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Serum fibroblast growth factor 19 level correlates inversely with clinical and endoscopic activity of inflammatory bowel disease

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Conflict of interest
None declared

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Abstract

Background. Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a chronic condition with relapsing–remitting course. Diarrhea and abdominal pain are the most common IBD symptoms. Fibroblast growth factor 19 (FGF19) is an endocrine factor that inhibits hepatic bile acid production and may be used as a diagnostic marker for bile acid malabsorption.

Objectives. To assess serum FGF19 levels in active and inactive phases of IBD and find a potential correlation between FGF19 and disease activity.

Materials and methods. Fasting serum FGF19 levels were measured in 105 IBD patients (47 UC patients, 41 CD patients without previous ileocecal resection (NR-CD), 17 CD patients after ileocecal resection (IR-CD), and 17 control subjects). The disease activity was assessed using clinical, laboratory and endoscopic criteria.

Results. Inverse correlations were found between FGF19 level and intensity of diarrhea (in UC), abdominal pain intensity (in UC and IR-CD) and inflammatory markers (in UC and IR-CD). Moreover, FGF19 concentration was inversely correlated with clinical and endoscopic activity indices in UC and CD.

Conclusions. Fluctuations in FGF19 level related to clinical and endoscopic activity of UC and CD revealed a clear pattern of higher values in remission than in active disease phases. Fibroblast growth factor 19 may serve as a potential diagnostic biomarker and constitute a new therapeutic target in IBD.

Key words: disease activity, fibroblast growth factor 19, inflammatory bowel disease

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Background

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a chronic condition with relapsing–remitting course. The not fully understood pathogenesis of IBD encompasses genetic predisposition, immune system response disturbances and environmental factors.[1,2]

Bile acids (BAs) play a crucial role in regulating various gastrointestinal functions, including secretion, motility, immune response, intestinal mucosa integrity, and visceral sensitivity.[3] During absorption in the terminal ileum, BAs activate farnesoid X receptor (FXR) and promote the transcription of fibroblast growth factor 19 (FGF19),[4] a human factor with endocrine properties. Fibroblast growth factor 19 is secreted into the enterohepatic circulation, and after reaching the liver, it inhibits hepatic BA production.[5] Bile acid malabsorption (BAM) leads to a disturbance in FGF19 expression, resulting in elevated BA synthesis. Therefore, lower FGF19 level has been suggested as a diagnostic marker for BAM.[6]

Due to decreased FGF19 expression, BA production in the liver is enhanced, and more unabsorbed BAs enter the colon lumen, leading to BA diarrhea and abdominal pain deterioration.[7–10] In IBD patients, ileal resection is not the only factor leading to impaired FGF19 secretion. Recent research indicates that inflammatory cytokines decrease FXR expression, affecting FGF19 production. Moreover, FXR agonists exhibit anti-inflammatory effects.[11] Given the critical role of FGF19 in modulating gastrointestinal function via BA synthesis regulation and its interactions with FXR exerting an immunomodulatory effect, this factor is emerging as a potential new diagnostic and therapeutic target in IBD.

Objectives

This study aimed to assess fasting serum FGF19 levels during active and inactive phases of IBD and explore the correlations between FGF19 level and intensity of the main IBD symptoms, indices of IBD activity and inflammatory markers.

Materials and methods

Study participants

In total, 113 IBD patients were enrolled in the study, with an IBD diagnosis confirmed using histological examination. The exclusion criteria were: other bowel diseases, chronic liver diseases (except single cysts and steatosis), diabetes, body mass index (BMI) >30 kg/m^2, hyperlipidemia treatment, malignancies, alcohol dependence syndrome, and a history of abdominal surgical procedures (except appendectomy and procedures related to IBD, such as ileocecal resection). The control group consisted of 17 healthy volunteers, including 9 men and 8 women, with a median age of 28 (27–30) years and without any gastroenterological symptoms.

Eight patients were excluded from the final analyses (2 due to missing data, 2 due to outlier test results and 4 due to discrepancies between the clinical status and the results of additional tests). Among the 105 patients involved in the final analyses, 3 subgroups were distinguished: UC (n = 47), CD without ileocecal surgery in the past (NR-CD) (n = 41) and CD after ileocecal resection (IR-CD) (n = 17).

The study was approved by the Ethics Committee of Wroclaw Medical University, Poland (approval No. KB-700/2020). Written informed consent was obtained from all participants before study enrollment.

Assessment of disease activity

All enrolled patients underwent a detailed clinical interview based on a questionnaire to assess their symptoms. Stool type was assessed using the Bristol Stool Form Scale (BSFS), diarrhea was defined as having a minimum of 3 bowel movements per day, with loose or watery stools, and pain intensity was assessed using the visual analogue scale (VAS).

Standard laboratory tests of blood, urine and stool were also conducted, though colonoscopy and enterography were only undertaken in subjects with clinical indications for such examinations. The clinical and endoscopic activity of IBD was assessed based on validated scales and indices, with the Rachmilewitz index and the Mayo Endoscopic Score used in UC patients, and Crohn's disease activity index (CDAI) and the simple endoscopic score for CD (SES-CD) applied in CD patients. Patients were classified as having an inactive phase of the disease based on fecal calprotectin level lower than 200 μg/g, 0–4 points in the Rachmilewitz index and 0–2 points in the Mayo Endoscopic Score in UC patients, and CDAI score lower than 200 points and SES-CD score lower than 7 points in CD patients. All other subjects were assigned to the active subgroup. Crohn's disease patients with active changes in enterography were automatically assigned to the active phase subgroup.

In the control group, a detailed interview identified exclusion criteria, and fasting serum FGF19 and fecal calprotectin levels were tested.

Quantitative evaluation of serum FGF19 and fecal calprotectin levels

Participants provided a fasting blood sample, taken before 9 AM, and a stool sample, which were stored at –80°C until analysis. The quantitative evaluation of serum FGF19 [pg/mL] and fecal calprotectin [μg/g] levels used immunoenzymatic methods: human FGF-19 ELISA (BioVendor, Laboratorni Medicina a.s., Brno, Czech Republic) and EK-CAL (Bühlmann Laboratories, Schönenbuch, Switzerland), respectively.

Statistical analyses

Individual values were presented as numbers with percentages, mean with standard deviation (±SD), or median with 1st and 3rd quartiles (Q1–Q3). When the number of observations was below 10, the normality of the data distribution was not checked and was considered non-normal. When the number of observations was between 10 and 50, the normality of the data distribution was determined using the Shapiro–Wilk test. The Kolmogorov–Smirnov test with Lilliefors correction was used when the number of observations was equal to or greater than 50.

To compare categorical variables, the assumption of expected frequencies was assessed for values <5 in a maximum of 20% of cell fields for the χ^2 test. Pearson's χ^2 test of independence without Yates's continuity correction was used if the assumption was met. Otherwise, Fisher's exact test was used.

Quantitative variables with a normal distribution were assessed for homogeneity of variance using Levene's test. Student's t-test was then employed if there were no significant differences. Otherwise, a t-test with independent variances was conducted. The Mann–Whitney U test (MWU) was used to compare quantitative variables with non-normal distribution. Kruskal–Wallis test followed by Dunn's multiple comparisons were employed to compare quantitative variables in more than 2 groups.

Spearman's rank correlation (r) or Kendall's Tau-c correlation (Tau-c) were calculated to test associations between variables. The assumptions of normal distribution and multicollinearity required for Pearson's linear correlation were unmet. Monotonicity, the strength of monotonicity, function return, and, whenever possible, the sign of the derivative for Spearman's correlation were assessed using the original data. The involvement of tied ranks was examined, defined as the proportion of observations sharing the same rank, regardless of the number of unrelated ranks. When the involvement of tied ranks was significant (20% of tied ranks), Kendall's correlation was employed. The Bonferroni correction was incorporated into the family of hypotheses.

Results

Group characteristics

The detailed characteristics of the patient subgroups are presented in Table 1. There were no significant differences between the subgroups with respect to sex, age, BMI, and disease duration. The whole group consisted of 68 men (65%) and 37 women (35%) with a median age of 33 (27–41) years and disease duration of 63 (13–132) months.

The clinical and endoscopic disease activity indices and data on disease localization in CD patients are given in Table 1. As expected, patients with active UC had diarrhea more frequently than those with inactive UC. Patients with active CD also experienced diarrhea more often, though the difference was not statistically significant. During flares, patients with CD and UC reported higher levels of abdominal pain, though this was only statistically significant in NR-CD. Comparing the frequency of medications used in active and inactive phases, only steroids were administered more frequently during UC exacerbation (Table 1).

To verify whether other variables affected the concentration of FGF19, its levels were compared with respect to the duration of the disease and used medications. No statistically significant differences were found (Table 2,3).

Active UC patients exhibited significantly higher inflammatory parameters, lower hemoglobin levels, and decreased total cholesterol and albumin levels than inactive UC patients. Such alterations were not observed in CD subgroups. In patients with NR-CD, the only difference between the exacerbation and remission phases concerned fecal calprotectin levels. All patients also underwent testing for serum BA levels. However, no significant differences were found between active and inactive phases of the disease in particular subgroups with respect to that parameter (Table 4).

Serum FGF19 level in particular subgroups

Lenicek et al.[12] established FGF19 cutoff value below 60 pg/mL to identify patients with BAM. Therefore, the same cutoff was used in this study. Fibroblast growth factor 19 values below 60 pg/mL occurred in 16 patients, including 7 with active UC, 1 with active NR-CD, 2 with inactive NR-CD, and 6 with active IR-CD. An increased FGF19 level was found in 11 patients, including 1 with active UC, 4 with inactive UC, 4 with active NR-CD, and 2 with inactive NR-CD.

Fluctuations in FGF19 level related to the type of disease and its activity were observed. The median FGF19 level in active UC was significantly lower compared to inactive UC. However, there was no significant difference in FGF19 level between active UC and controls. Moreover, the median FGF19 level in inactive UC was higher than in the control group (Fig. 1).

No statistically significant differences in FGF19 level were observed between active and inactive NR-CD subgroups or the controls. Patients with active IR-CD had significantly lower FGF19 than those with inactive IR-CD. However, there was no difference between the subgroups and the control group. Moreover, median FGF19 in active IR-CD was significantly lower than in active and inactive NR-CD (Fig. 2).

The median serum FGF19 levels in CD with respect to disease localization and activity are presented in Table 5.

Table 1. Detailed characteristics of the studied patients' subgroups

Variable	Active UC (Group 1)	Inactive UC (Group 2)	Active NR-CD (Group 3)	Inactive NR-CD (Group 4)	Active IR-CD (Group 5)	Inactive IR-CD (Group 6)	Statistical test 1 vs 2	Statistical test 3 vs 4	Statistical test 5 vs 6
Group characteristics									
n	31	16	25	16	11	6	–	–	–
Men, n (%)	23 (74.2)	9 (56.3)	16 (64.0)	9 (56.3)	7 (63.6)	4 (66.7)	χ^2 test = 1.56 df = 1 p = 0.211	χ^2 test = 0.25 df = 1 p = 0.619	p = 1.000*
Age, median (Q1–Q3)	36 (26–40)	34 (24–46)	31 (27–34)	30 (26–40)	33 (27–45)	41 (35–47)	z = –0.06 p = 0.955**	z = –0.20 p = 0.841**	z = –1.31 p = 0.191**
Duration of the disease [months], median (Q1–Q3)	18 (2–60)	58 (13–108)	53 (12–96)	108 (27–159)	132 (108–204)	186 (120–216)	z = –1.65 p = 0.099**	z = –1.55 p = 0.121**	z = –0.76 p = 0.449**
BMI, mean ±SD	21.79 ±3.58	22.24 ±4.20	21.87 ±4.01	22.51 ±3.09	21.99 ±4.23	23.91 ±2.08	t = –0.38 df = 45 p = 0.704#	t = –0.54 df = 39 p = 0.592#	z = –1.06 p = 0.291**
Disease localization (ileitis/ileocolitis/colitis)	–	–	5/13/6	5/8/3	2/9/0	1/5/0	–	–	–
Disease activity index									
CDAI, median (Q1–Q3)	–	–	231.10 (164.66–415.60)	86.43 (42.89–110.03)	337.24 (196.29–364.96)	66.75 (31.85–199.26)	–	z = 4.26 p < 0.001**	z = 2.46 p = 0.014**
SES-CD, median (Q1–Q3)	–	–	77 (3–11)	33 (2–6)	88 (4–11)	55 (2–9)	–	t = 2.47, df = 20 p = 0.023##	z = 1.22 p = 0.221**
Rachmilewitz index, median (Q1–Q3)	9.0 (5–12)	1.5 (0–4)	–	–	–	–	z = 4.16 p < 0.001**	–	–
Mayo Encoscopic Score, median (Q1–Q3)	3 (2–3)	0 (0–1)	–	–	–	–	z = 4.47 p < 0.001**	–	–
Symptoms									
Diarrhea, n (%)	19 (61.3)	2 (12.5)	10 (40.0)	3 (18.9)	7 (63.6)	1 (16.7)	p = 0.002*	p = 0.187*	p = 0.131*
BSFS, median (Q1–Q3)	6 (5–7)	4 (3–5)	4 (4–6)	5 (4–6)	6 (5–7)	6 (4–6)	z = 3.59 p < 0.001**	t = –0.53 df = 39 p = 0.596#	z = 0.79 p = 0.427**
Number of liquid stools per week, median (Q1–Q3)	35 (3–72)	0 (0–6)	7 (1–28)	23 (1–13)	10 (6–20)	7 (5–11)	z = 3.80 p < 0.001**	z = 0.90 p = 0.367**	z = 0.51 p = 0.608**
Abdominal pain in VAS per week, median (Q1–Q3)	4.2 (1.7–5.5)	0.4 (0–3.5)	4.6 (2.6–7.3)	0 (0–0)	6.8 (4.8–7.7)	0 (0–1.2)	z = 2.56 p = 0.010**	z = 4.97 p < 0.001**	z = 2.09 p = 0.037**
Abdominal bloating, n (%)	15 (48.4)	11 (68.8)	17 (68.0)	10 (62.5)	8 (72.7)	5 (83.3)	χ^2 test = 1.77 df = 1 p = 0.813	χ^2 test = 0.13 df = 1 p = 0.717	p = 1.000*
Treatment									
Mesalamine, n (%)	31 (100)	15 (93.8)	17 (68.0)	11 (68.8)	6 (54.5)	3 (50.0)	p = 0.340*	χ^2 test = 0.00 df = 1, p = 0.959	p = 1.000*
Steroids, n (%)	23 (77.4)	3 (18.8)	12 (48.0)	3 (18.8)	5 (45.5)	0 (0)	p < 0.001*	p = 0.097*	p = 0.102*
Azathioprine, n (%)	9 (29.0)	3 (18.8)	11 (44.0)	5 (31.3)	2 (18.2)	0 (0)	p = 0.505*	χ^2 test = 0.67 df = 1, p = 0.414	p = 0.515*
Biological treatment, n (%)	1 (3.2)	2 (12.5)	2 (8.0)	3 (18.8)	0 (0)	0 (0)	p = 0.264*	p = 0.362*	–
Antibiotics, n (%)	8 (25.8)	3 (18.8)	8 (32.0)	1 (6.3)	4 (36.4)	0 (0)	p = 0.725*	p = 0.066*	p = 0.237*
Probiotics, n (%)	6 (19.4)	2 (12.5)	3 (12.0)	2 (12.5)	3 (27.3)	2 (33.3)	p = 0.697*	p = 1.000*	p = 1.000*

UC – ulcerative colitis; NR-CD – Crohn's disease without ileocecal surgery in the past; IR-CD – Crohn's disease after ileocecal resection in the past; BMI – body mass index; CDAI – Crohn's disease activity index; SES-CD – simple endoscopic score for Crohn's disease; BSFS – Bristol Stool Form Scale; VAS – visual analogue scale; Q1 – 1st quartile; Q3 – 3rd quartile; SD – standard deviation; χ^2 test – Pearson's χ^2 test of independence without Yates's continuity correction; df – degrees of freedom; *Fisher's exact test; z – value of the Mann–Whitney U test statistic; **Mann–Whitney U test; t – value of the test statistic; #Student's t-test; ##t-test with independent variance estimation. The Bonferroni correction was incorporated into the family of hypotheses. The statistical significance level was set in group characteristics part at p < 0.013, in disease activity index part at p < 0.025, in symptoms part at p < 0.010, and in treatment part as p < 0.008.

Table 2. Median serum FGF19 level depending on disease duration

Median serum FGF19 [pg/mL] level depending on disease duration			
<2 years	2–10 years	>10 years	p-value (Kruskal–Wallis test)
160.70 (101.00–223.55)	125.12 (70.50–175.50)	145.30 (81.10–181.85)	p = 0.136, H = 3.9, df = 2

FGF19 – fibroblast growth factor 19; H – value of the test statistic of the Kruskal–Wallis test; df – degrees of freedom.

Table 3. Median serum FGF19 level depending on used medications

Median serum FGF19 [pg/mL] level depending on medication taken		
Medication		p-value (Mann–Whitney U-test)
With steroids 120.30 (66.84–163.65)	Without steroids 164.68 (97.56–200.59)	z = –2.44, p = 0.015
With antibiotics 107.80 (52.80–199.80)	Without antibiotics 159.96 (91.41–187.90)	z = –1.63, p = 0.103
With probiotics 133.80 (63.69–181.85)	Without probiotics 158.58 (88.45–191.28)	z = –1.28, p = 0.199
With vitamin D 147.50 (108.00–181.85)	Without vitamin D 145.90 (81.10–187.90)	z = 0.42, p = 0.677

FGF19 – fibroblast growth factor 19; z – value of the Mann–Whitney U test. The Bonferroni correction was incorporated into the family of hypotheses. The statistical significance level was set at $p < 0.013$.

Table 4. Laboratory test results of the studied patients' subgroups

Variable	Active UC (Group 1)	Inactive UC (Group 2)	Active NR-CD (Group 3)	Inactive NR-CD (Group 4)	Active IR-CD (Group 5)	Inactive IR-CD (Group 6)	Statistical test 1 vs 2	Statistical test 3 vs 4	Statistical test 5 vs 6
Hemoglobin [g/dL], mean ±SD	11.6 ±1.6	14.1 ±1.9	12.3 ±2.5	13.2 ±2.2	12.5 ±1.9	14.8 ±1.4	t = –4.73 df = 45 p < 0.001#	t = –1.25 df = 39 p = 0.219#	z = –2.26 p = 0.024*
CRP [mg/L], median (Q1–Q3)	16.6 (5.2–46.8)	1.8 (0.9–6.9)	8.0 (4.8–35.0)	4.2 (1.3–9.5)	78.0 (2.3–22.2)	1.2 (0.8–1.9)	z = 3.54 p < 0.001*	z = 2.07 p = 0.038*	z = 2.76 p = 0.006*
Fecal calprotectin [µg/g], mean ±SD	1528.7 ±673.5	78.9 ±61.2	1499.7 ±678.7	78.4 ±48.5	730.8 ±575.6	68.1 ±29.1	t = 10.86 df = 26 p < 0.001##	t = 9.97 df = 23 p < 0.001##	z = 1.91 p = 0.056*
Total cholesterol [mg/dL], median (Q1–Q3)	135.0 (122.0–168.0)	192.5 (169.0–228.5)	150.0 (139.0–187.0)	171.0 (138.5–197.0)	120.0 (99.0–163.0)	172.5 (159.0–198.0)	z = 3.45 p < 0.001*	t = –0.76 df = 39 p = 0.452#	z = –2.26 p = 0.024*
LDL [mg/dL], mean ±SD	85.1 ±27.7	115.4 ±36.3	86.4 ±30.5	97.6 ±40.3	62.4 ±24.5	97.0 ±23.9	t = –3.16 df = 44 p = 0.003#	t = –1.01 df = 39 p = 0.318#	z = –2.46 p = 0.014*
HDL [mg/dL], mean ±SD	41.3 ±13.9	53.6 ±15.0	51.9 ±13.5	55.4 ±16.9	43.1 ±12.7	54.0 ±11.9	t = –2.69 df = 44 p = 0.009#	t = –0.73 df = 39 p = 0.469#	z = –1.46 p = 0.144*
Triglycerides [mg/dL], median (Q1–Q3)	104.5 (68.0–125.0)	88.5 (65.0–122.0)	88.0 (70.5–105.5)	80.0 (66.5–115.5)	99.0 (62.0–108.0)	110.0 (108.0–136.0)	z = 1.02 p = 0.310*	z = 0.08 p = 0.934*	z = –1.71 p = 0.087*
Albumin [mg/dL], mean ±SD	3.5 ±0.6	4.3 ±0.5	3.9 ±0.5	4.1 ±0.5	3.6 ±0.5	4.3 ±0.2	t = –4.75 df = 44 p < 0.001#	t = –1.49 df = 39 p = 0.143#	z = –2.67 p = 0.008*
Bile acids [µmol/L], median (Q1–Q3)	1.3 (1.0–2.7)	1.7 (1.0–2.8)	1.6 (1.2–2.5)	1.8 (1.3–3.1)	2.5 (1.4–4.7)	2.6 (1.9–3.6)	z = –0.45 p = 0.659*	z = –0.58 p = 0.566*	z = 0.00 p = 1.000*

UC – ulcerative colitis; NR-CD – Crohn's disease without ileocecal surgery in the past; IR-CD – Crohn's disease after ileocecal resection in the past; CRP – C-reactive protein; LDL – low-density lipoprotein; HDL – high-density lipoprotein; SD – standard deviation; Q1 – 1st quartile; Q3 – 3rd quartile; z – value of the Mann–Whitney U test statistic; *Mann–Whitney U test; t – value of the test statistic; df – degrees of freedom; #Student's t-test; ##t-test with independent variance estimation. The Bonferroni correction was incorporated into the family of hypotheses. The statistical significance level was set at $p < 0.006$.

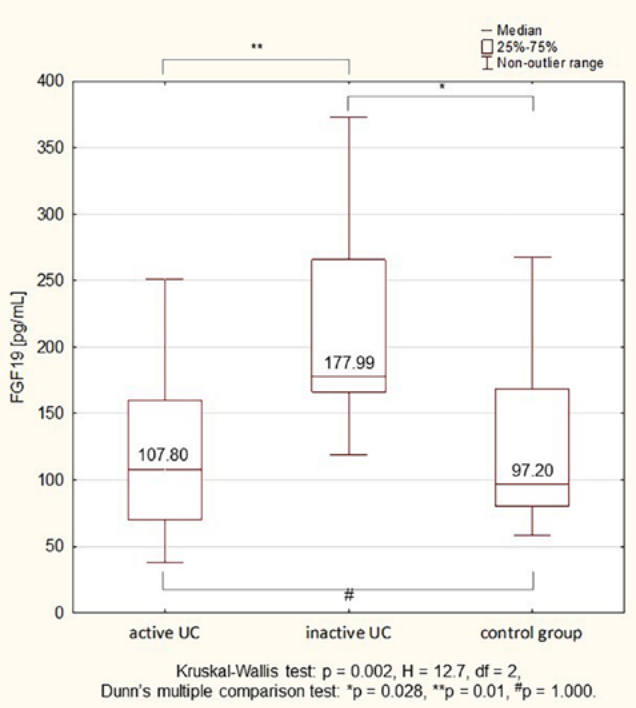

Fig. 1. Median fibroblast growth factor 19 (FGF19) levels in patients with ulcerative colitis (UC)

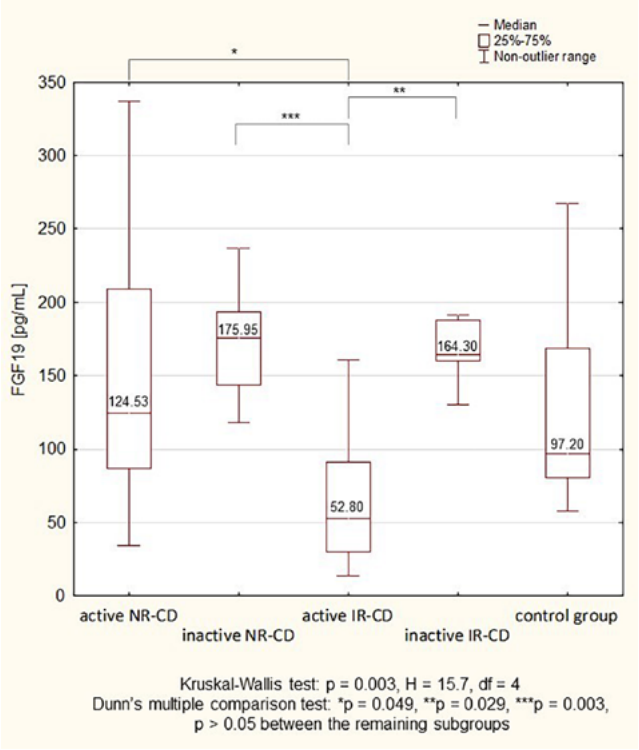

Fig. 2. Median fibroblast growth factor 19 (FGF19) levels in patients with Crohn's disease (CD)

Table 5. Median serum FGF19 level in Crohn's disease patients with respect to disease localization of the disease and activity

Crohn's disease localization and activity	n	FGF19 [pg/mL] median (Q1–Q3)
Active ileitis	8	76.64 (32.35–164.70)
Inactive ileitis	6	136.44 (110.80–175.50)
Active ileocolitis	21	140.81 (78.10–165.30)
Inactive ileocolitis	13	164.05 (97.56–186.23)
Active colitis	6	114.94 (83.70–394.80)
Inactive colitis	3	336.80 (83.90–510.40)

FGF19 – fibroblast growth factor 19; Q1 – 1st quartile; Q3 – 3rd quartile.

Correlations of FGF19 level with specific variables

A strong inverse correlation was observed between FGF19 and C-reactive protein (CRP) levels in the IR-CD patient subgroup, though not in the NR-CD nor UC subgroups. Regarding fecal calprotectin, FGF19 level was inversely correlated with that marker in UC patients, while no correlation was identified in CD patients (Table 6).

Inverse correlations between fasting serum FGF19 and measures of diarrhea severity, including BSFS and the number of liquid stools per week, were found in the UC patients. However, no correlation between FGF19 level and diarrhea severity score was demonstrated in CD patients. Interestingly, abdominal pain intensity correlated inversely with FGF19 level in UC and IR-CD patients (Table 6).

Inverse correlations were found between FGF19 and clinical and endoscopic activity indices, including the Rachmilewitz activity index (Fig. 3), the Mayo Endoscopic Score (Fig. 4), CDAI (Fig. 5), and SES-CD (Fig. 6, Table 7).

Discussion

The results of the current study demonstrate fluctuations in FGF19 levels related to the clinical and endoscopic activity of UC and CD, with a clear pattern of lower values in the active phase than in remission. Previous studies have reported that in UC patients serum FGF19 level was elevated[13] or in a range[12] comparable to healthy controls. Another study showed similar fluctuations in FGF19 level based on UC activity, with higher FGF19 in remission and lower in active disease, but the differences were not statistically significant.[14] The larger sample size in the current study probably contributed to achieving statistical significance.

Decreased FGF19 in active UC correlated inversely with fecal calprotectin as a marker of intestinal inflammation. Pro-inflammatory cytokines, secreted during flares, disrupt the regulation of the FXR-FGF19 axis through inhibition of the expression of gene encoding apical sodium-dependent bile acid transporter (ASBT), which is responsible for the active BA absorption.[15] A previous study

Table 6. Correlation of serum FGF19 level with individual variables

Variables	UC patients		NR-CD patients		IR-CD patients	
	correlation coefficient	p-value	correlation coefficient	p-value	correlation coefficient	p-value
FGF19 and BSFS	Tau-c = –0.24	0.022	Tau-c = –0.03	0.759	Tau-c = –0.15	0.392
FGF19 and number of liquid stools per week	Tau-c = –0.23	0.026	Tau-c = –0.03	0.711	Tau-c = –0.22	0.230
FGF19 and abdominal pain intensity	Tau-c = –0.22	0.043	Tau-c = –0.08	0.462	Tau-c = –0.48	0.008
FGF19 and CRP	r = –0.25	0.098	r = –0.22	0.166	r = –0.59	0.012
FGF19 and fecal calprotectin	r = –0.34	0.046	Tau-c = –0.17	0.176	r = –0.47	0.088

Involvement of tied ranks in UC patients: FGF19 (0%), BSFS (98%), number of liquid stools per week (60%), abdominal pain intensity (47%), CRP (0%), fecal calprotectin (19%); in NR-CD patients: FGF19 (0%), BSFS (100%), number of liquid stools per week (61%), abdominal pain intensity (41%), CRP (0%), fecal calprotectin (42%); in IR-CD patients: FGF19 (0%), BSFS (88%), number of liquid stools per week (56%), abdominal pain intensity (41%), CRP (0%), fecal calprotectin (0%). UC – ulcerative colitis; NR-CD – Crohn's disease without ileal surgery in the past; IR-CD – Crohn's disease after ileocecal resection in the past; FGF19 – fibroblast growth factor 19; BSFS – Bristol Stool Form Scale, CRP – C-reactive protein; r – Spearman's rank correlation coefficient; Tau-c – Kendall Tau-c correlation coefficient.

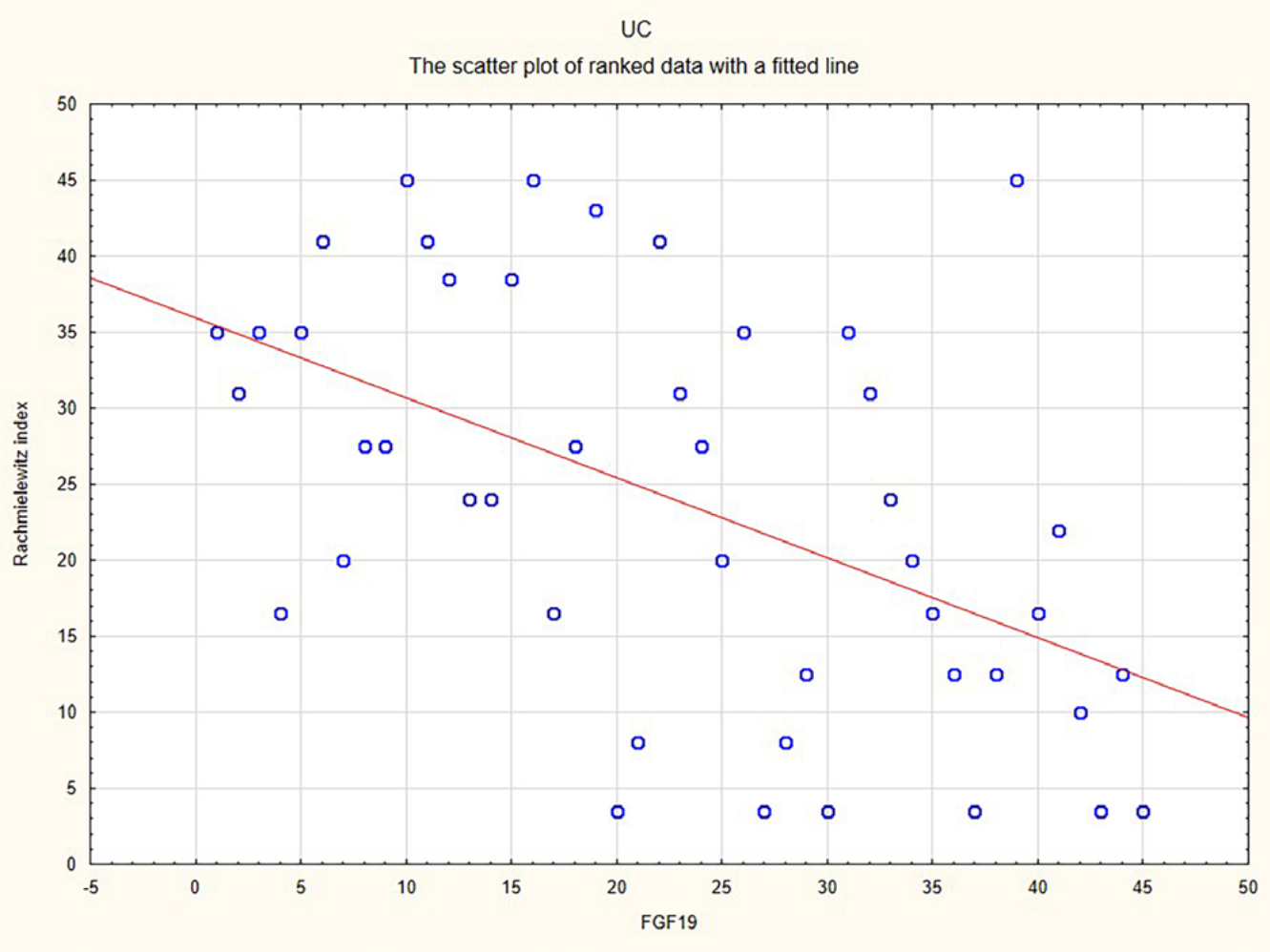

Fig. 3. An inverse correlation between serum fibroblast growth factor 19 (FGF19) and Rachmilewitz index in ulcerative colitis (UC) patients; Tau-c = –0.37, $p < 0.001$

Tau-c – Kendall Tau-c correlation coefficient.

demonstrated reduced ASBT expression in descending colon tissue samples from patients with active UC compared to healthy individuals.[16] Moreover, inflammatory cytokines may directly diminish FXR activation, subsequently decreasing FGF19 expression.[11]

Another factor affecting FGF19 fluctuations may be related to IBD treatment, in particular steroids used for flares, with available data suggesting that steroid therapy is associated with decreased FXR activation.[11] Potentially, the enhancement of FGF19 production in IBD remission

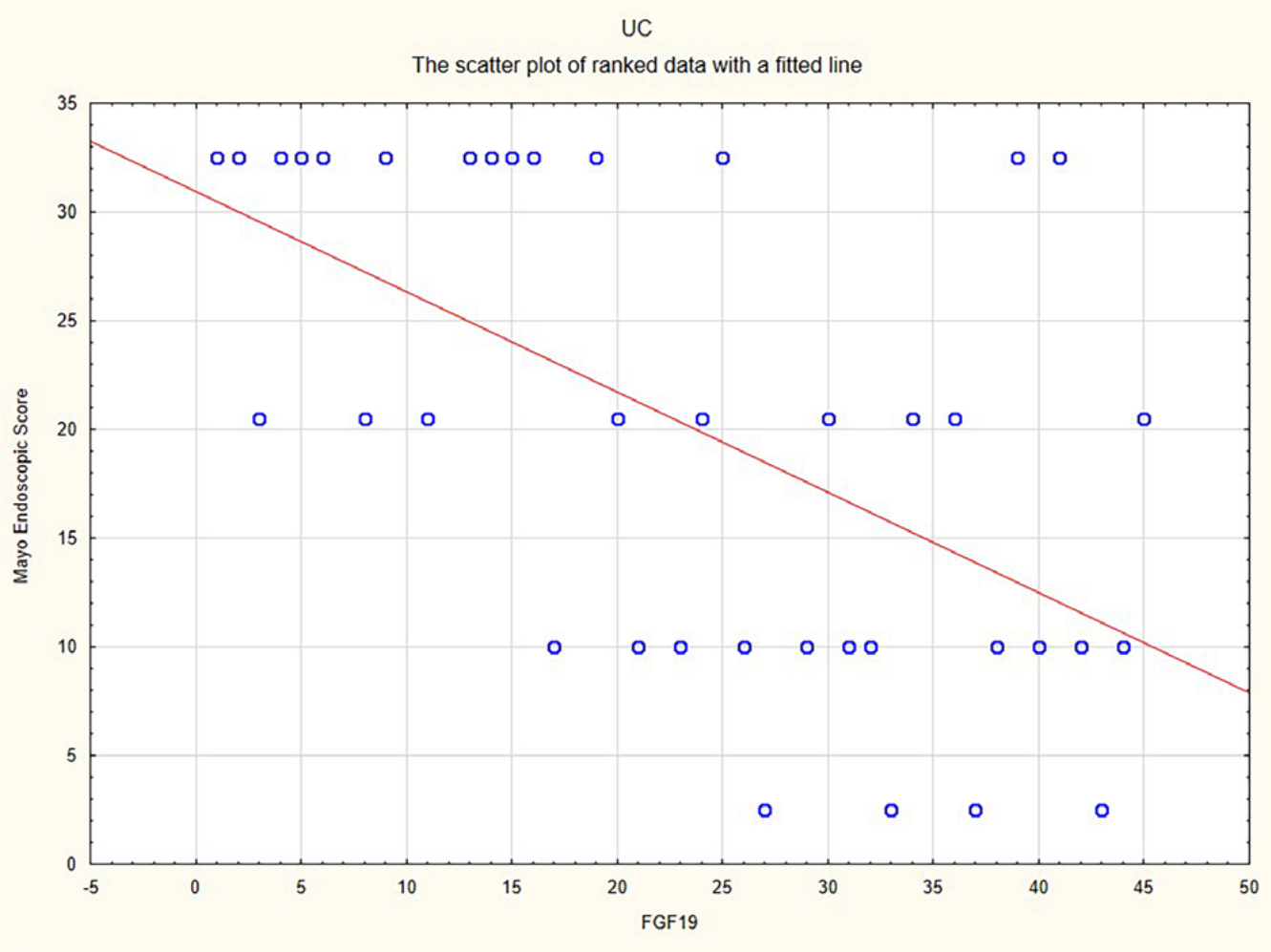

Fig. 4. An inverse correlation between serum fibroblast growth factor 19 (FGF19) and Mayo Endoscopic Score in ulcerative colitis (UC) patients; Tau-c = –0.43, $p < 0.001$

Tau-c – Kendall Tau-c correlation coefficient.

may be influenced by a post-steroid therapy effect since corticosteroids, besides their anti-inflammatory effect, enhance BA absorption and stimulate ASBT expression.[17] However, steroid use was not associated with lower FGF19 concentrations in the current study.

Furthermore, deficiency of nutritional components and vitamins in the diet can lead to reduced activation of receptors other than FXR that participate in the regulation of FGF19 expression, such as vitamin D receptor, retinoid X receptor and pregnane X receptor.[18] In addition, the shorter transit time during flares and the consequent malabsorption may also contribute to BAM.[14]

In this study, 26.7% of patients with active UC had FGF19 level below 60 pg/mL, corresponding to BAM. Lower FGF19 level can lead to enhanced BA production and symptom aggravation.[19] Indeed, we demonstrated a negative correlation between FGF19 level, BSFS, number of liquid stools, and abdominal pain intensity.

The analysis of FGF19 in CD patients was more complex due to the different disease localizations and anatomical alterations caused by ileocecal resection.

In patients with NR-CD, we did not observe fluctuations in FGF19 level related to disease activity. Moreover, this subgroup did not demonstrate any correlation between FGF19 level and inflammatory parameters or the intensity of the main symptoms. Most NR-CD patients had ileocolonic localization of the disease, as in the study by Wilson et al.,[20] who also reported no significant difference in FGF19 level between active and inactive NR-CD subjects.

Based on previous reports that CD patients with colitis only had comparable FGF19 level with healthy controls and showed no fluctuations in FGF19 level depending on disease activity,[7,12] colonic involvement in patients with NR-CD could affect the results.

When analyzing the FGF19 level in relation to disease localization, the lowest concentrations were observed in ileitis, with a trend towards lower values during the active phase. Previously, reduced ASBT expression was shown in ileal tissue samples from CD patients compared to healthy controls.[16] Earlier reports also found that CD patients with ileitis or after ileocecal resection were

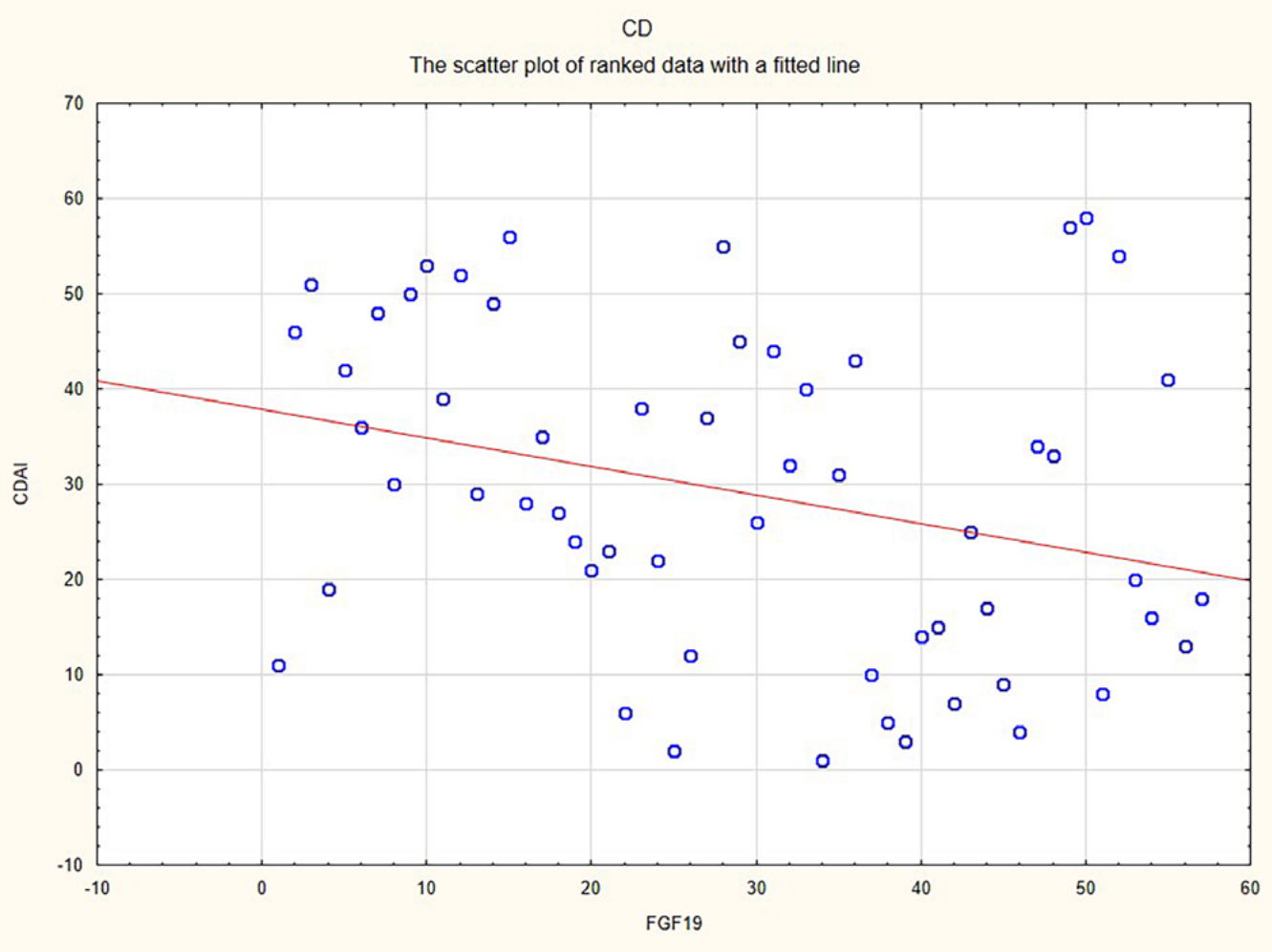

Fig. 5. An inverse correlation between serum fibroblast growth factor 19 (FGF19) and Crohn's disease (CD) activity index in CD patients; r = –0.29, p = 0.026

r – Spearman's rank correlation coefficient.

characterized by lower FGF19 levels,[12,13,21] consistent with our results.

In the current study, the lowest FGF19 levels were observed in active IR-CD patients, but patients with inactive IR-CD were characterized by higher FGF19 levels. This finding suggests that ileocecal resection is not the only determinant of reduced FGF19 level. The process of active inflammation seems to be important in this case. In that subgroup, we observed a strong negative correlation of FGF19 with CRP. Lyutakov et al.[22] did not confirm a correlation between FGF19 and CRP in IBD patients. However, Nolan et al.[7] found a negative correlation between serum FGF19 and CRP in NR-CD patients with ileitis. The evidence confirms that patients with active IBD are more likely to have BAM than those in remission.[23] In this study, 54.5% of patients with active IR-CD had FGF19 values pointing to BAM.

Previous studies have shown inverse correlations between FGF19, BSFS and stool frequency among patients with CD.[7,22] However, such a correlation was not found in the current study, probably due to the limited sample size. Although FGF19 level was related to disease activity in the examined IR-CD patients, the intensity of diarrhea in those with active and inactive disease was not significantly different. Notably, an inverse correlation was also shown between FGF19 level and abdominal pain intensity.

Alongside the fluctuations in FGF19 level associated with IBD activity, we also demonstrated inverse correlations between FGF19 level and clinical and endoscopic activity indicators. No previous studies have confirmed an association between FGF19 level and disease activity using validated scales, including the Mayo Endoscopic Score, Rachmilewitz index[14,22] and CDAI.[22]

Fibroblast growth factor 19, as a product of FXR activation, can serve as a marker of FXR activity,[13] with the results of recent studies pointing to an immunomodulatory effect of FXR activation.[24–26] The association of FGF19 level with disease activity, inflammatory markers and primary symptoms may suggest potential new diagnostic markers and a novel therapeutic target of FGF19 analogs or FXR agonists. The results of preliminary studies with 2 FGF19 analogs, aldafermin and M52, are encouraging.[25,27–31]

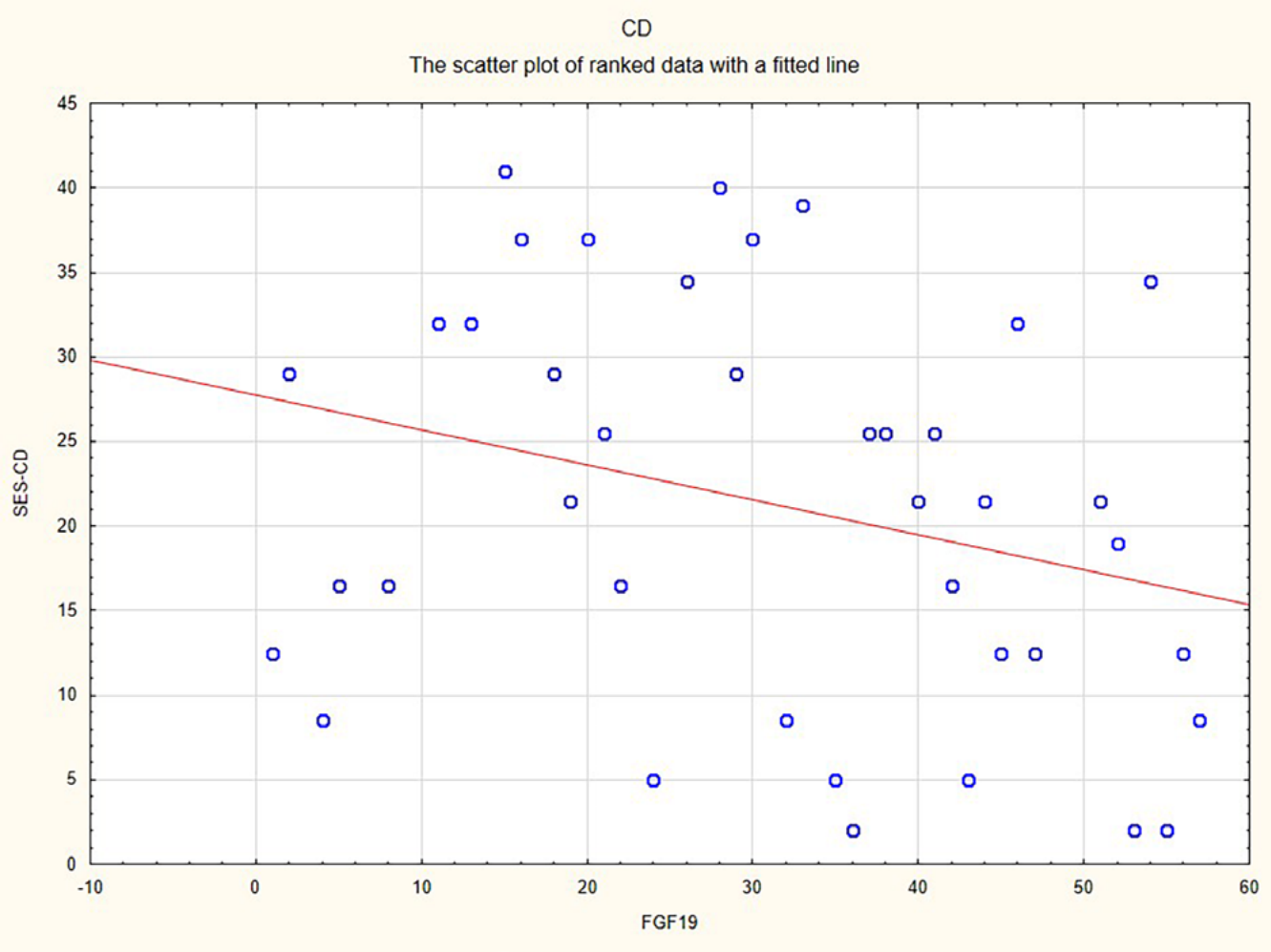

Fig. 6. An inverse correlation between serum fibroblast growth factor 19 (FGF19) and simple endoscopic score for Crohn's disease (CD) in CD patients; Tau-c = –0.23, p = 0.038

Tau-c – Kendall Tau-c correlation coefficient.

Table 7. Correlation of serum FGF19 level with clinical and endoscopic activity indices

Variables	Correlation coefficient	p-value
FGF19 and Rachmilewitz index	Tau-c = –0.37	<0.001
FGF19 and Mayo Endoscopic Score	Tau-c = –0.43	<0.001
FGF19 and CDAI	r = –0.29	0.026
FGF19 and SES-CD	Tau-c = –0.23	0.038

Involvement of tied ranks in patients with ulcerative colitis: FGF19 (0%), Rachmilewitz index (82%), Mayo Endoscopic Score (100%); in patients with Crohn's disease: FGF19 (0%), CDAI (0%), SES-CD (88%); CDAI – Crohn's disease activity index; SES-CD – simple endoscopic score for Crohn's disease; r – Spearman's rank correlation coefficient; Tau-c – Kendall Tau-c correlation coefficient.

Limitations

Among the limitations of the current study was the relatively small sample size of particular subgroups, especially patients with CD after ileocecal resection. However, the FGF19 level in this group was analyzed separately in patients in remission and flare for the first time. Hence, we indicated that the disease activity is an important factor affecting FGF19 expression apart from ileocecal resection. Moreover, a detailed evaluation of the exact length of resected ileum was unavailable. The number of subjects in the remaining subgroups was comparable to other studies.[7,13,14,20] Another limitation of this study was its cross-sectional design.

A substantial drawback of the study is that no additional tests were performed to confirm the existence of suspected BAM. However, while interpreting the current results, we relied on the recently reported cutoff value of FGF19 below 60 pg/mL to identify BAM in IBD patients (test sensitivity and specificity of 80% and 65%, respectively).[12] The designated cutoff was confirmed by Lyutkaov et al.[32] Regarding the novelty of the study, this is the first report on the inverse correlation between FGF19 level and validated scales of IBD activity.

Conclusions

The current results confirm an association between clinical and endoscopic IBD activity and serum FGF19 level. Local intestine inflammation in UC, reflected by fecal calprotectin level, significantly impacted FGF19 expression. Lower values of FGF19 were associated with the severity of diarrhea and abdominal pain. Regarding CD, FGF19 fluctuations related to disease activity were only observed in IR-CD patients. Higher FGF19 values in inactive compared to active IR-CD indicate that inflammation is a critical factor influencing FGF19 level. Assessing FGF19 can help identify patients who could benefit from sequestrant therapy as a treatment for BAM and a marker of disease activity. Furthermore, novel medications targeting the FXR-FGF19 pathway could have potential anti-inflammatory effects. Further studies exploring the efficacy and safety of FXR agonists and FGF19 analogs in intestinal inflammation are awaited.

Supplementary data

The Supplementary materials are available at https://doi.org/10.5281/zenodo.10690921. The package includes the following files:

Supplementary Data 1. Median FGF19 levels in subgroups of UC. Description of statistical analysis.

Supplementary Data 2. Median FGF19 levels in patients with CD). Description of statistical analysis.

Supplementary Data 3. Detailed characteristics of the patient subgroups. Description of statistical analysis.

Supplementary Data 4. Median serum FGF19 levels depending on disease duration and medications used. Description of statistical analysis.

Supplementary Data 5. Laboratory test results of the patient subgroups. Description of statistical analysis.

Supplementary Data 6. Correlation between serum FGF19 level and individual variables. Scatter plots.

Supplementary Data 7. Correlation between serum FGF19 level and clinical and endoscopic activity indices. Scatter plots.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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