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ORIGINAL PAPER

Prevalence of Pancreatic Insufficiency in Inflammatory Bowel Diseases. Assessment by Fecal Elastase-1

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Abstract Pancreatic insufficiency (PI) may be an extraintestinal manifestation of inflammatory bowel diseases (IBD). We report the results of a cross-sectional study that was carried out to investigate both the prevalence of PI in IBD patients and its clinical course over a 6-month follow-up period. In total, 100 Crohn's disease (CD) patients, 100 ulcerative colitis (UC) patients, and 100 controls were screened for PI by the fecal elastase-1 (FE-1) test. The decision limits employed were: ≤ 200 μg/g stool for PI and ≤ 100 μg/g for severe PI. Patients with abnormal FE-1 values were re-tested after 6 months. Odds ratios (OR) for PI were estimated by unconditional logistic regression analysis. PI was found in 22 UC and 14 CD patients. The OR for the FE-1 test ≤ 200 μg/g was 10.5 [95% confidence interval (CI): 2.5–44.8] for IBD patients compared to the controls. The risk of PI was related to three or more bowel movements per day (OR = 25.0), the passage of loose stools (OR = 7.7), and previous surgery (OR = 3.7). At the 6-month follow-up, FE-1 values became normal in 24 patients and showed persistently low concentrations in 12. These patients had a larger number of bowel movements per day (OR = 5.4), previous surgery (OR = 5.7), and a longer duration of the disease (OR = 4.2). PI is frequently found in IBD patients, particularly in those with loose stools, a larger number of bowel movements/day and previous surgery. PI is reversible in most patients, and persistent PI is not associated with clinically active disease.

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Introduction

Pancreatitis may be an extraintestinal manifestation of inflammatory bowel diseases (IBD) and has been suggested to be an autoimmune disease [1]. It may be silent or subclinical, and the symptoms may be mistakenly attributed to the IBD [2–4]. Pancreatic insufficiency (PI) may occur in some patients suffering from pancreatitis associated with IBD. The reported prevalence of this condition varies considerably, depending on patient selection and the diagnostic tests used [5]. To date, only one study has investigated the prevalence of pancreatic exocrine dysfunction in unselected IBD patients, reporting a PI prevalence of 30% using the paraminobenzoic acid (PABA) test [6]. However, this abnormality was confirmed in only 19% of these patients following the secretin-cerulein test [6].

The causes and risk factors as well as the clinical course and symptoms related to PI in IBD patients remain to be defined.

Evaluation of human pancreatic fecal elastase-1 (FE-1) in the stool is currently the most reliable and sensitive non-invasive procedure for the diagnosis of PI, with a

sensitivity ranging from 54 to 95% and a specificity of approximately 80% [7–11]. A commercial enzyme-linked immuno-sorbent assay (ELISA) method is currently available to measure FE-1 concentration in stool samples, thus providing the potential for a simple, reliable, and non-invasive evaluation of pancreatic function in IBD patients [10].

The aims of this prospective cross-sectional study were to assess the prevalence and risk factors of abnormal levels of FE-1 indicative of PI in a series of unselected, consecutive IBD patients. The behavior of PI in IBD patients with this complication was also prospectively evaluated in a 6-month follow-up study as were the clinical and demographic features related to the persistence of abnormal FE-1 concentrations.

Patients and methods

Patients

Over a 1-year period, 200 consecutive active or quiescent IBD patients with a definite diagnosis of Crohn's disease (CD, 100 patients) or ulcerative colitis (UC, 100 patients) were included in this prospective cross-sectional study. Demographic and clinical characteristics of the study population are outlined in Table 1.

Patients were questioned about the number of bowel movements/day, the presence of loose stools, abdominal pain, and weight loss during the last month. Clinical activity of the diseases was assessed using the Crohn's Disease Activity Index (CDAI) for CD [12] and Truelove & Witts score for UC [13]. The disease was considered to be clinically active if the CDAI exceeded 150 or the Truelove & Witts score >1.

The control group consisted of 100 apparently healthy individuals recruited from the student body and medical and nursing staff.

Fecal elastase-1 assay

The level ofFE-1 was determined in all patients and controls using the ELISA method in a microplate sandwich format (SheBoTech Gmbh, Giessen, Germany). Following collection, the stools were frozen at –20°C until FE-1 determination.

Decision limits employed for FE-1 were ≤ 200 μg/g stool for PI and ≤ 100 μg/g for severe PI, respectively. These limits have been validated in previously studies [10, 14]

In patients with FE-1 concentrations ≤ 200 μg/g, the test was repeated twice to confirm the values and again 4–6 months later to evaluate the behavior of abnormal FE-1 levels over time and the clinical features of patients with persistently low FE-1 levels.

Data analysis

The odds ratios (OR) and corresponding 95% confidence intervals (CI) for PI were estimated by unconditional multiple logistic regression models, including terms for categories of age [<35/35–54/≥55 years], gender, and type of disease. Models adjusted for age and gender only were also performed. However, since the estimates did not differ substantially, we only show the fully adjusted ORs in the Results section. The Mann–Whitney and Kruskall-Wallis test were used in comparisons between groups.

Results

The concentrations of FE-1 were lower in UC patients than in CD patients and the healthy controls (Fig. 1).

FE-1 concentrations ≤ 200 μg/g were found in two healthy controls, in 14 CD patients, and in 22 UC patients ($P < 0.001$). Compared to control subjects, the multivariate ORs for PI were 8.34 (95% CI: 1.34–37.89) for CD patients and 12.95 (95% CI: 2.91–57.58) for UC patients. Severe PI, as defined by FE-1 concentrations ≤ 100 μg/g, was found in five CD and nine UC patients but not in any of the healthy controls.

The risk of PI was significantly higher for IBD patients with clinically active disease (multivariate OR = 3.21) and, moreover, was directly associated with three bowel movements per day (OR = 25.0), the passage of loose stools (OR = 7.68), abdominal pain (OR = 2.61), and previous surgery (OR = 3.67) (Table 2). Indeed, three or more bowel movements per day and the passage of loose stools were directly associated with PI, both in CD (OR = 12.1; 95% CI: 2.61–56.1 and OR = 9.51; 95% CI: 1.86–48.6, respectively) and in UC patients (OR = ∝; 95% CI: 5.58–∞ and OR = 6.29; 95% CI: 2.04–19.5, respectively), whereas previous surgical resection was a risk factor for PI in UC patients only (OR = 5.02; 95% CI: 1.32–19.0). Disease activity was associated with PI in CD and UC patients, but was statistically significant only for CD (OR = 4.42; 95% CI: 1.09–17.96 for CD; OR = 2.47; 95% CI: 0.91–6.72 for UC). The number of bowel movements per day in active IBD patients was significantly greater in those with FE-1 ≤ 200 μg/g (Fig. 2).

Factors significantly related to FE-1 ≤ 100 μg/g were passage of loose stools (OR = 5.23; 95% CI: 1.39–19.8) and three or more bowel movements per day (OR = ∞; 95% CI: 3.77–∞) (Table 3).

No significant association was found between PI, or severe PI, and other clinical variables.

Table 1 Clinical and demographic characteristics of patients with inflammatory bowel diseases (IBD) participating in the present study

	CD (n = 100)	UC(n = 100)
Female/male	55/45	33/67
Height (cm; mean ± SD)	166.8 ± 24.4	169.6 ± 9.6
Weight (kg; mean ± SD)	67.1 ± 18.6	65.4 ± 14.1
Age (years; mean ± SD)	41.4 ± 14.4	47.1 ± 14.7
Duration of IBD (years; mean ± SD)	9.3 ± 7.3	9.3 ± 7.8
Age at diagnosis (years; mean ± SD)	32.4 ± 13.0	38.1 ± 14.9
Previous surgery (%)	46	5
Intestinal CD location (%)		
Stomach, duodenum and ileum	3	
Small bowel only	38	
Colon only	12	
Small bowel and colon	44	
Stomach or duodenum and colon	3	
Intestinal UC extension (%)		
Pancolitis		30
Left-sided colitis		43
Proctitis		27
Family history of IBD (%)	19	7
Patients with extra-intestinal manifestations (%)	67	26
Arthritis	43	20
Osteoporosis	15	5
Hepatobiliary	13	4
Cutaneous	11	4
Ocular	20	1
Hematological	2	2
Smoking habits (%)[a]		
Non-smokers	34	57.6
Smokers	42	12.1
Ex-smokers	24	30.3
Alcohol use (%)	40	36
Gallstones and/or cholecystectomy (%)	24	12
Active disease (%)	45	46
Concomitant medications (%)		
Aminosalicylates	43	44
Sulfasalazine	21	18
Corticosteroids	17	26
AZA/6-MP	13	9
None	31	19
Previous therapy (>12 months) (%)		
Aminosalicylates	57	71
Sulfasalazine	13	39
Corticosteroids	34	33
AZA/6-MP	31	9
Antibiotics	3	2
None	23	18

CD, Crohn's disease;UC, ulcerative colitis; AZA/6-MP, azathioprine/6-mercaptopurine

[a] The sum does not add up to the total because of one missing value

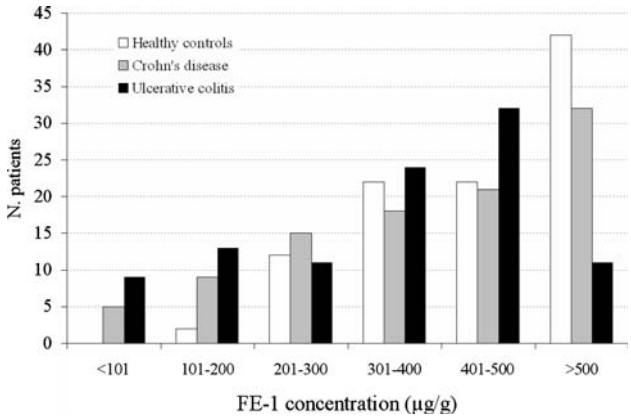

Fig. 1 Fecal elastase-1 (*FE-1*) concentrations in patients with ulcerative colitis and Crohn's disease and in healthy controls

Follow-up of patients with abnormal FE-1 concentrations

When re-tested after 4–6 months, the two control subjects previously presenting with low FE-1 levels had returned to normal concentrations (from 186 to 330 and from 107 to 316 µg/g, respectively). Of the 36 IBD patients with FE-1 concentrations ≤ 200 µg/g, 12 (eight UC, four CD patients) (33.3%) showed persistently low FE-1 concentrations, and 24 presented with FE-1 values >200 µg/g (Fig. 3).

The risk of persistence of PI was significantly associated with three or more bowel movements per day (OR = 5.40; 95% CI: 1.14–25.6), previous surgical resections (OR = 5.74; 95% CI: 1.10–30.0), and disease duration ≥10 years (OR = 4.20; 95% CI: 1.04–17.0), but not with disease activity (Table 3).

Discussion

The data obtained in the present study as well as data from several previously reported case and clinical studies confirm that PI can occur as an extraintestinal manifestation of IBD [1–3, 6, 15].

Using FE-1 levels as an indirect test to determine the presence of PI, we found that 18% of IBD patients presented with FE-1 levels ≤ 200 µg/g, among whom 7% had FE-1 values suggesting severe PI – i.e., FE-1 concentrations ≤ 100 µg/g. When the variability due to patient selection and the diagnostic tests used is taken into consideration, these percentages are in agreement with those of other studies [5, 6]. Heikius et al. obtained abnormal PABA test results in 21.8% of UC patients and in 26% of CD patients as well as abnormal exocrine function of the pancreas, as diagnosed by the secretin-cerulein test, in 4.2% of the entire IBD population [6]. Using the secretin-cerulein test, Angelini et al. showed a decrease in bicarbonate and enzyme output in 35% of CD patients and 50% of UC patients [5].

As previously pointed out, even if the concept of PI in IBD is not novel, in this study we assessed, for the first time, the prevalence of PI in IBD patients using FE-1 values as the evaluation criterium. FE-1 values are currently considered to be the more accessible and clinically applicable test for pancreatic function.

We also found that the presence of PI was related to disease activity, particularly in patients with CD, partially confirming the data of Hegnohj et al. who also observed a correlation between an abnormal Lundh meal test and the extension and activity of CD [16]. These findings suggest that PI is associated with IBD and that its prevalence in the IBD population is related to the distribution of CD and UC patients and to the clinical activity of the disease, thus explaining the variability of estimates of PI prevalence in the IBD population.

We found that PI is associated with alterations in bowel habits, namely with a large number of bowel movements per day and with the passage of loose stools, but not with abdominal pain or weight loss. However, even if it is difficult to discriminate between alterations in bowel habits due to PI from those due to disease activity, it is possible that PI may be responsible for more severe clinical manifestations in active IBD patients, thereby increasing the number of daily bowel movements.

Indeed, the study design did not help us to clarify the significance and importance of low FE-1 levels in IBD patients with loose stools. In fact, it is possible that diarrhea results in falsely decreased FE-1 levels in IBD patients with non-pancreatic diarrhea and that the lower FE-1 levels in patients with frequent and loose stools are the results of a dilution of FE-1 levels due to increased water in the stools. FE-1 levels are known to be affected by dilution in patients with watery stools [17]. In the present study, confirmatory investigations to assess the exocrine function of the pancreas as well as morphological pancreatic evaluations, such as secretin test, endoscopic retrograde pancreatography, and/or nuclear magnetic resonance pancreatography, were not performed. Therefore, we cannot confirm the presence of PI or appropriately evaluate the sensitivity and specificity of FE-1. However, even if no study has as yet been performed to specifically assess the accuracy of FE-1 in detecting PI in IBD patients, currently available data, including those from a meta-analysis, have shown that FE-1 can be used to diagnose exocrine PI with a mean specificity >80% and with a sensitivity varying according to the severity of the pancreatic disease, ranging from

Table 2 Distribution of IBD patients with pancreatic insufficiency (PI), as determined by fecal elastase-1 (FE-1) concentrations ≤ 200 μg/g, in terms of to age, gender and other selected variables. Only important correlations are shown

Factors	Number of subjects	Subjects with PI (%)	OR[a]	95% CI
Gender				
Male	112	20.5	1.00[b]	[b]
Female	88	14.8	0.74	0.34–1.60
Age (years)				
<35	62	19.4	1.00	[b]
35–54	87	12.6	0.57	0.23–1.41
≥55	51	25.5	1.26	0.50–3.13
Type of disease				
Crohn's disease	100	14.0	1.00	[b]
Ulcerative colitis	100	22.0	1.55	0.72–3.36
Age at diagnosis (years)				
<30	82	18.3	1.00	[b]
30–39	45	17.8	0.93	0.29–3.05
≥40	73	17.8	0.42	0.09–1.88
Duration (years)				
<10	117	17.9	1.00	[b]
≥10	83	18.1	1.03	0.47–2.27
Previous surgical resection				
No	149	16.1	1.00	[b]
Yes	51	23.5	3.67	1.27–10.6
Smoking habit[c]				
Never	94	18.1	1.00	[b]
Ex- or current	105	18.1	1.27	0.59–2.75
Alcohol				
Non-drinkers	116	19.0	1.00	[b]
Drinkers	84	16.7	0.86	0.39–1.87
Family history for IBD				
No	176	17.6	1.00	[b]
Yes	24	20.8	1.33	0.44–3.99
Active disease				
No	104	10.6	1.00	
Yes	96	26.0	3.21	1.45–7.12
Current bowel movements/day				
<3	101	2.0	1.00	[b]
≥3	99	34.3	25.0	5.77–109
Usual bowel movements/day				
<2	92	14.1	1.00	[b]
≥2	108	21.3	1.62	0.76–3.46
Current abdominal pain				
No	116	13.8	1.00	[b]
Yes	84	23.8	2.61	1.18–5.76
Usual abdominal pain				
No	168	16.7	1.00	[b]
Yes	32	25.0	2.18	0.83–5.73
Weight loss (>5 kg last 6 months)				
No	122	13.9	1.00	[b]
Yes	78	24.4	1.94	0.92–4.12
Loose stools				
No	110	6.4	1.00	[b]
Yes	90	32.2	7.68	3.09–19.1

OR, Odds ratio; CI, confidence interval

[a] Estimated by unconditional logistic regression equations after adjustment for age, gender, and type of disease, when appropriate

[b] Reference category

[c] The sum does not add up to the total because of one missing value

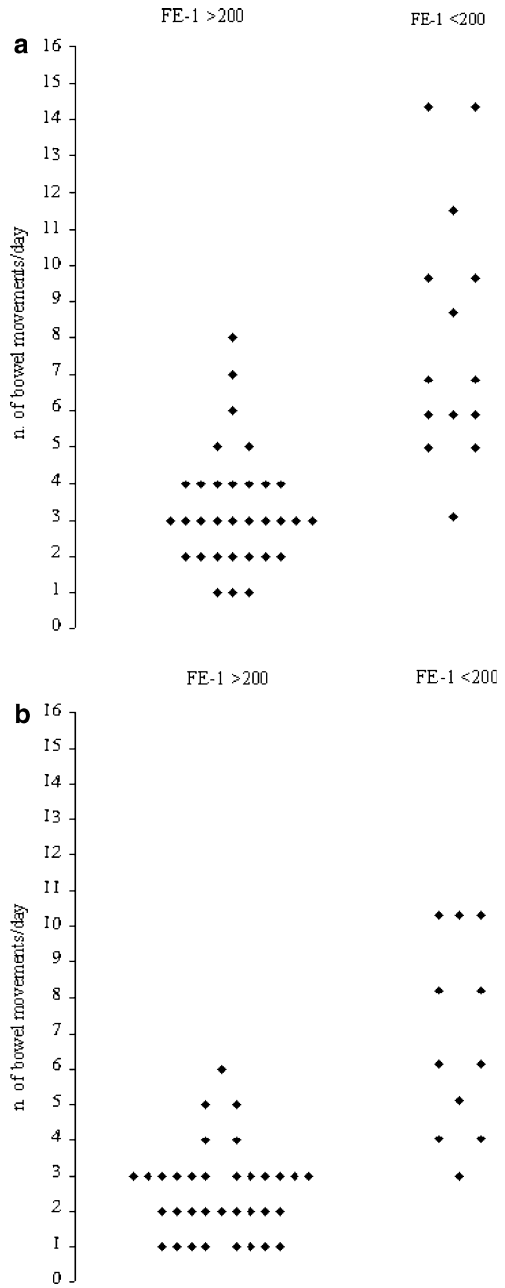

Fig. 2 Number of bowel movements per day in active ulcerative colitis (UC) (**a**) and Crohn's disease (CD)(**b**) patients according to presence of pancreatic insufficiency (PI) defined as FE-1 levels ≤ 200 μg/g. Both active UC and CD patients with PI showed a significantly greater number of bowel movements per day compared with patients with normal FE-1 concentration ($P < 0.0001$)

54% for slight exocrine PI to 75% for moderate exocrine PI, and to 95% for severe exocrine PI [11]. In this study, we have shown that PI in IBD is frequently a transient condition.

In order to evaluate the behavior of abnormal FE-1 levels over time and the clinical features of patients with persistently low FE-1 levels, we repeated the test after an interval of 4–6 months. Since the aim was not to assess the accuracy of the FE-1 test, we did not repeat the evaluation in all individuals. In our population, abnormal FE-1 concentrations returned to normal values in two thirds of all patients. This normalization was more frequent in IBD patients presenting with clinically active disease. In most of these patients, PI regressed when the disease became quiescent. This finding is in keeping with that of Masoero et al., who described the normalization of FE-1 in 50% of IBD patients following adequate treatment [18]. These authors suggested that the decrease in FE-1 concentrations in IBD patients may be due to an extraintestinal complication, possibly of autoimmune origin, affecting pancreatic exocrine secretion, which is related to disease activity [16]. As we have shown a significant association between abnormal FE-1 levels and loose stools, the possibility that improvement in FE-1 levels was due to a reduced IBD activity, resulting in more sold stools, rather than to a true improvement of pancreatic function cannot be excluded.

The presence of a persistent form of PI in patients with predominantly quiescent and long-standing IBD and with a history of a larger number of bowel movements per day is more difficult to explain. It may be the result of repeated episodes of transient PI. Indeed, the pathogenesis of chronic pancreatitis still remains to be fully elucidated, but pancreatic fibrosis as a consequence of repeated episodes of acute pancreatitis is one of the most qualified competing hypotheses [19].

The existence of different forms of chronic pancreatitis in IBD has already been described [20–22]. Studies focusing on morphological and pathological features of idiopathic pancreatitis associated with IBD have found frequent and different macroscopic and microscopic abnormalities. Autopsy studies have revealed pancreatic lesions in up to 53% of UC patients and in 38% of CD patients, none of whom had previous clinical evidence of pancreatic disease [20, 21]. The presence of pancreatic lesions in IBD patients has also been reported by Barthet et al. who showed that chronic pancreatitis associated with UC differed from that observed in CD due to the more frequent presence of pancreatic duct stenosis [15].

In our experience, the persistence of PI is not related to disease activity, even if characterized by a larger number of bowel movements per day. However, in most patients with persistently low FE-1 levels, the symptoms have been mild and well tolerated and did not require enzyme replacement. Whether these patients have a specific form of chronic pancreatitis (autoimmune?) and would benefit from treatment with pancreatic enzyme supplementation needs to be assessed in future studies.

Our results show that PI, as detected by low FE-1 concentrations, is frequent in patients with IBD but is often characterized by a reversible and benign outcome, at least

Table 3 Distribution of IBD patients with to PI, as defined by FE-1 levels ≤ 100 μg/g and the persistence of FE-1 concentrations ≤ 200 μg/g at follow-up, in terms of age, gender and other selected variables. Only relevant correlations are shown

Factors	*N*. subjects	FE-1 ≤ 100 μg/g			FE-1 ≤ 200 μg/g at follow-up		
		%	OR[a]	(95% CI)	Percentage	OR[a]	95% CI
Gender							
Male	112	8.9	1.00	[b]	5.4	1.00	[b]
Female	88	4.5	0.53	(0.16–1.81)	6.8	1.57	0.47–5.24
Age (years)							
<35	62	9.7	1.00	[b]	3.2	1.00	[b]
35–54	87	5.7	0.53	(0.15–1.83)	6.9	2.14	0.41–11.0
≥55	51	5.9	0.48	(0.11–2.09)	7.8	2.23	0.38–13.0
Type of disease							
Crohn's disease	100	5.0	1.00	[b]	4.0	1.00	[b]
Ulcerative colitis	100	9.0	1.81	(0.56–5.89)	8.0	2.12	0.59–7.66
Age at diagnosis (years)							
<30	82	6.1	1.00	[b]	4.9	1.00	[b]
30–39	45	8.9	4.50	(0.73–27.7)	8.9	1.08	0.20–5.80
≥40	73	6.8	5.16	(0.51–52.7)	5.5	0.28	0.03–2.41
Duration (years)							
<10	117	9.4	1.00	[b]	2.6	1.00	[b]
≥10	83	3.6	0.40	(0.10–1.58)	10.8	4.20	1.04–17.0
Previous surgical resection							
No	149	6.7	1.00	[b]	4.7	1.00	[b]
Yes	51	7.8	2.74	(0.57–13.3)	9.8	5.74	1.10–30.0
Smoking status[c]							
Never	94	5.3	1.00	[b]	6.4	1.00	[b]
Ex- or current	105	8.6	2.08	(0.63–6.89)	5.7	1.01	0.30–3.48
Alcohol							
Non drinkers	116	7.8	1.00	[b]	6.0	1.00	[b]
Drinkers	84	6.0	0.66	(0.20–2.19)	6.0	1.10	0.32–3.82
Family history for IBD							
No	176	7.4	1.00	[b]	6.3	1.00	[b]
Yes	24	4.2	0.57	(0.07–4.77)	4.2	0.83	0.10–6.93
Active disease							
No	104	3.9	1.00	[b]	6.7	1.00	[b]
Yes	96	10.4	3.11	(0.92–10.51)	5.2	0.79	0.24–2.62
Current bowel movements/day							
<3	101	0.0	1.00	[b]	2.0	1.00	[b]
≥3	99	14.1	∞	(3.77-∞)	10.1	5.40	1.14–25.6
Usual bowel movements/day							
<2	92	4.3	1.00	[b]	4.3	1.00	[b]
≥2	108	9.3	2.29	(0.68–7.69)	7.4	1.87	0.54–6.50
Current abdominal pain							
No	116	6.0	1.00	[b]	6.0	1.00	[b]
Yes	84	8.3	1.74	(0.55–5.49)	6.0	0.89	0.26–3.10
Usual abdominal pain							
No	168	6.5	1.00	[b]	6.0	1.00	[b]
Yes	32	9.4	1.76	(0.43–7.24)	6.3	1.22	0.24–6.23

Table 3 continued

Factors	*N.* subjects	FE-1 ≤ 100 μg/g			FE-1 ≤ 200 μg/g at follow-up		
		%	OR[a]	(95% CI)	Percentage	OR[a]	95% CI
Weight loss (>5 kg)							
No	122	4.1	1.00	[b]	6.6	1.00	[b]
Yes	78	11.5	2.92	(0.92–9.26)	5.1	0.73	0.21–2.56
Loose stools							
No	110	2.7	1.00	[b]	3.6	1.00	[b]
Yes	90	12.2	5.23	(1.39–19.8)	8.9	2.66	0.76–9.28

[a] Estimated by unconditional logistic regression equations after adjustment for age, gender and type of disease, when appropriate

[b] Reference category

[c] The sum does not add up to the total because of one missing value

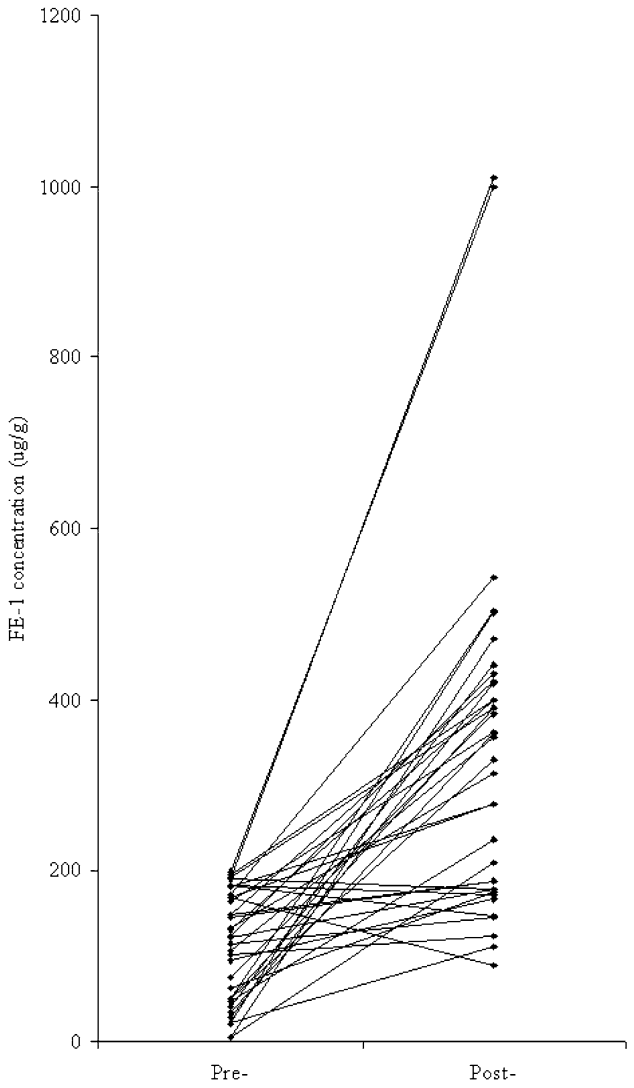

Fig. 3 Behavior of FE-1 concentrations in patients with PI defined as FE-1 ≤ 200 μg/g at baseline (*pre-*)

in the short-term evolution. However, it should be borne in mind that the presence of loose or watery stools in IBD patients may be a relevant confounding factor that is responsible for a considerable percentage of false positive results.

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