ORIGINAL ARTICLE

# Associations between vitamin D, bone mineral density, and the course of inflammatory bowel disease in Polish patients

Alicja E. Ratajczak[1,2], Aleksandra Szymczak-Tomczak[1], Michał Michalak[3], Anna M. Rychter[1,2], Agnieszka Zawada[1], Agnieszka Dobrowolska[1], Iwona Krela-Kaźmierczak[1]

1 Department of Gastroenterology, Dietetics and Internal Diseases, Poznan University of Medical Sciences, Poznań, Poland
2 Doctoral School, Poznan University of Medical Sciences, Poznań, Poland
3 Department of Computer Science and Statistics, Poznan University of Medical Sciences, Poznań, Poland

**KEY WORDS**

bone mineral density, Crohn disease, inflammatory bowel disease, ulcerative colitis, vitamin D

**ABSTRACT**

**INTRODUCTION** There are various factors contributing to the pathogenesis of osteoporosis in inflammatory bowel disease (IBD), including steroid therapy, malnutrition, and vitamin D deficiency.

**OBJECTIVES** The study aimed to assess the vitamin D level among IBD patients and to investigate the relationship between vitamin D concentration and bone mineral density (BMD).

**PATIENTS AND METHODS** The study participants included 239 adult patients with IBD and a control group of 45 healthy adults. Densitometric measurements of the lumbar spine (L1–L4) and femoral neck (FN) were conducted using dual-energy X-ray absorptiometry. All patients completed a questionnaire referring to vitamin D supplementation.

**RESULTS** Significant differences were observed with regard to the body mass, body mass index, BMD, the Z-score, and the T-score of the FN and L1–L4. Only approximately 25% of all participants presented optimal or high concentrations of vitamin D. The research revealed no differences in vitamin D levels with regard to the disease extent and severity among the patients with ulcerative colitis. No differences were observed in terms of the disease localization, behavior, and the patient age at the time of diagnosis in the patients with Crohn disease. Furthermore, no differences were found in BMD, T-score, and Z-score of the FN and L1–L4 between the group of patients who supplemented and did not supplement vitamin D.

**CONCLUSIONS** Vitamin D may not be the only factor affecting BMD. Patients with IBD should supplement a higher dose of vitamin D than healthy adults.

Correspondence to:
Alicja E. Ratajczak, MSc, Department of Gastroenterology, Dietetics and Internal Diseases, Poznan University of Medical Sciences, ul. Przybyszewskiego 49, 60-355 Poznań, Poland, phone: +48 61 869 13 43, email: alicjaewaratajczak@gmail.com
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**INTRODUCTION** Osteoporosis is a common clinical problem among patients suffering from inflammatory bowel disease (IBD), including individuals with Crohn disease (CD) and ulcerative colitis (UC), and it affects about 20% to 50% of patients in these groups.[1] The pathogenesis of osteoporosis is multifactorial and comprises such elements as steroid therapy, low body mass index (BMI), malnutrition, genetic predispositions, and vitamin D deficiency.[2] It is essential to note that vitamin D not only affects calcium and phosphate metabolism, but it also decreases parathyroid hormone levels, and activates vitamin D receptors found in the bone tissue.[3] The level of vitamin D plays a role in many diseases.[4] One of the most discussed consequences of vitamin D deficiency is bone loss.[5] Consequently, individuals suffering from osteoporosis and osteopenia present lower serum concentrations of vitamin D than the healthy adults.[6] The diagnostic thresholds determining serum concentrations of 25-hydroxyvitamin D (25[OH]D) approved in Central Europe are shown in Supplementary material, *Table S1*.[7]

Furthermore, it is vital to notice that due to malabsorption and nutritional deficiency, IBD patients demonstrate a lower concentration of fat-soluble vitamins, including vitamin D, than the healthy individuals.[8] Additionally, previous studies indicated that treatment with vitamin D contributed to the reduction in IBD relapse rates.[9]

## WHAT'S NEW?

Our results are based on the first comprehensive study investigating the relationship between vitamin D and bone mineral density (BMD) among Polish patients suffering from inflammatory bowel disease (IBD). The study demonstrated that osteopenia and osteoporosis were common in the course of Crohn disease and ulcerative colitis. Furthermore, vitamin D deficiency was observed both in patients with IBD and in healthy individuals. Concluding, although there are a number of factors contributing to low BMD in IBD, our study indicated that vitamin D supplementation was essential for the prevention and treatment of osteopenia and osteoporosis among patients with IBD.

In order to determine the IBD phenotype, clinicians use the Montreal classification. Supplementary material, *Table S2* presents the Montreal classification for CD according to the patient age, disease localization, behavior, as well as the Montreal classification for UC, according to the severity of exacerbation (Supplementary material, *Table S3*).[10]

The presented study evaluated the prevalence of osteoporosis and osteopenia, as well as the association between bone mineral density (BMD), vitamin D level, and its supplementation among patients suffering from IBD. In addition, the effect of vitamin D supplementation on vitamin D levels was evaluated, as well as the impact of the course of the disease on vitamin D concentration and BMD.

The aims of the study were to assess vitamin D level among patients with IBD, including CD and UC, to investigate the association between serum level of vitamin D and BMD in CD and UC patients, and to compare the results between the patients and the controls.

**PATIENTS AND METHODS** The study comprised 239 adult patients suffering from IBD (120 CD patients and 119 UC patients), treated at the Department of Gastroenterology, Dietetics and Internal Medicine of Poznan University of Medical Sciences, and the control group (CG, 45 individuals). In order to participate in the study, all patients provided their written informed consent. The local Bioethics Committee approved the study (39/20). The diagnosis of IBD was based on the endoscopic, histopathological, and radiological criteria. The exclusion criteria comprised age under 18 or over 50 years, pregnancy, the presence of other diseases affecting BMD (diabetes, liver diseases, chronic kidney diseases, thyroid diseases, rheumatoid arthritis, chronic obstructive pulmonary disease, celiac disease, active neoplastic disease, other serious disorders, immunological diseases, and ongoing chronic inflammatory processes), and a lack of the written informed consent to participate in the study.

All patients included in the study were treated according to the current standards of the Polish Society of Gastroenterology and the European Crohn's and Colitis Organization, depending on their clinical status. The severity of the patients' condition was evaluated according to the Montreal classification,[10] which accounts for the patient age at the disease onset, disease location and behavior in the cases of CD, and the disease extent and severity regarding UC.

Densitometric measurements of the lumbar spine (L1–L4) and the femoral neck (FN) were conducted using dual-energy X-ray absorptiometry with Lunar DPX-Plus (Lunar, Inc., Madison, Wisconsin, United States). The following densitometric parameters were recorded: BMD, T-score, and Z-score. The T-score represented the difference between the obtained BMD measurement and the mean BMD for young adults, divided by the standard deviation for young adults. The Z-score was calculated as the difference between the measured BMD and the age-adjusted mean BMD divided by the standard deviation in the general population.

All patients and controls completed the original questionnaire referring to the supplementation of vitamin D. Additionally, serum 25(OH)D concentration was assessed using the electrochemiluminescence binding method test and the Cobas e 601 analyzers (Roche, Basel, Switzerland).

**Statistical analysis** Since the data did not follow the normal distribution (the Shapiro–Wilk test), the continuous variables were reported as medians and interquartile ranges (IQRs). Categorical data were presented as numbers and percentages. The comparison of interval parameters between the 2 groups was performed using the Mann–Whitney test. The Kruskal–Wallis test was used in the cases where more than 2 groups were compared. For significant results, additionally the Dunn post-hoc test was employed to determine differences between particular pairs of groups. The categorical data were analyzed using the $\chi^2$ test for independence. The relationship between 2 interval variables was assessed by the Spearman rank correlation coefficient. The analysis was performed using TIBCO's package Statistica, version 13 (Tibco, Palo Alto, California, United States). All tests were considered significant at $P$ below 0.05.

**RESULTS** The study involved 119 patients suffering from UC (60 women and 59 men), 120 patients with CD (61 women and 59 men) and 45 healthy adults (26 women and 19 men). The characteristics of the study groups are shown in TABLE 1. Significant differences were found between the groups for the body mass, BMI, BMD, Z-score, and T-score of the FN and lumbar spine (L1–L4), but not for the age and vitamin D concentration.

Only about 25% all participants presented optimal or high concentrations of vitamin D (TABLE 2). Moreover, optimal and high vitamin D concentrations were more frequently (but not significantly) observed among the patients with IBD than those in the controls.

Based on the T-score, the patients were divided into the groups with normal and decreased

**TABLE 1** Characteristics of the study groups

| Parameter | CD (n = 120) | UC (n = 119[a]) | CG (n = 45) | *P* value |
|---|---|---|---|---|
| Age, y | 30.35 (24.90–37.80) | 30 (25–40.1) | 28 (26–33) | 0.86 |
| Body mass, kg | 62.25 (54.00–71.94) | 63 (55–76.9) | 70 (63–80) | <0.01[b] |
| | | | | 0.03[c] |
| | | | | 0.62[d] |
| BMI, kg/m$^2$ | 20.31 (18.83–22.86) | 21.26 (18.75–24.42) | 23.15 (21.95–25.71) | <0.001[b] |
| | | | | <0.001[c] |
| | | | | 0.65[d] |
| BMD (L1–L4), g/cm$^2$ | 1.141 (1.020–1.237) | 1.169 (1.061–1.258) | 1.212 (1.170–1.284) | <0.001[b] |
| | | | | 0.01[c] |
| | | | | 0.99[d] |
| T-score (L1–L4) | –0.53 (–1.5 to 0.28) | –0.2 (–1.23 to 0.3) | 0.16 (–0.42 to 0.79) | <0.001[b] |
| | | | | 0.01[c] |
| | | | | 0.99[d] |
| Z-score (L1–L4) | –034 (–1.17 to 0.6) | –0.165 (–1.15 to 0.56) | 0.11 (–0.22 to 0.55) | 0.03[b] |
| | | | | 0.07[c] |
| | | | | 0.99[d] |
| BMD (neck), g/cm$^2$ | 0.976 (0.871–1.123) | 1.008 (0.884–1.105) | 1.050 (0.984–1.161) | 0.02[b] |
| | | | | 0.08[c] |
| | | | | 1.00[d] |
| T-score (FN) | –0.445 (–1.295 to 0.505) | –0.19 (–1 to 0.7) | 0.4 (–0.42 to 0.9) | <0.001[b] |
| | | | | 0.02[c] |
| | | | | 0.64[d] |
| Z-score (FN) | –0.125 (–0.960 to 0.795) | 0.000 (–0.73 to 0.83) | 0.36 (–0.15 to 1.04) | 0.04[b] |
| | | | | 0.20[c] |
| | | | | 0.99[d] |
| 25(OH)D, ng/ml | 23.32 (16.29–31.55) | 22.73 (15.57–32.00) | 20.21 (16.82–28.00) | 0.59 |

Data are shown as median (interquartile range). *P* values <0.05 were considered significant.

**a** n = 118 for BMD (L1–L4), Z-score (L1–L4), and T-score (L1–L4)

**b** CD vs CG

**c** UC vs CG

**d** CD vs UC

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density; BMI, body mass index; CD, Crohn disease; CG, control group; FN, femoral neck; UC, ulcerative colitis

**TABLE 2** Degree of vitamin D supplementation in the study groups

| Category | CD (n = 120) | UC (n = 119) | CG (n = 45) | All groups (n = 284) |
|---|---|---|---|---|
| Severe deficiency | 16 (13.33) | 13 (10.92) | 4 (13.33) | 33 (11.62) |
| Deficiency | 31 (25.83) | 33 (27.73) | 17 (37.78) | 81 (28.52) |
| Suboptimal concentration | 42 (35.00) | 37 (31.09) | 16 (35.56) | 95 (33.45) |
| Optimal concentration | 25 (20.83) | 32 (26.89) | 7 (15.56) | 64 (22.54) |
| High concentration | 6 (5.00) | 4 (3.36) | 1 (2.22) | 11 (3.87) |
| Toxic concentration | 0 | 0 | 0 | 0 |

Data are shown as number (percentage).

Abbreviations: see **TABLE 1**

BMD (T-score <–1.0), as shown in **TABLE 3**. Differences were observed in the prevalence of decreased BMD of the FN and of L1–L4 between the following groups: UC, CD, and CG (*P* <0.001).

Additionally, reduced BMD of the FN and L1–L4 was more frequent in the IBD groups than in the CG (both *P* <0.001).

The research showed no differences in vitamin D concentrations depending on the disease extent and severity among UC patients, and with regard to the disease localization, behavior, and patient age at the time of the diagnosis in individuals suffering from CD. **TABLE 4** and **TABLE 5** present BMD, the T-score, and Z-score of FN and L1–L4, frequency of osteopenia, osteoporosis, normal bone mass, vitamin D concentrations and level depending on the disease extent and severity among UC patients, and depending on the disease localization, behavior, and patient age at the time of the diagnosis among CD patients.

**TABLE 3** Prevalence of decreased bone mineral density (based on the T-score) of the femoral neck and the lumbar spine in the study groups

| BMD status | UC | CD | IBD | CG |
|---|---|---|---|---|
| Femoral neck | | | | |
| Normal (T-score >–1.0) | 90 (75.63) | 81 (67.50) | 171 (71.55) | 45 (100) |
| Lower BMD (T-score <–1.0) | 29 (24.37) | 39 (32.50) | 68 (28.45) | 0 |
| Lumbar spine (L1–L4) | | | | |
| Normal (T-score >–1.0) | 82 (68.91) | 77 (64.17) | 159 (66.53) | 45 (100) |
| Lower BMD (T-score <–1.0) | 37 (31.09) | 43 (35.83) | 80 (33.47) | 0 |

Data are shown as number (percentage).

Abbreviations: IBD, inflammatory bowel disease; others, see **TABLE 1**

Supplementary material, *Table S4* shows the frequency of treatment with different drugs in the course of the disease. No associations were found between vitamin D concentration and the administration, at any time, of sulfasalazine, steroids, azathioprine, melasazine, infliximab, adalimumab, ustekinumab, vedolizumab, or biopharmaceuticals.

We found no differences in BMD, the T-score and Z-score of the FN and L1–L4 between the patients who did and did not supplement vitamin D (**TABLE 6** and **TABLE 7**). Nevertheless, the patients who supplemented vitamin D presented higher 25(OH)D concentrations when compared with those without supplementation. Moreover, no differences were found between BMD of L1–L4 and the FN among the patients with vitamin D concentrations above and below 50 ng/ml, as well as above and below 30 ng/ml (reference ranges in Supplementary material, *Table 1*).

Additionally, no correlation was demonstrated between vitamin D and BMD of the lumbar spine and BMI. In fact, an association between BMD of the FN and vitamin D concentration was only observed in the CG, and it was a negative correlation.

Furthermore, no correlation was found between vitamin D, the T-score, and the Z-score in any of the groups. There were also no significant differences in vitamin D concentrations between women and men in the study groups.

A positive correlation was found between BMI and BMD of the FN and BMD of the lumbar spine ($P$ <0.001).

BMI correlated positively with the T-score and Z-score in the CD group ($P$ <0.001 and $P$ = 0.02, respectively), as well as with the T-score in the UC group ($P$ = 0.01).

Moreover, BMI correlated positively with age in all the groups (CD, $P$ <0.01; UC, $P$ <0.001; CG, $P$ = 0.02).

No correlation was observed between vitamin D concentration and BMI. Additionally, no association was demonstrated between vitamin D concentration, body mass, and age in the study groups.

**DISCUSSION** According to the research, osteopenia and osteoporosis affect about 24.37% to 35.83% of patients suffering from CU and CD. Nevertheless, Noble et al[11] reported that osteopenia affected 16% and 13% of patients with CD and UC, respectively, whereas osteoporosis was diagnosed in 18% and 19% of patients with CD and UC, respectively. Interestingly, according to the research conducted among Saudi patients,[12] individuals with CD presented reduced BMD more frequently than UC patients, while osteoporosis affected 37% and 25% of CD and UC patients, respectively, and osteopenia was diagnosed in 19% and 7% of CD and UC patients, respectively. Our study demonstrated significant differences in BMD, the T-score, and Z-score of the FN and lumbar spine (L1–L4) between patients suffering from CD, UC, and the healthy controls. Moreover, lower BMD (T-score <–1) was present more frequently among the IBD patients than in the CG. Additionally, according to the presented research, UC patients with ulcerative proctitis demonstrated higher BMD, the T-score and Z-score of L1–L4 than the patients with pancolitis. Thus, it is likely that the patients with severe lesions in the bowel in the course of exudative enteropathy may experience the loss of protein and mineral compounds. Furthermore, these patients may require a more extensive treatment which, in turn, might affect bone tissue.[13]

Vitamin D deficiency constitutes a common clinical problem not only among IBD patients, but also in the healthy adults. In our study, more than 33% of the CD and UC patients presented a significant or moderate deficiency of vitamin D. Additionally, its optimal or high concentration occurred in only about 25% of the participants, even though Horta et al[14] reported that a higher percentage of IBD patients might present with vitamin D deficiency, as in their case 75% of patients showed 25(OH)D level below 20 ng/ml.

Another study[15] indicated that IBD patients with BMI above 30 kg/m$^2$, as well as individuals from the African American population, presented a higher risk of vitamin D deficiency.

It is vital to note that vitamin D deficiency among IBD patients results from a decreased intake of products rich in vitamin D, avoidance of sunlight, and impaired vitamin D absorption and metabolism.[16] Our study shows that the patients supplemented a dose of 2000 IU, recommended for healthy adults in Central Europe. Furthermore, the patients suffering from UC or CD are also at a risk of vitamin D deficiency. Therefore, according to the studies, a dose of vitamin D should be adjusted to 25(OH)D concentration,[17] as Kojecký et al[18] reported that a dose of 2000 IU of vitamin D was insufficient for IBD patients.

Our study demonstrated no differences in vitamin D concentrations in the CD, UC, and CG groups and no differences in the duration of vitamin D supplementation between the patients with CD and UC. A study in the population of New Zealand[19] found that vitamin D

**TABLE 4** Characteristics and clinical parameters of patients with Crohn disease presented according to the Montreal classification, based on the patient age at the time of diagnosis, localization of intestinal mucosal changes, and the course of the disease (continued on the next page)

| Parameter | | A1 (n = 20) | A2 (n = 98) | A3 (n = 2) | *P* value | L1 (n = 32) | L2 (n = 31) | L3 (n = 57) | *P* value | B1 (n = 49) | B2 (n = 31) | B3 (n = 40) | p (n = 13) | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| BMD (L1–L4), g/cm$^2$ | | 1.102 (0.987–1.177) | 1.175 (1.025–1.263) | 1.234 (1.109–1.359) | 0.14 | 1.175 (1.062–1.245) | 1.195 (1.054–1.215) | 1.120 (1.005–1.224) | 0.14 | 1.007 (1.003–1.206) | 1.113 (1.022–1.238) | 1.205 (1.099–1.293) | 1.143 (1.017–1.204) | 0.47 |
| | | | | | | | | | | | | | | 0.051[a] |
| | | | | | | | | | | | | | | 0.25[b] |
| | | | | | | | | | | | | | | 0.99[c] |
| T-score (L1–L4) | | –0.830 (–1.865 to –0.530) | –0.300 (–1.480 to 0.400) | 0.115 (–0.760 to 0.990) | 0.10 | –0.345 (–1.490 to 0.280) | –0.20 (–1.12 to 0.80) | –0.600 (–1.700 to 0.000) | 0.16 | –1.00 (–1.70 to –0.14) | –0.76 (–1.46 to 0.10) | –0.015 (–0.780 to 0.810) | –0.4 (–1.5 to 0.2) | 0.01[a] |
| | | | | | | | | | | | | | | 0.16[b] |
| | | | | | | | | | | | | | | 0.99[c] |
| Z-score (L1–L4) | | –0.460 (–1.430 to –0.105) | –0.245 (–1.100 to 0.690) | 0.32 (–0.26 to 0.90) | 0.18 | –0.41 (–1.23 to 0.34) | –0.15 (–0.60 to 1.10) | –0.5 (–1.3 to 0.4) | 0.27 | –0.5 (–1.4 to –0.1) | –0.26 (–1.19 to 0.60) | 0.165 (–0.810 to 1.030) | –0.1 (–0.8 to 0.4) | 0.03[a] |
| | | | | | | | | | | | | | | 0.38[b] |
| | | | | | | | | | | | | | | 1.00[c] |
| Bone mass | Normal BMD | 11 (55) | 64 (65.31) | 2 (100) | 0.04 | 19 (59.38) | 23 (74.19) | 35 (61.4) | 0.04 | 27 (55.1) | 19 (61.29) | 31 (77.5) | 8 (61.54) | 0.08 |
| | Osteopenia | 5 (25) | 31 (31.63) | 0 | | 13 (40.63) | 8 (25.81) | 15 (26.32) | | 21 (42.86) | 9 (29.03) | 6 (15) | 4 (30.77) | |
| | Osteoporosis | 4 (20) | 3 (3.06) | 0 | | 0 (0.005) | 0 | 7 (12.28) | | 1 (2.04) | 3 (9.68) | 3 (7.5) | 1 (7.69) | |
| BMD (FN), g/cm$^2$ | | 0.915 (0.861–1.031) | 1.002 (0.889–1.132) | 1.003 (0.764–1.242) | 0.59 | 1.029 (0.879–1.143) | 1.068 (0.905–1.214) | 0.939 (0.849–1.054) | 0.19[a] | 1.003 (0.870–1.133) | 0.923 (0.829–1.058) | 1.034 (0.904–1.159) | 0.969 (0.873–1.088) | 0.06 |
| | | | | | | | | | 0.02[b] | | | | | |
| | | | | | | | | | 0.99[c] | | | | | |
| T-score (FN) | | –0.610 (–1.430 to –0.250) | –0.320 (–1.240 to 0.590) | –0.235 (–1.800 to 1.330) | 0.48 | –0.170 (–1.085 to 0.555) | –0.100 (–1.000 to 1.100) | –0.600 (–1.390 to –0.100) | 0.21[a] | –0.400 (–1.320 to 0.510) | –0.60 (1.39 to –0.10) | –0.195 (–0.895 to 0.800) | –0.5 (–1.3 to 0.3) | 0.51[a] |
| | | | | | | | | | 0.03[b] | | | | | 0.02[b] |
| | | | | | | | | | 0.99[c] | | | | | 0.37[c] |
| Z-score (FN neck) | | –0.185 (–1.65 to 0.13) | 0.000 (–0.90 to 0.84) | 0.275 (–1.170 to 1.720) | 0.46 | –0.08 (–0.80 to 0.80) | 0.36 (–0.69 to 1.40) | –0.20 (–1.21 to 0.30) | 0.65[a] | 0.000 (–1.04 to 0.90) | –0.32 (–1.11 to 0.00) | 0.25 (–0.61 to 1.20) | 0.1 (–0.7 to 0.9) | 0.14 |
| | | | | | | | | | 0.03[b] | | | | | |
| | | | | | | | | | 0.74[c] | | | | | |
| Bone mass | Normal BMD | 12 (60) | 69 (70.41%) | 1 (50) | 0.59 | 24 (75) | 24 (77.42) | 34 (59.65) | 0.16 | 33 (67.35) | 17 (58.06) | 26 (77.5) | 8 (61.54) | 0.27 |
| | Osteopenia | 8 (40) | 25 (25.21) | 1 (50) | | 8 (25) | 7 (22.58) | 19 (33.33) | | 14 (28.57) | 11 (35.48) | 9 (22.5) | 5 (38.46) | |
| | Osteoporosis | 0 | 4 (4.08) | 0 | | 0 | 0 | 4 (7.02) | | 2 (4.08) | 2 (6.45) | 0 | 0 | |

**TABLE 4** Characteristics and clinical parameters of patients with Crohn disease presented according to the Montreal classification, based on the patient age at the time of diagnosis, localization of intestinal mucosal changes, and the course of the disease (continued from the previous page)

| Parameter | | A1 (n = 20) | A2 (n = 98) | A3 (n = 2) | *P* value | L1 (n = 32) | L2 (n = 31) | L3 (n = 57) | *P* value | B1 (n = 49) | B2 (n = 31) | B3 (n = 40) | p (n = 13) | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 25(OH)D, ng/ml | | 25.00 (12.82–32.35) | 23.32 (16.58–31.10) | 29.03 (15.14–42.91) | 0.95 | 25.09 (17.51–36.54) | 25.40 (19.91–36.52) | 20.00 (14.69–29.31) | 0.09 | 25.75 (19.69–31.10) | 25.00 (15.51–36.72) | 25.00 (15.51–36.72) | 20 (16–30) | 0.11 |
| Vitamin D level | Severe deficiency | 5 (25) | 11 (11.22) | 0 | 0.68 | 3 (9.38) | 3 (9.68) | 10 (17.54) | 0.15 | 3 (6.67) | 5 (16.67) | 7 (21.88) | 1 (7.69) | 0.28 |
| | Deficiency | 3 (15) | 27 (27.55) | 1 (50) | | 7 (21.88) | 5 (16.13) | 19 (33.33) | | 10 (22.22) | 6 (20) | 9 (28.13) | 6 (46.15) | |
| | Suboptimal concentration | 7 (35) | 35 (35.71) | 0 | | 9 (28.13) | 14 (45.16) | 19 (33.33) | | 20 (44.44) | 9 (30) | 10 (31.25) | 3 (23.08) | |
| | Optimal concentration | 4 (20) | 20 (20.41) | 1 (50) | | 11 (34.38) | 6 (19.35) | 8 (14.04) | | 10 (22.22) | 10 (33.33) | 4 (12.5) | 1 (7.69) | |
| | High concentration | 1 (5) | 5 (5.1) | 0 | | 2 (6.25) | 3 (9.68) | 1 (1.75) | | 2 (4.44) | 0 | 2 (6.25) | 2 (15.38) | |

Data are shown as median (interquartile range) or number (percentage). *P* values <0.05 were considered significant.

**a** 1 vs 3; **b** 2 vs 3; **c** 1 vs 2

Abbreviations: A1, age at diagnosis below 16 years old; A2, age at diagnosis between 17 and 40 years old; A3, age at diagnosis above 40 years old; L1, localization: ileal; L2, localization: colonic; L3, localization: ileocolonic; B1, behavior: non-stricting, non-penetrating; B2, behavior: stricting; B3, behavior: penetrating; p, behavior: perinal disease modifier (may be added to B1-B3); others, see **TABLE 1**

concentration was the same in patients with CD, UC, and in the CG. Conversely, researchers from India[20] indicated that serum vitamin D level was significantly lower among IBD patients when compared with the CG, although the concentration did not differ between normal and decreased BMD. Moreover, 25(OH)D level was lower in UC and CD patients when compared with healthy adults. Additionally, the study by Tan et al[21] demonstrated that vitamin D level negatively correlated with the severity of the diseases. On the other hand, Gromny and Poniewierka[22] reported that vitamin D concentration was higher among patients with CD than healthy adults, while Ko et al[23] showed that the disease activity correlated negatively with vitamin D deficiency in CD patients ($P = 0.007$), although not in UC patients. Interestingly, according to the results provided by our study, no differences were observed in vitamin D concentration with regard to the course of the disease. The association between vitamin D, the exacerbation of intestinal inflammation, and the course of the disease was probably the result of the immunomodulatory effect. Additionally, an active form of vitamin D, that is, the hormone which affects both directly and indirectly bone cells and influences calcium balance, stimulates lymphocytes to produce anti-inflammatory cytokines.[24] It also participates in the formation and functioning of bone tissue. However, in our study no correlation was found between vitamin D and BMD, the T-score, and Z-score of the FN and L1–L4 in the IBD groups. In fact, Soare et al[25] also presented an insignificant influence of vitamin D on BMD in patients suffering from IBD. Moreover, a meta-analysis[26] showed no significant differences between BMD in patients who received various doses of vitamin D. Therefore, a decreased BMD in IBD probably stems from a number of factors, which include low BMI, malnutrition, smoking, decreased body mass, and inflammation.[2,27] Additionally, the consumption of alcohol and coffee did not seem to affect BMD, although physical activity may prevent bone loss.[28]

Genetic factors play a vital role in the pathogenesis of osteoporosis among IBD patients. In fact, BMD may depend on genetics, for example, the vitamin D receptor gene, the low-density lipoprotein receptor-related protein 5 gene, and the transforming growth factor beta-1 gene.[29]

Notably, the patients suffering from CD were more frequently treated with steroids, azathioprine, infliximab, adalimumab, ustekinumab, and biopharmaceuticals than the UC patients. Therefore, pharmacological causes, in particular the therapy with steroids, might also affect BMD.[30] Some studies showed that biopharmaceuticals in fact prevented bone loss,[31-33] while other works suggested a lack of impact of azathioprine on BMD.[34,35] Our previous study indicated a negative correlation between cumulative glucocorticosteroid dose and the T-score

**TABLE 5** Characteristics and clinical parameters of patients with ulcerative colitis presented according to the Montreal classification, based on the disease extent and the severity of exacerbation

| Parameter | | E1 (n = 34) | E2 (n = 40) | E3 (n = 45) | *P* value | S0 (n = 19) | S1 (n = 21) | S2 (n = 41) | S3 (n = 38) | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| BMD (L1–L4), g/cm² | | 1.243 (1.107–1.313) | 1.172 (1.049–1.239) | 1.113 (1.016–1.215) | 0.01[a] | 1.212 (1.024–1.276) | 1.207 (1.105–1.294) | 1.118 (1.045–1.234) | 1.177 (1.084–1.237) | 0.34 |
| | | | | | 0.67[b] | | | | | |
| | | | | | 0.17[c] | | | | | |
| T-score (L1–L4) | | 0.02 (–0.98 to 0.96) | –0.150 (–1.430 to 0.445) | –0.63 (–1.50 to –0.10) | 0.01[a] | –0.1 (–1.4 to 0.3) | –0.03 (–1.00 to 0.89) | –0.50 (–1.56 to 0.03) | –0.20 (–1.12 to 0.49) | 0.23 |
| | | | | | 0.33[b] | | | | | |
| | | | | | 0.38[c] | | | | | |
| Z-score (L1–L4) | | 0.09 (–0.80 to 1.00) | –0.015 (–1.250 to 0.755) | –0.465 (–1.300 to 0.150) | 0.049[a] | –0.4 (–1.2 to 0.4) | 0.250 (–1.30 to 0.89) | –0.5 (–1.5 to 0.4) | –0.10 (–0.81 to 0.64) | 0.26 |
| | | | | | 0.37[b] | | | | | |
| | | | | | 0.99[c] | | | | | |
| Bone mass | Normal BMD | 27 (79.41) | 27 (67.5) | 28 (62.22) | 0.53 | 14 (73.86) | 16 (76.19) | 25 (60.98) | 27 (71.05) | 0.79 |
| | Osteopenia | 6 (17.65) | 11 (27.5) | 13 (28.89) | | 4 (21.05) | 4 (19.05) | 12 (29.27) | 10 (26.32) | |
| | Osteoporosis | 1 (2.94) | 2 () | 4 (8.89) | | 1 (5.26) | 1 (4.76) | 4 (9.76) | 1 (2.63) | |
| BMD (FN), g/cm² | | 1.010 (0.936–1.130) | 1.006 (0.843–1.103) | 1.005 (0.906–1.074) | 0.38 | 1.123 (0.920–1.192) | 0.985 (0.939–1.103) | 0.965 (0.865–1.050) | 1.011 (0.929–1.098) | 0.13 |
| T-score (FN) | | –0.06 (–0.80 to 1.03) | –0.145 (–1.180 to 0.600) | –0.30 (–1.00 to 0.28) | 0.25 | 0.40 (–1.20 to 1.25) | –0.50 (–1.01 to 0.90) | –0.60 (–1.16 to 0.28) | –0.075 (–0.990 to 0.500) | 0.3 |
| Z-score (FN) | | 0.03 (–0.63 to 1.50) | 0.055 (–0.970 to 0.970) | 0.000 (–0.70 to 0.59) | 0.4 | 0.74 (–0.70 to 1.58) | –0.11 (–0.80 to 0.90) | –0.35 (–0.80 to 0.50) | 0.005 (–0.630 to 0.800) | 0.25 |
| Bone mass | Normal BMD | 27 (79.41) | 28 (70) | 34 (75.5) | 0.83 | 14 (73.68) | 15 (71.43) | 29 (70.73) | 31 (81.58) | 0.5 |
| | Osteopenia | 7 (20.59) | 11 (27.5) | 10 (22.22) | | 4 (21.05) | 5 (23.81) | 12 (29.27) | 7 (18.42) | |
| | Osteoporosis | 0 | 1 (2.5) | 1 (2.22) | | 1 (5.26) | 1 (4.76) | 0 | 0 | |
| 25(OH)D, ng/ml | | 22.53 (15.57–31.28) | 23.45 (15.53–31.00) | 21.39 (16.40–35.00) | 0.99 | 25.25 (17.34–41.00) | 30.00 (21.22–35.00) | 22.33 (16.78–29.04) | 18.87 (14.00–29.54) | 0.06 |
| Vitamin D level | Severe deficiency | 2 (8.82) | 2 (5) | 8 (17.78) | 0.68 | 2 (10.53) | 1 (4.76) | 2 (4.88) | 8 (21.05) | 0.14 |
| | Deficiency | 9 (26.47) | 14 (35) | 10 (22.22) | | 3 (15.79) | 4 (19.05) | 13 (31.71) | 13 (34.21) | |
| | Suboptimal concentration | 11 (32.35) | 13 (32.5) | 13 (28.89) | | 6 (31.58) | 6 (28.57) | 17 (41.46) | 8 (21.05) | |
| | Optimal concentration | 10 (29.41) | 9 (22.5) | 13 (28.89) | | 7 (36.84) | 8 (38.1) | 9 (21.95) | 8 (21.05) | |
| | High concentration | 1 (2.94) | 2 (5) | 1 (2.22) | | 1 (5.26) | 2 (9.52) | 0 | 1 (2.63) | |

Data are shown as median (interquartile range) or number (percentage). *P* values <0.05 were considered significant.

**a** 1 vs 3; **b** 2 vs 3; **c** 1 vs 2

Abbreviations: E1, extent: ulcerative proctitis; E2, extent: left side ulcerative colitis; E3, extent: extensive ulcerative colitis; S0, severity: clinical remission; S1, severity: mild ulcerative colitis; S2, severity: moderate ulcerative colitis; S3, severity: severe ulcerative colitis; others, see **TABLE 1**

of L1–L4 and BMD, the T-score and Z-score of the FN.[2] Moreover, the treatment of low BMD in IBD patients represents an essential element of therapy. According to a meta-analysis, bisphosphonate is well tolerated and effective in patients suffering from CD and UC.[36] On the other hand, data concerning the supplementation of calcium and vitamin D and the treatment with fluoride or calcitonin are insufficient, thus, more control trials are necessary.[36] Furthermore, frequent medication use among CD patients suggests a poorer course of the disease when compared with UC. In fact, inflammation was associated with a low BMD.[37] Therefore, further studies regarding the role of medication in the protection against the bone mass loss are essential.

**TABLE 6** Comparison of vitamin D concentration, bone mineral density, the T-score and Z-score of the lumbar spine (L1–L4) and femoral neck in Crohn disease patients with and without vitamin D supplementation

| Parameter | Vitamin D supplementation | | *P* value |
|---|---|---|---|
| | Yes | No | |
| 25(OH)D, ng/ml | 29.4 (23.0–37.0) | 21.92 (14.28–29.70) | 0.04 |
| BMD (L1–L4), g/cm$^2$ | 1.132 (1.101–1.282) | 1.173 (1.018–1.236) | 0.84 |
| T-score (L1–L4) | –0.60 (–1.0 to 0.68) | –0.56 (–1.69 to 0.22) | 0.85 |
| Z-score (L1–L4) | 0.000 (–0.60 to 0.41) | –0.375 (–1.260 to 0.600) | 0.67 |
| BMD (FN), g/cm$^2$ | 0.922 (0.866–1.076) | 0.952 (0.870–1.132) | 0.62 |
| T-score (FN) | –0.66 (–1.57 to –0.30) | –0.52 (–1.32 to 0.59) | 0.52 |
| Z-score (FN) | –0.36 (–1.10 to 0.90) | –0.265 (–1.010 to 0.760) | 0.75 |

Data are shown as median (interquartile range). *P* values <0.05 were considered significant.

Abbreviations: see **TABLE 1**

**TABLE 7** Comparison of vitamin D concentration, bone mineral density, the T-score and Z-score of the lumbar spine (L1–L4) and femoral neck between ulcerative colitis patients with and without vitamin D supplementation

| Parameter | Vitamin D supplementation | | *P* value |
|---|---|---|---|
| | Yes | No | |
| 25(OH)D, ng/ml | 31.00 (20.18–39.00) | 21.31 (14.94–29.54) | 0.03 |
| BMD (L1–L4), g/cm$^2$ | 1.165 (0.995–1.313) | 1.181 (1.080–1.259) | 0.98 |
| T-score (L1–L4) | –0.18 (–1.71 to 1.10) | –0.16 (–1.20 to 0.29) | 0.73 |
| Z-score (L1–L4) | –0.20 (–0.88 to 1.40) | –0.16 (–1.02 to 0.52) | 0.54 |
| BMD (FN), g/cm$^2$ | 0.903 (0.812–1.085) | 1.009 (0.920–1.107) | 0.16 |
| T-score (FN) | –0.65 (–1.63 to 0.30) | 0.02 (–0.99 to 0.89) | 0.13 |
| Z-score (FN) | –0.6 (–1.2 to 0.6) | 0.055 (–0.700 to 0.900) | 0.18 |

Data are shown as median (interquartile range). *P* values <0.05 were considered significant.

Abbreviations: see **TABLE 1**

Our study has some limitations. First, low BMD risk factors were not evaluated; however, the objective was to assess only the association between vitamin D and BMD, without taking other factors into account. Secondly, although the study included the administered drugs, additional calculation of cumulative dose of steroids would increase the quality of our research. Still, it was impossible as many patients have been suffering grom their diseases for years and collecting data about every steroid therapy would be very difficult. Another limitation is the lack of data on the environmental, nutritional, and genetic factors, which might have affected both BMD and the course of the disease. Therefore, further extensive studies referring to these factors are required. Besides, it would be valuable to correlate the biochemical parameters of inflammation with the vitamin D levels in the examined groups of patients.

Our study has been the first research focusing on the role of vitamin D in BMD, which involved over 230 Polish patients suffering from IBD. Simultaneously, it has been one of the most extensive studies referring to vitamin D in the course of IBD in Europe.

It is worth noting that social awareness regarding the role of vitamin D has increased significantly in recent years, and the issues associated with its deficiency and supplementation have become a significant clinical problem. This is reflected in the development of guidelines and their subsequent updates, as well as numerous media campaigns and advertisements promoting vitamin D supplementation. However, considering our recent research on vitamin D in IBD patients, the issue of deficiency and supplementation in this unique group of patients still seems to pose a significant challenge for clinicians.[38,39] Interestingly, there is a lack of differences in vitamin D concentration depending on the course of the disease and localization of the inflammation, even though vitamin D affects the immunological system and modulates inflammation.[40] Gromny and Poniewierka[22] also did not find any correlation between vitamin D concentration and activity of the disease, as assessed by the Crohn Disease Activity Index. Differences in the composition of vitamin D supplements and absorption and time of supplementation may influence the results. We need more studies in this area.

Furthermore, there is a lack of personalized guidelines regarding the treatment and supplementation of vitamin D in IBD patients. Future research should investigate the impact of vitamin D on the course of the disease and BMD in patients suffering from IBD. Nevertheless, vitamin D supplementation in higher doses is necessary, as it may prevent bone mass loss and improve the course of the disease.

In conclusion, our study demonstrated that vitamin D supplementation is essential in the prevention and treatment of osteopenia and osteoporosis among IBD patients. However, the supplementation should not be the only strategy for patients with decreased BMD. Therefore, the role of vitamin D and molecular mechanisms of its action require further research.

## SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

## ARTICLE INFORMATION

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