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# Bone turnover markers in patients with inflammatory bowel disease in remission: a cross-sectional comparison of anti-TNF $\alpha$ therapy with conventional maintenance therapy

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**Introduction:** Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are associated with increased risk of bone loss due to chronic inflammation, nutritional deficiencies, and pharmacological treatment.

**Purpose:** The purpose of this study was to evaluate bone mineral density (BMD) and selected bone turnover markers in IBD patients in clinical and endoscopic remission, treated with conventional therapy or anti-TNF- $\alpha$  agents.

**Methods:** This single-center study included 100 participants: 35 with CD, 37 with UC, and 28 age-matched healthy controls. Patients IBD participated in the study received conventional treatment or anti-TNF- $\alpha$  therapy with ADA (adalimumab) or IFX (infliximab). IBD patients were in confirmed remission, without steroid use or comorbidities affecting bone metabolism. BMD was measured using dual-energy X-ray absorptiometry (DXA) at the lumbar spine (L2–L4), the left femoral neck, and whole body. Serum levels of osteocalcin (OC), parathyroid hormone (PTH), sclerostin (SOST), fibroblast growth factor 23 (FGF23), Dickkopf-1 (DKK1), osteoprotegerin (OPG), and osteopontin (OPN) were assessed.

**Results:** The IBD group demonstrated a statistically significant higher OPN value ( $p < 0.001$ ) compared to the control group. Additionally, the total T-score revealed a significant difference between the groups ( $p = 0.005$ ), with the control group exhibiting the highest values. No significant differences were found in the levels of other bone density markers studied between the biologically treated group and the conventionally treated group.

**Conclusions:** Our study indicates that patients with IBD are at risk of developing reduced bone mineral density and osteoporosis. While some bone turnover markers appear to normalize during remission, anti-TNF- $\alpha$  treatment does not offer added benefits for bone metabolism compared to conventional therapy.

#### KEYWORDS

Crohn's disease, inflammatory bowel disease, osteoporosis, TNF $\alpha$ , ulcerative colitis

## 1 Introduction

Inflammatory bowel diseases (IBD) include Crohn's disease (CD), ulcerative colitis (UC) and microscopic inflammatory bowel disease. They go through periods of remission and exacerbation. In CD, inflammation can be localized in any part of the gastrointestinal tract, from the mouth, through the esophagus, stomach, small intestine, large intestine, and rectum. Inflammation can affect the entire thickness of the gastrointestinal wall. In UC, inflammation usually begins in the rectum and spreads proximally to the large intestine. The nature of inflammatory changes is continuous and involves the mucosa and submucosa (1, 2).

IBDs are characterized by recurrent immune disorders involving both anti-inflammatory and pro-inflammatory factors. An abnormal inflammatory response can lead to a range of clinical manifestations (3). The goal of treatment is to achieve and maintain deep remission (healing of the intestinal mucosa), thus reducing the risk of the need for surgical treatment. When considering the implementation of appropriate treatment, the activity and severity of the disease course, the response to previously used medications, and concomitant extraintestinal symptoms, among other factors, should be taken into account. Treatment modalities can be divided into pharmacological and surgical. An adjunctive component of primary treatment is nutritional therapy (4). The most common pharmacological treatment is based on traditional drugs (5-ASA, Sulfasalazine) and biological treatment based on the use of anti-TNF- $\alpha$  drugs (3).

The prevalence of low bone density in patients with CD and UC is about 42% (5). IBD has a higher risk of reduced bone density than the general population. This is due in part to the prolonged active phase of the disease. During the occurrence of inflammation, cytokines are produced that enhance bone resorption (increase RANKL—RANK receptor ligand to OPG—osteoprotegerin). During prolonged remission of the disease, patients may increase bone mineral density (BMD) (6). Patients with IBD often have progressive clinical symptoms due to worsening nutritional deficiencies, the treatment used, the inflammation present, or a genetic predisposition (7, 8). After achieving remission in patients with IBD, without other risk factors for osteoporosis, bone turnover markers should return to normal. However, whether this is also the case in patients treated with TNF- $\alpha$  blocking drugs remains an open question. It is known that in terms of preventing bone loss, anti-TNF drugs do not have an advantage over traditional IBD treatment (9, 10). However, more recent data indicate that anti-TNF $\alpha$  therapy is associated with increased bone turnover markers and decreased BMD in the femoral neck (11).

The aim of the study was to determine whether bone mineral density and selected regulatory molecules [OC (osteocalcin), PTH (parathyroid hormone), SOST (sclerostin), FGF23 (fibroblast growth factor 23), DKK1 (Dickkopf-related protein 1), OPG, OPN (osteopontin)] in patients with IBD during remission maintenance treatment are normalized or remain outside normal limits.

## 2 Material and methods

### 2.1 Study population

This was a single-center study conducted among patients with CD and UC. Patients recruited for the study received conventional treatment or anti-TNF- $\alpha$  therapy with ADA (adalimumab) or IFX (infliximab; without hormone therapy). It was carried out in the tertiary IBD center in Rzeszow (Poland), according to the Good Clinical Practice Guidelines, the Declaration of Helsinki principles, and was approved by the local Ethics Committee (KE-0254/68/2015 and 23/04/2016).

A total of 100 subjects were recruited for the study, including 35 subjects with a diagnosis of CD, 37 subjects with a diagnosis of UC, and 28 healthy volunteers who were in a suitable age-matched group for the study. Patients with IBD were in remission of the disease.

The main inclusion criteria for the study were: IBD diagnosis CD or UC at least 2 years before entry to the study remission phase of the disease, standard treatment with 5-aminosalicylic or a standard dose of an immunosuppressive drug (e.g., Azathioprine 1 mg/kg) or IFX or ADA.

The exclusion criteria for the study were: current steroid use, active phase of the disease, pregnancy, with chronic comorbidities or therapy that could affect bone turnover marker levels.

We verify the diagnosis of IBD according to the 2018 recommendations of the American College of Gastroenterology (12, 13) and the European Organization for Crohn's and Colitis (14, 15).

### 2.2 Measurement of bone density

The bone mineral density was assessed using dual-energy x-ray absorptiometry (DXA). The study was conducted at the University of Rzeszów using a Lunar iDXA densitometer from GE Healthcare Lunar (Madison, Wisconsin, USA), which was equipped with enCORE software. Bone mineral density was measured in the lumbar spine (L2–L4 area), the left femoral neck, and the entire

body. The estimated precision errors for the above scan areas are 0.010 g/cm<sup>2</sup> (1%) (16). The DXA scan was performed on patients on average 7.1 years after diagnosis (Me = 7 years, SD  $\pm$  4.37,  $n$  = 54).

## 2.3 Measurement of bone turnover markers

Bone turnover markers in serum samples were measured using multiplex MILLIPLEX<sup>®</sup> Human Bone Magnetic Bead Panel (Millipore Sigma; St. Louis, MO) and MagPix (Diasorin; Austin, TX) instrument. According to the manufacturer, intra-assay CV was <10% and inter-assay CV <15%, with no cross-reactivity observed between analytes. Curve fitting and initial data analysis were performed with Belysa Immunoassay Curve Fitting Software (Millipore Sigma).

## 2.4 Laboratory assessments

All laboratory tests (hsCRP, calprotectin, blood morphology) were performed using routine commercial tests. CRP was measured using the CRP4 Tina-quant C-Reactive Protein IV CRP (Roche Diagnostics GmbH, Mannheim, Germany). Detection limit 0.1–0.22 mg/L, sensitivity 0.042 mg/dL (0.42 mg/L), while calprotectin was measured using the Bühlmann fCAL turbo assay (Bühlmann Diagnostics, Schönenbuch, Switzerland; measuring range 20–8000  $\mu$ g/g).

## 2.5 Statistical analysis

All results are expressed as median, standard deviation. The Kruskal-Wallis test was used, followed by Dunn's *post-hoc* test with Bonferroni correction. For normally distributed variables, ANOVA with Tukey's HSD test was used, which automatically corrects the results for multiple comparisons. In the case of correlations, Spearman's rank correlation was used due to the skewed distribution of biochemical markers. All analyses were performed using Statistica version 13 computer statistical software licensed from the University of Rzeszow. A level of  $p$  < 0.05 was considered the level of statistical significance.

## 3 Results

There were no significant differences between the groups (CD, UC and the control group) in terms of age, height, weight, body mass index (BMI) and, basic laboratory assessments like hemoglobin, high sensitivity C-reactive protein (hs-CRP) and calprotectin. The mean time to disease diagnosis was comparable between CD and UC (Supplementary material).

All patients had no clinical symptoms of CD or UC followed by normal values of inflammatory markers, which confirmed remission of the disease. Moreover, within the last 6 months, all patients passed endoscopic examination which also confirmed endoscopic remission. The criteria for CD remission were a simple Endoscopic Score for Crohn's Disease (SES-CD) of no greater than

4, with at least a 2-point reduction compared to the baseline of induction and no subscore greater than 1 (17), and for UC as a Mayo endoscopy Subscore (MES) (18).

A detailed *post-hoc* analysis (Dunnett's test with Bonferroni correction) revealed different patterns of significance for the markers studied. OPN values were significantly higher in the CD and UC groups compared to the control group ( $p$  < 0.001). In addition, statistically significant differences between groups were observed in OC levels ( $p$  = 0.028). The other markers (DKK1, OPG, SOST, PTH, and FGF23) did not show statistically significant differences (Table 1).

There were no significant differences in L2–L4 BMD, L2–L4 T-score, L2–L4 Z-score, Total Z-score, and BMC values between all study groups. Only the total T-score showed a significant difference between the groups ( $p$  = 0.005), with the highest values in the control group (Table 2).

Analysis of the impact of treatment type (anti-TNF $\alpha$  vs. conventional therapy) on bone turnover markers showed a statistically significant difference only in the case of OC. Patients treated conventionally had significantly higher median OC concentrations compared to patients receiving biological treatment ( $p$  = 0.041). No significant differences were observed between the subgroups for the other biochemical markers ( $p$  > 0.05; Table 3).

There were no differences in L2–L4 BMD, L2–L4 T-score, L2–L4 Z-score, Total T-score, Total Z-score, and BMC values between the biologically and conventionally treated groups (Table 4).

The only significant correlation in patients treated with anti-TNF $\alpha$  was a negative correlation between FGF23 concentration and BMC ( $\rho$  =  $-0.36$ ;  $p$  < 0.05). However, no significant correlations were found between the other bone markers (DKK1, OPG, OC, OPN, SOST, and PTH) and bone density indices in this subgroup. Within the biochemical markers themselves, a statistically significant positive correlation was observed between DKK1 protein and OPG ( $\rho$  = 0.41;  $p$  < 0.05) and a significant negative correlation between SOST and OC ( $\rho$  =  $-0.43$ ;  $p$  < 0.05; Table 5).

In the group of patients treated conventionally, a negative correlation was found between FGF23 and BMC ( $\rho$  =  $-0.59$ ;  $p$  < 0.05). In addition, a strong positive correlation was observed between PTH and SOST ( $\rho$  = 0.61;  $p$  < 0.05). However, no direct correlations were found between the other markers (DKK1, OPG, OC, and OPN) and bone density indices (Table 6).

## 4 Discussion

Chronic inflammation persistent in IBD patients may significantly impact bone turnover. Although it was shown in both CD and UC that bone loss is associated with the action of pro-inflammatory (19–21). However, patients with CD at higher risk of skeletal pathology compared to those with UC (22). Bone marrow TNF- $\alpha$  cells show the ability to promote osteoclastogenesis and excessive bone resorption (23). CX3CL1 expression can promote M1 macrophage polarization and osteoclast differentiation, while inhibition of CX3CL1 expression can reduce inflammation, thereby reducing the predisposition to reduced bone density (24, 25). IBD treatment aims to reduce inflammation, resulting in reduced bone resorption and increased BMD (26, 27). Treatment with anti-TNF $\alpha$

TABLE 1 Serum levels of bone turnover markers in the studied groups.

Variables	CD group			UC group			Control group			p-value
	N	Me	IQR	N	Me	IQR	N	Me	IQR	
DKK1 (pg/mL)	35	4,303.72	3,099.02	37	4,798.27	2,627.51	27	4,222.69	1,995.19	0.362
OPG (pg/mL)	35	561.08	244.14	37	666.59	327.71	27	604.11	192.00	0.272
OC (pg/mL)	35	21,318.54	30,557.49	37	21,018.84	26,565.15	27	43,977.93	73,437.61	<b>0.028</b>
OPN (pg/mL)	35	19,345.59	11,439.38	37	15,735.60	20,380.77	28	7,951.33	5,727.69	<b>&lt;0.001</b>
SOST (pg/mL)	19	817.95	1,795.60	23	1,726.65	1,492.10	19	968.05	1,182.75	0.147
PTH (pg/mL)	34	88.80	70.05	37	97.53	67.33	27	104.98	59.80	0.800
FGF23 (pg/mL)	22	64.72	29.43	32	69.68	21.98	28	71.38	19.00	0.083

DKK1, Dickkopf-related protein 1; OPG, osteoprotegerin; OC, osteocalcin, OPN, osteopontin, SOST, sclerostin; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23; CD, Crohn's disease; UC, ulcerative colitis; Me, median; IQR, Interquartile range.

TABLE 2 Differences between groups in bone mineral density and bone mineral content values.

Variables	CD			UC			Control group			p-value
	N	Mean	SD	N	Mean	SD	N	Mean	SD	
L2–L4 BMD	35	1.169	0.161	37	1.182	0.160	28	1.227	0.153	0.337
L2–L4 T-score	35	−0.260	1.327	37	−0.149	1.328	28	0.225	1.280	0.326
L2–L4 Z-score	35	−0.271	1.308	37	−0.186	1.316	28	0.007	1.178	0.684
Total T-score	35	0.246	1.173	37	0.451	1.050	28	1.146	1.046	<b>0.005</b>
Total Z-score	35	0.443	1.098	37	0.551	1.019	28	0.964	0.954	0.121
BMC	35	2,660.000	510.947	37	2,606.946	487.456	28	2,620.321	505.018	0.899

CD, Crohn's disease; UC, ulcerative colitis; SD, standard deviation; BMC, bone mineral content; BMD, bone mineral density.

through various mechanisms affects the activity of both osteoclasts and osteoblasts (28).

In our study, BMD (lumbar) and BMC values were similar between the study groups, with the exception of the T-score, which was lower in patients with IBD, especially in CD. Similar results were obtained by Cortés-Berdonces et al. (29) which confirms a certain regularity. However, no differences in BMD and BMC were observed between patients depending on the therapy used, although some data suggest an improvement in BMD after anti-TNF $\alpha$  treatment (30, 31). As shown by Pazianas et al. (31), an increase in BMD was observed mainly with the simultaneous use of infliximab and bisphosphonates, while infliximab treatment alone did not affect BMD.

The most pronounced difference between the groups was elevated OPN levels in patients with CD and UC compared to controls. Although the results of the studies are inconsistent, some authors confirm similar observations (32, 33). Furthermore, Mishima et al. (34) found a positive correlation between serum OPN levels and clinical activity indices in patients with IBD, and therefore propose that OPN be used as a clinical marker of disease activity. OPN reflected inflammation in the colon and rectum, as its plasma levels were reduced and correlations completely disappeared after proctocolectomy (34). In our study, patients were in remission, which may explain the absence of such correlations. However, elevated OPN may reflect increased bone cell activity and constitute a late marker of bone formation, which does not necessarily normalize after anti-TNF $\alpha$  therapy, despite reduced disease activity (35).

With regard to OC, OPG, SOST, PTH, and FGF23, no significant differences were found between patients with CD, UC, and controls, which may indicate a beneficial effect of maintaining remission on bone metabolism parameters. OPG, as an inhibitor of bone resorption by blocking RANKL-RANK interaction (36, 37), should theoretically be modulated by TNF- $\alpha$  and anti-TNF $\alpha$  treatment (38, 39). However, the literature is inconsistent: some studies indicate lower OPG levels (22, 40), others higher in selected groups (41–43). Miheller et al. (44) demonstrated a decrease in OPG after anti-TNF $\alpha$  treatment, whereas in our study, the levels were similar between the groups, with slightly lower values in CD. It is likely that the diagnostic value of OPG may be limited in the assessment of bone metabolic activity in this group of patients.

With regard to the Wnt pathway, DKK-1 plays a role in the pathogenesis of CD and bone metabolism (45, 46). The reduction in DKK-1 in pediatric patients treated with anti-TNF $\alpha$  (45) indicates the potential involvement of this pathway in epithelial regeneration and bone remodeling. In our study, DKK-1 levels did not differ significantly between treatment groups, which may reflect the complex regulation of this molecule. The observed positive correlation of DKK-1 with OPG in patients treated with anti-TNF $\alpha$  can be interpreted as a compensatory element in response to chronic inflammation. Similarly, SOST, which acts by inhibiting the Wnt pathway (47), showed no differences between treatment groups, although its values were lower in CD, consistent with other reports (45, 48). Anti-SOST antibody therapy has the potential to restore bone mass (46), but in our study, OC, which is functionally related to osteoblast activity, did not differ significantly between

TABLE 3 Comparison of serum bone turnover marker levels in patients receiving biological (anti-TNF $\alpha$ ) vs. conventional treatment.

Variables	anti-TNF $\alpha$ treatment			Conventional treatment			<i>p</i> -value
	N	Me	IQR	N	Me	IQR	
DKK1 (pg/mL)	55	4,503.75	2,814.67	17	4,339.54	3,172.58	0.750
OPG (pg/mL)	55	561.08	273.64	17	676.23	212.66	0.254
OC (pg/mL)	55	20,919.74	24,122.55	17	35,069.54	43,691.44	<b>0.041</b>
OPN (pg/mL)	55	18,947.26	19,147.71	17	17,727.19	13,909.93	0.624
SOST (pg/mL)	30	893.00	1,721.41	12	1,633.86	1,671.02	0.404
PTH (pg/mL)	54	84.42	77.44	17	97.53	39.93	0.952
FGF23 (pg/mL)	40	67.20	19.26	14	70.01	38.91	0.176

DKK1, Dickkopf-related protein 1; OPG, osteoprotegerin; OC, osteocalcin; OPN, osteopontin; SOST, sclerostin; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23; Me, median; IQR, interquartile range; Statistical significance assessed using Mann-Whitney U test.

TABLE 4 Comparison of bone mineral density and bone mineral content in patients receiving biological (anti-TNF $\alpha$ ) vs. conventional treatment.

Variables	Anti-TNF $\alpha$ treatment			Conventional treatment			<i>p</i> -value
	N	Mean	SD	N	Mean	SD	
L2–L4 BMD	55	1.171	0.161	17	1.193	0.156	0.620
L2–L4 T-score	55	−0.251	1.339	17	−0.047	1.277	0.581
L2–L4 Z-score	55	−0.295	1.316	17	−0.012	1.276	0.438
Total T-score	55	0.311	1.138	17	0.482	1.025	0.581
Total Z-score	55	0.449	1.064	17	0.659	1.030	0.477
BMC	55	2,625.436	515.226	17	2,656.353	442.567	0.824

SD, standard deviation; BMC, bone mineral content; BMD, bone mineral density; Statistical significance assessed using independent samples t-test.

groups and was lower in patients treated with biologics, although the literature indicates a possible increase in OC after anti-TNF $\alpha$  therapy (44, 49).

Furthermore, OC was negatively correlated with SOST in this group of patients, which may suggest that higher SOST activity may be associated with inhibition of osteoblast activity. However, reduced values of these parameters may suggest an imbalance in bone metabolism resulting from chronic inflammation. Marini et al. (50) indicate that treatment with monoclonal antibodies against SOST may promote bone mass restoration, thus preventing bone fractures caused by bone fragility. PTH has been shown to increase calcium reabsorption and inhibit phosphate reabsorption (51).

With regard to PTH, we observed negative correlations between PTH and some DXA parameters, in line with previous reports (52). However, no changes in PTH were found depending on the therapy, which is consistent with some studies (53), although others suggest an increase in OC after anti-TNF $\alpha$  therapy (54). FGF23, synthesized by osteocytes and osteoblasts, may correlate with inflammation and bone turnover (55). Exacerbation of IBD is associated with elevated FGF23 and lower BMD (56). In our study, we observed a negative correlation between FGF23 and BMD in patients treated with anti-TNF $\alpha$ , consistent with previous observations (56). At the same time, its levels did not differ between therapies, and the positive correlation of FGF23 with BMC may indicate secondary, compensatory changes in the hormonal axis (57–59).

The results of our study confirm the presence of bone metabolism abnormalities, which may be present during clinical

remission. Therefore, it is worth considering a multiminer supplement for such patients with IBD (60). Biological treatment did not have a clear effect on most of the bone markers we studied, suggesting a varied response to therapies and multifactorial regulation of bone metabolism in IBD. This points to the need for further studies evaluating the long-term effects of chronic inflammation and the treatment used on the skeletal system, taking into account the clinical stage of the disease and the differences between CD and UC. However, individual conclusions cannot be extrapolated to the entire remission.

## 5 Limitations

Our study also has certain limitations. It was a cross-sectional study, and all biochemical and densitometric measurements were taken at a single point in time, during remission of the disease. Therefore, the results obtained reflect the state of bone turnover during maintenance treatment and do not allow for the assessment of changes over time or for conclusions to be drawn about the impact of therapy. In the future, it would also be useful to include information on the individual clinical data of all participants, including detailed disease activity indices (e.g., the Mayo scale) and a complete history of supplementation. The lack of this information may have been an uncontrolled confounding factor affecting the assessed markers of bone turnover. In addition, the study did not measure reference markers of bone turnover, such as PINP and CTX, due to technical limitations and the availability of laboratory

**TABLE 5** Correlation analysis of bone turnover markers and bone density indices in a group of patients receiving anti-TNF $\alpha$  treatment.

Parameters	L2–L4 BMD	L2–L4 T-score	Total T-score	BMC	DKK1	OPG	OC	OPN	SOST	PTH	FGF23
L2–L4 BMD	-	1.00*	0.68*	0.71*	-0.05	0.03	0.03	0.02	0.05	-0.09	-0.29
L2–L4 T-score	1.00*	-	0.67*	0.71*	-0.05	0.03	0.02	0.03	0.05	-0.09	-0.29
Total T-score	0.68*	0.67*	-	0.67*	-0.19	-0.07	0.13	-0.12	0.10	0.01	-0.23
BMC	0.71*	0.71*	0.67*	-	-0.17	-0.18	0.19	0.14	-0.06	0.04	-0.36*
DKK1	-0.05	-0.05	-0.19	-0.17	-	0.41*	-0.21	-0.05	-0.03	0.07	0.15
OPG	0.03	0.03	-0.07	-0.18	0.41*	-	0.04	-0.04	0.23	0.01	0.21
OC	0.03	0.02	0.13	0.19	-0.21	0.04	-	-0.23	-0.43*	0.01	-0.21
OPN	0.02	0.03	-0.12	0.14	-0.05	-0.04	-0.23	-	0.03	0.18	0.10
SOST	0.05	0.05	0.10	-0.06	-0.03	0.23	-0.43*	0.03	-	0.09	0.11
PTH	-0.09	-0.09	0.01	0.04	0.07	0.01	0.01	0.18	0.09	-	0.05
FGF23	-0.29	-0.29	-0.23	-0.36*	0.15	0.21	-0.21	0.10	0.11	0.05	-

\*p < 0.05.

BMC, bone mineral content; BMD, bone mineral density; DKK1, Dickkopf-related protein 1; OPG, osteoprotegerin; OC, osteocalcin; OPN, osteopontin; SOST, sclerostin; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23, Spearman’s rank correlation coefficient was used due to non-normal distribution of biochemical markers.

**TABLE 6** Correlation analysis of bone turnover markers and bone density indices in a group of conventional treatment.

Parameters	L2–L4 BMD	L2–L4 T-score	Total T-score	BMC	DKK1	OPG	OC	OPN	SOST	PTH	FGF23
L2–L4 BMD	-	1.00*	0.86*	0.36	-0.34	-0.07	0.02	-0.33	-0.11	0.30	-0.15
L2–L4 T-score	1.00*	-	0.87*	0.36	-0.34	-0.06	0.02	-0.31	-0.12	0.27	-0.18
Total T-score	0.86*	0.87*	-	0.30	-0.25	-0.16	-0.27	-0.37	-0.17	0.22	-0.21
BMC	0.36	0.36	0.30	-	-0.01	0.16	0.03	0.15	0.48	-0.09	-0.59*
DKK1	-0.34	-0.34	-0.25	-0.01	-	0.10	-0.11	0.07	-0.04	0.08	-0.01
OPG	-0.07	-0.06	-0.16	0.16	0.10	-	0.15	0.42	0.11	-0.08	0.24
OC	0.02	0.02	-0.27	0.03	-0.11	0.15	-	0.04	-0.15	0.13	-0.01
OPN	-0.33	-0.31	-0.37	0.15	0.07	0.42	0.04	-	0.05	-0.42	-0.34
SOST	-0.11	-0.12	-0.17	0.48	-0.04	0.11	-0.15	0.05	-	0.61*	-0.21
PTH	0.30	0.27	0.22	-0.09	0.08	-0.08	0.13	-0.42	0.61*	-	0.31
FGF23	-0.15	-0.18	-0.21	-0.59*	-0.01	0.24	-0.01	-0.34	-0.21	0.31	-

\*p < 0.05.

BMC, bone mineral content; BMD, bone mineral density; DKK1, Dickkopf-related protein 1; OPG, osteoprotegerin; OC, osteocalcin; OPN, osteopontin; SOST, sclerostin; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23, Spearman’s rank correlation coefficient was used due to non-normal distribution of biochemical markers.

methods. This limits the ability to directly compare the results obtained with other studies using these standard parameters.

## 6 Conclusions

Our results indicate that the choice of anti-TNF $\alpha$  therapy should not be based on the expected differential effects of individual drugs on bone metabolism. Decisions regarding biological therapy should therefore continue to focus primarily on controlling disease activity, while bone status requires parallel and independent assessment and monitoring. In this context, bone turnover markers can serve as complementary tools for identifying patients who require more intensive monitoring or additional supportive interventions to prevent long-term bone complications.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by Bioethics Committee of the Medical University of Lublin (KE-0254/68/2015) and Bioethics Committee of Rzeszów University (23/04/2016). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

SJ-C: Data curation, Investigation, Project administration, Visualization, Writing – original draft, Writing – review & editing. PK: Investigation, Methodology, Writing – original draft, Writing – review & editing. DP: Data curation, Investigation, Writing – original draft, Writing – review & editing. AS-D: Data curation, Visualization, Writing – original draft, Writing – review & editing. WG: Writing – original draft, Writing – review & editing. RR: Writing – original draft, Writing – review & editing. JS: Writing – original draft, Writing – review & editing. RF: Conceptualization, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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## Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmed.2026.1729584/full#supplementary-material>

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