. Meanwhile, a recent study evaluated fecal calprotectin, which showed a significant inverse correlation with vitamin D levels.

Our study has one interesting finding. The risk of vitamin D deficiency is generally high in the elderly, but in our study, vitamin D deficiency was significantly higher in the younger age. A recent American cohort study of patients with IBD also found the similar results. These findings may have been presumed to be caused by intake of vitamin D-containing nutrients without prescription or by differences in lifestyle and eating habits.

Our investigation has some limitations. First, this study was retrospective and performed on a limited number of patients at a single outpatient clinic; hence, the results were difficult to generalize. In addition, previously limited screening conditions and cost problems have not led to the examination of intestinal inflammatory markers, such as fecal calprotectin in many patients with IBD, which can provide better information on disease activity. Furthermore, we did not evaluate the influence of vitamin D supplementation on disease activity, patient symptoms, quality of life, and treatment changes.

In conclusion, vitamin D deficiency is frequently found in patients with IBD. In addition, vitamin D deficiency is associated with increased disease activity in patients with CD. However, no significant association between vitamin D levels and serum inflammatory markers was found. Because of the high rate of vitamin D deficiency in patients with IBD, appropriate vitamin D screening and supplementation with proper amounts of vitamin D may be helpful. More large prospective studies and clinical trials are needed to clarify the role of vitamin D in the clinical course of patients with IBD and to recognize its importance.
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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTION


REFERENCES


