RESEARCH LETTER

Calcium and phosphate metabolism in patients with inflammatory bowel diseases

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Introduction Inflammatory bowel diseases (IBDs), which include Crohn disease (CD) and ulcerative colitis (UC), have constituted a significant medical challenge in recent years owing to an increase in morbidity. Because IBDs do not affect one organ only, they should be treated as systemic diseases with a number of extraintestinal manifestations.[1-3]

Osteopenia and osteoporosis seem to be one of the most important systemic complications of IBDs. Moreover, according to current data, the majority of IBD patients have vitamin D deficiency. The etiology of these disturbances includes poor diet, reduced exposure to sunlight, cigarette smoking, high disease activity, and postgastrointestinal tract resection states.[4] While the knowledge on vitamin D disorders in IBDs is still increasing, there are few data on the frequency and characteristics of calcium and phosphate metabolism disturbances in these diseases, which are directly related to vitamin D deficiency.

The aim of the present study was to analyze and compare patients with IBDs in terms of calcium and phosphate metabolism and its main regulators such as 25(OH)D (vitamin D) and parathormone (PTH).

Patients and methods The analysis included IBD patients treated at the Department of Gastroenterology, Human Nutrition and Internal Diseases of the Poznan University of Medical Sciences in Poznań, Poland, between 2009 and 2013 and healthy volunteers who constituted a control group. All IBD patients were admitted to the hospital to perform control investigations. The patients were in clinical remission. Data on the current treatment and nutritional status of the patients were collected. Serum calcium and phosphate levels were determined in all participants. The coefficients of variation were from 0.8% to 2.5% for calcium and from 0.6% to 0.7% for phosphate. Serum 25(OH)D levels were determined by an electrochemiluminescence binding assay with a recommended value of 30 to 80 ng/ml; functional sensitivity was determined at 4.01 ng/ml (coefficient of variation, 18.5%). Severe deficiency was defined as a vitamin D level of 0–10 ng/ml; medium deficiency, as >10–20 ng/ml; mild deficiency, as >20–30 ng/ml; and toxic level, as >100 ng/ml. The serum concentration of PTH was determined by an enzyme-linked immunosorbent assay (ELISA), a sandwich enzyme immunoassay using the BioVendor-Laboratorni medicina a.s. (Czech Republic) ELISA assay, and a Sunrise™ microplate reader (Tecan Group Ltd., Switzerland) with an analytical sensitivity of 2 pg/ml. The coefficients of variation were as follows: 5.4% (intraassay) and 6.1% (interassay).

A statistical analysis was performed using the Statistica 10 software. First we categorized variables depending on clinical application (high, low, and normal level). For statistical description, means with standard deviations for each value of biochemical tests were calculated. To verify the normal distribution, the Shapiro–Wilk test was used. The distribution of all of the analyzed variables differed significantly from the normal distribution. To compare the groups for the levels of factors, the Kruskal–Wallis test was used. In the case of significant results, the Dunn's test for a multiple comparison was used. To assess the relationship between the variables, the Spearman rank correlation coefficient was used. The level of statistical significance was set at a P value of less than 0.05. The study was approved by the local bioethics committee.

Results The study included 177 patients with IBD: 88 patients with CD (mean age, 35 ±12 years) and 89 patients with UC (mean age, 40 ±15 years). Characteristics of the patients are presented in Supplementary material online. The control group

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TABLE 1 Calcium, phosphate, parathormone, and vitamin D levels in the study groups

Group	Levels	Calcium, 2.15–2.55 mmol/l	Phosphate, 0.87–1.45 mmol/l	Parathormone, pg/ml	Vitamin D, 30–80 ng/ml
Crohn disease (n = 88)	low, n (%)	5 (5.7)	8 (9.1)	0	recommended level: 21 (23.9)
	normal, n (%)	81 (92.1)	79 (89.9)	54 (61.4)	mild deficiency: 23 (26.1)
	high, n (%)	2 (2.3)	1 (1.1)	34 (38.6)	medium deficiency: 27 (30.7)
	mean ± standard deviation	2.3 ±0.2	1.1 ±0.3	61.1 ±24.4	severe deficiency: 17 (19.3)
					21.3 ±12.2
ulcerative colitis (n = 89)	low, n (%)	2 (2.2)	8 (9)	0	recommended level: 19 (21.3)
	normal, n (%)	86 (96.6)	80 (89.9)	69 (77.5)	mild deficiency: 30 (33.7)
	high, n (%)	1 (1.1)	1 (1.1)	20 (22.5)	medium deficiency: 34 (38.2)
	mean ± standard deviation	2.4 ±0.1	1.1 ±0.3	53.1 ±20.9	severe deficiency: 6 (6.7)
					22 ±9.2 ng/ml
control group (n = 39)	low, n (%)	0	8 (2.6)	0	recommended level: 8 (20.5)
	normal, n (%)	38 (97.4)	33 (84.6)	21 (53.8)	mild deficiency: 12 (30.8)
	high, n (%)	1 (2.6)	5 (12.8)	18 (46.1)	medium deficiency: 16 (41)
	mean ± standard deviation	2.4 ±0.1	1.2 ±0.2	63.6 ±12.4	severe deficiency 3 (7.7)
					21.5 ±9.1

consisted of 39 healthy volunteers (mean age, 31 ±9 years).

A mean body mass index (BMI) in the IBD group was 22 ±4 kg/m^2. The BMI correlated negatively with the *P* level (r = –0.3; P <0.001). No correlations between the BMI and calcium, PTH, and vitamin D levels were noted.

On enrollment, aminosalicylates were administered in 93% of IBD patients; steroids, in 23%; and azathioprine, in 36%. There was a negative correlation between the dose of steroids and calcium levels in IBD patients (r = –0.2; P <0.01). No other correlations between the administered drugs and any of the other study parameters were noted.

The results of the biochemical analysis are shown in TABLE 1. A toxic level of vitamin D was not reported in any of the groups. A large percentage of patients had vitamin D deficiency (mild, medium, and severe): 78.6% of patients with UC, 76.1% of those with CD, and 79.5% of the control group. There were no differences in calcium levels between patients with UC, CD, and controls (H = 5.1; P >0.05). There were significant differences in phosphate levels between patients with UC, CD, and controls (H = 7.9; P<0.05). A detailed comparison revealed that controls had significantly higher phosphate levels than patients with UC (P <0.05). There were also differences in PTH levels between patients with UC, CD, and controls (H = 12.3; P <0.01). A detailed comparison revealed that controls had higher levels than patients with UC (P <0.01). There were no significant differences in the levels of vitamin D between patients with UC, CD, and controls (H = 0.63; P >0.05).

We also analyzed relationships between the variables. There was a negative correlation between PTH and calcium levels in patients with CD (r = –0.2; P <0.05), as well as a significant correlation between the level of PTH and phosphate for the CD group (r = 0.2; P <0.05). There was also a negative correlation between PTH and vitamin D levels in controls (r = –0.5; P <0.01). Moreover, there was a significant positive correlation between the level of vitamin D and CD in patients with CD (r = 0.4; P <0.001). There was a significant negative correlation between vitamin D and calcium only in patients with CG (r = –0.3; P <0.05).

CD patients with severe vitamin D deficiency had lower calcium levels than patients with moderate deficiency (P = 0.05) as well as those with the recommended concentration (P <0.001; a general difference between all groups: H = 18.8; P <0.001). Mean calcium levels were 2.17 ±0.35 mmol/l in patients with severe vitamin D deficiency, 2.35 ±0.09 mmol/l in those with medium deficiency, and 2.42 ±0.1 mmol/l in those with recommended levels.

Discussion According to the available data, up to 1 billion people could be affected by vitamin D deficiency.[5] Therefore, it is not surprising that almost 80% of the subjects in our study had a vitamin D level of less than 30 ng/ml. In this respect, there were no differences between patients with IBD and healthy volunteers. In the Polish population, this problem might result from insufficient sunlight exposure, while in patients with IBD, it could also be caused by inflammatory lesions in the gastrointestinal wall—the site of vitamin D absorption and elimination of foods that are a source of vitamin D. Similarly, gastrointestinal tract lesions may lead to a poorer absorption of calcium.[6] The current study also showed that patients with IBD had low calcium levels more frequently than controls, although the mean values did not differ significantly. Another known observation is a negative correlation between steroid dose and calcium levels, which was also confirmed in our study.[4,6] Patients with CD and insufficient vitamin D supply (severe deficiency) also had lower calcium levels compared with patients with only mild deficiencies.[7] IBD patients had also low phosphate levels more frequently (the difference was significant in the UC group) when compared with controls.

Silvennoinen et al.[8] reported that patients with IBD had lower vitamin D levels than healthy subjects, but similar PTH levels and similar intake of vitamin D. They demonstrated the effect of vitamin D on a change in fluidity of the intestinal brush border, on the synthesis of calbindin and calcium pump proteins, and therefore the mechanisms responsible for calcium absorption. In the event of a deficiency of the principal controlling factor, vitamin D, the intestinal absorption of calcium becomes impaired, which results in a reduction of its level in blood.[9] Dawson-Hughes et al.[10] suggested that reference vitamin D_3 levels should maximally suppress PTH. PTH functions as a calcium-mobilizing hormone when 25(OH)D levels are inadequate. The threshold has not been definitely established so far, but a minimum serum level is probably somewhere between 50 and 80 nmol/l of 25(OH)D.[10] Jørgensen et al.[11] concluded that oral vitamin D_3 supplementation in CD is safe and well-tolerated and is not associated with side effects or hypercalcemia. However, Yin et al.[12] showed significantly lower levels of $1,25(OH)_2D3$ in the serum of patients with IBD compared with controls, while PTH and 25(OH)D levels did not differ significantly between patients with UC, CD, and controls. Jahnsen and Falch[4] demonstrated that vitamin D deficiency, defined as a concentration of less than 30 nmol/l, occurred in 27% of patients with CD and 15% of patients with UC. Besides, patients with CD had significantly lower levels of vitamin D than patients with UC.[4]

In conclusion, we showed that patients with IBD have lower calcium and phosphate levels when compared with healthy people. There were also disturbances in the regulation of calcium and phosphate metabolism, as a physiological correlation between the levels of its main regulators, PTH and vitamin D, was only seen in healthy individuals. Although vitamin D deficiency is common not only among IBD patients but also in the general population, special attention should be paid to the assessment of the calcium and phosphate balance, which seems to be essential for the prevention of bone-related extraintestinal manifestations of IBD, such as osteopenia and osteoporosis. Therefore, it is important not only to consider supplementation of vitamin D but also dietary factors that improve calcium absorption or even supplementation of calcium in IBD patients.

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Supplementary material online Supplementary material is available with the online version of the article at www.pamw.pl.

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