Bile Acid Deficiency in Subgroup of Patients With Irritable Bowel Syndrome With Constipation Based on Biomarkers in Serum and Fecal Samples

Priya Vijayvargiya, MD, **Irene Busciglio, BS**, **Duane Burton, MHA**, **Leslie Donato, PhD**[*], **Alan Lueke, MS**[*], and **Michael Camilleri, MD**

Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Mayo Clinic, Rochester, MN

[*]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

Abstract

Background & Aims—Short-term administration of delayed-release chenodeoxycholic acid to patients with irritable bowel syndrome with constipation (IBS-C) accelerates colonic transit and reduces symptoms. A preliminary study has shown that patients with IBS-C have reduced levels of bile acids (BAs) in feces and reduced synthesis of BA. We compared levels of primary and secondary BAs in fecal samples collected over a 48-hr period from patients with IBS-C on a diet that contained 100 g fat per day, and compared them will levels in samples from healthy volunteers (controls). We also examined the relationship between overall colonic transit and biomarkers of BAs in patients with IBS-C.

Methods—We performed a retrospective study of 45 patients with IBS-C and 184 controls. For controls, we estimated the 10th percentile of fasting serum levels of C4 (n=184) and 48-hr fecal BAs (n=46), and the 90th percentile of fasting serum level of fibroblast growth factor 19 (FGF19, n=50). Colonic transit was measured in patients using a validated scintigraphic method. Data from patients with IBS-C were analyzed using Spearman correlations to determine relationships among levels of C4, FGF19, fecal BAs, and colonic transit.

Results—Among the patients with IBS-C, 2/45 had low serum levels of C4, 4/43 had increased serum levels of FGF19, and 6/39 had low levels of BAs in feces collected over 48-hrs. Patients

with IBS-C had a significant increase in proportions of fecal lithocholic acid compared with controls (P=.04) and decrease in deoxycholic acid compared to controls (P=.03). In patients with IBS-C, there were inverse relationships between serum levels of C4 and FGF19 and correlations among levels of 48-hr fecal BAs, colonic transit, and serum C4 and FGF19.

Conclusion—Approximately 15% of patients with IBS-C have reduced total BAs and level of deoxycholic acid in fecal samples collected over 48 hrs on a 100 g fat diet. In these patients, lower levels of excretion of BAs into feces correlated with slower colonic transit.

Keywords

cholic acid; chenodeoxycholic acid; 7α-hydroxy-4-cholesten-3-one; GPBAR1 (G protein coupled bile acid receptor 1)

INTRODUCTION

Bile acids (BAs) are amphipathic, detergent molecules synthesized by the liver, and they facilitate the small intestinal absorption of lipids and fat soluble vitamins.[1] Their overall structure resembles a cholesterol molecule, but the changes made by colonic bacteria change the BAs effects on colonic permeability and secretion. Lithocholic acid (LCA) and deoxycholic acid (DCA) are the major BAs present in the colon and stool. Chenodeoxycholic acid (CDCA) and DCA are the known secretory BAs.[2] Increase in the fecal excretion and change in the proportion of the various BAs in stool characterize bile acid malabsorption (BAM), resulting in diarrhea or irritable bowel syndrome with diarrhea (IBS-D),[3, 4] which are associated with increased colonic water and mucus secretion, colonic motility, and membrane permeability.[5] [6]

BAM has been reported in 10–33% of patients with IBS-D or functional diarrhea.[7] Diagnosis of BAM is based on measurement of ^{75}SeHCAT retention, where available, or on 48 hour fecal BA excretion and fasting serum biomarkers: 7α-hydroxy-4-cholesten-3-one (C4), a direct marker of hepatic BA synthesis; and fibroblast growth factor (FGF19), an endocrine hormone released by enterocytes providing negative feedback for BA synthesis. [8, 9] Multiple studies have confirmed the presence of increased fecal BAs, C4, colonic transit, and decreased FGF19 in patients with BAM as compared to healthy volunteers and constipation controls.[10, 11] Additionally, there are increased proportions of individual secretory BAs, DCA and CDCA, in 48-hour fecal BA measurements[12, 13] in patients with IBS-D.

Less is known about the potential role of BAs in patients with constipation. In a preliminary study, Shin et al. established that, although there was no significant decrease in total fecal BAs in patients with irritable bowel syndrome with constipation (IBS-C) as compared to healthy volunteers, patients with IBS-C had decreased proportions of DCA and CDCA and increased proportion of the nonsecretory LCA as compared to healthy volunteers.[12] Fasting serum C4 was not significantly different in IBS-C and healthy volunteers, and serum C4 and FGF19 measurements did not augment the utility of measurement of total fecal BAs for discriminating among IBS-C, IBS-D and healthy volunteers.[8] An interesting report described a paradoxical increase in serum C4 in patients with slow transit constipation

compared to functional constipation, suggesting a compensatory increase in BA synthesis to provide an endogenous laxative agent.[14] This intriguing observation has not been corroborated or replicated.

The aims of this study were to compare fecal BAs and serum BAM biomarkers (C4 and FGF19) in IBS-C and healthy volunteers, and to assess the relationship of these biomarkers and colonic transit in patients with IBS-C.

METHODS

Participants and Study Design

This was a single-center, retrospective study. There were 45 patients with IBS-C, defined by Rome III criteria, and 184 healthy volunteers who had participated in research studies within the last 10 years. Eligibility criteria, methods of selection, periods of recruitment, and data collection were included in prior publications.[8, 11, 12, 15] Patients with IBS-C resided in local communities in southeastern Minnesota to avoid tertiary referral bias.

We collected previously measured fasting serum FGF19 and C4, 48 hour total and individual (CDCA, CA, DCA, LCA) fecal BA data from patients with IBS-C and healthy volunteers. From the IBS-C cohort, we also obtained 24 and 48 hour colonic transit data. Figure 1 shows the distribution of patients with available quantitative data between the two cohorts.

Measurement of Quantitative Data

Fasting serum C4 and FGF19—The C4 assay performed in our center (adapted from Galman et al.)[16] is based on HPLC/tandem mass spectrometry.[17]

FGF19 was measured by ELISA (FGF19 Quantikine Enzyme-Linked Immunosorbent Assay Kit, R&D Systems, Minneapolis, MN), as in previous studies.[18]

48 hour total and individual fecal bile acids—Patients were instructed to consume a 100 gram fat diet for 2 days before stool collection was started and for 2 days during stool collection. The details of extraction, measurement by LC-MS/MS, analysis and performance characteristics have been described in detail previously.[12] The 48 hour total fecal BAs (μmol/48h) and the absolute values (μmol/48h) and proportions of individual BAs (%) were measured.

24 and 48 hour colonic transit—The scintigraphic colonic transit test and its performance characteristics have been described in detail.[19] Briefly, after an overnight fast, patients ingest ^{111}In adsorbed on activated charcoal in a methacrylate-coated, delayed-release capsule that has been shown to dissolve in the ileocolonic region. Patients are then fed 3 meals of known calorie value and standard proportions of carbohydrates, protein, and fat. Abdominal scintiscans are obtained every hour for the first 6 hours and at 8, 24, and 48 hours after ingestion of the ^{111}In capsule. The validated colonic transit measurements are geometric center at 24 and 48 hours.

Statistical Analysis

Since our sample sizes for both healthy volunteers and patients with IBS-C were relatively small, we elected to utilize the 10th % and 90th % for our parameter cut-offs. Altman et al. demonstrated that, for skewed samples, the 10th % and 90th % would be more appropriate than the traditional 5th % and 95th % cut-offs.[20] We calculated the 10th percentile of C4 values (ng/mL) in the 184 healthy volunteers and fecal BAs (μmol/48h) in 46 healthy volunteers to represent the lower normal limit. We appraised the 90th percentile of FGF19 in 50 healthy volunteers, as it is known that low serum FGF19 is associated with diarrhea due to BAM.

We estimated the number of patients with IBS-C with results below the 10th percentile of healthy volunteers for total fecal BAs (in 39 IBS-C patients) and serum C4 (in 45 IBS-C patients), and above the 90th percentile of healthy volunteers based on FGF19 (in 43 IBS-C patients).

For analysis of the individual BAs, we compared the proportions and absolute values of IBS-C and healthy volunteers using the Wilcoxon rank sum test.

To understand the relationships among C4, FGF19, fecal BAs and colonic transit, we performed Spearman correlations and graphed the data with best fitting regression lines using the regression wizard on SigmaPlot (Systat Software, San Jose, CA). The graphs are variations of rectangular hyperbola and hyperbolic decay, depending on which model best fit the data on scatter plots. The specific type of graph and the associated equations are described in the figures. Bonferroni correction for multiple correlation tests was not utilized because this is a hypothesis-generating, post-hoc analysis, and the results of the individual tests are more important than the collective analysis.[21]

RESULTS

Demographics

In the healthy volunteers, there was a 1.5 ratio of female to male participants (110:74) and comparable average age (42.3±13 years) to those in the IBS-C cohort. Patients with IBS-C were all female participants, overweight [average BMI: 26.2±4.2 (SD) kg/m^2], and aged 43.8±9.5 years.

Serum Biomarkers and Total and Individual Fecal BAs in Healthy Volunteers

Because the patient cohort (IBS-C) consisted of only female volunteers, we calculated the healthy volunteer-based cut-offs for the combined group of both males and females, and exclusively for the female cohort.

Male and female healthy volunteer parameter cut-offs—The 10th percentile of serum C4 (n=184) was 5.05 ng/mL and the 48 hour fecal BAs (n=46) was 109.5 μmol/48h. The 90th percentile of serum FGF19 (n=50) was 267.0 pg/mL.

Table 1 demonstrates the proportions and absolute values of the individual fecal BAs (n=25) in healthy volunteers.

Exclusively female healthy volunteer parameter cut-off—The 10th percentile of serum C4 (n=110) was 4.28 ng/mL and of the 48-hour fecal BAs (n=35) was 105.5 μmol/ 48h. The 90th percentile of serum FGF19 (n=39) was 277.4 pg/mL.

Fasting Serum C4 and FGF19 and 48 Hour Total and Individual Fecal BAs in Patients with IBS-C

Utilizing male and female healthy volunteer parameter cut-offs—Of the 39 IBS-C patients with 48-hour total fecal BAs measurements, 6 (15.4%) demonstrated low fecal BAs. The serum fasting FGF19 was increased in 4/43 (9.3%), and the C4 was decreased in 2/45 (4.4%). However, there was not complete concordance between abnormal serum biomarkers and decreased 48-hour total fecal BAs.

Table 1 demonstrates the proportions and values for the individual fecal BAs. There was a significantly higher percent of LCA (p=0.034) and a lower percent of DCA (p=0.027) in patients with IBS-C.

Utilizing exclusively female healthy volunteer parameter cut-off—Even with the cut-offs for 48-hour total fecal BAs and fasting serum C4, the number of patients with IBS-C with bile acid deficiency did not change, 6/39 (15.4%) and 2/45 (4.4%) respectively. For fasting serum FGF19, there was one less patient who demonstrated bile acid deficiency [3/43 (7.0%)].

Relationships between Serum and Fecal Biomarkers and Colonic Transit in Patients with IBS-C

Table 2 contains the Spearman correlations, and Figures 2, 3, and 4 are the scatter plots with best fit regression lines of the data collected from patients with IBS-C. Figure 2 demonstrates a significant reciprocal relationship between fasting serum FGF19 and C4. Figure 3 shows direct correlations between serum C4 or the 48 hour fecal BAs and 48 hour colonic transit. Figure 4 shows the inverse correlation of FGF19 and colonic transit.

DISCUSSION

Our study demonstrates there is a subgroup of ~15% patients with IBS-C who has decreased 48 hour fecal BAs. Of the fasting serum biomarkers, 4.3% of patients with IBS-C had low serum C4 and 9.3% had elevated serum FGF19. When adjusting the control group to include only female participants to match the IBS-C patient cohort of exclusively females, the prevalence of bile acid deficiency did not alter significantly. There was a significant direct correlation between fecal BAs excretion and serum C4 and colonic transit, and there was an inverse correlation between serum FGF19 and colonic transit. As demonstrated in Figure 2, serum FGF19 and C4 demonstrated a significant inverse relationship. Though demonstrated in multiple prior studies evaluating bile acid diarrhea in patients with IBS-D, this has not previously been described in patients with IBS-C. These observations demonstrate that a portion of patients with IBS-C may suffer from colonic bile acid deficiency as the underlying pathophysiology. Importantly, when such patients with IBS-C are refractory to standard treatment of constipation, they may be candidates for treatment with strategies that

increase intra-colonic bile acid concentrations such as bile acid supplementation or inhibitors of the ileal bile acid transporter (IBAT), as discussed below.

The observations in this study have practical and clinical implications for future studies as well as insights relative to prior clinical trials. For example, Rao et al. provided supplemental chenodeoxycholate to patients with IBS-C and functional constipation and showed improvement in colonic transit time, frequency and consistency of stool.[22] In addition, when elobixibat, an inhibitor of the ileal bile acid transporter which is responsible for ~95% of BA reabsorption in the terminal ileum, was administered to patients with functional constipation, it also improved colonic transit, stool consistency and frequency.[23] Elobixibat resulted in increased fasting serum C4 and decreased FGF19, secondary to increased BA synthesis after increased fecal BA loss.[24, 25] Thus, there are potential therapeutic approaches to correct the abnormal biochemical parameters, given that the patients' fasting serum C4 was increased to >10 ng/mL with elobixibat,[24] which could correct the low C4 (5.05 ng/mL) in a subgroup of patients with IBS-C in our current study.

Previous studies have demonstrated decreased fecal BAs in a subset of patients with IBS-C compared to patients with IBS-D, but were unable to demonstrate statistical significance when compared to healthy volunteers.[11, 12] When evaluating the percentage of major, individual primary and secondary BAs, our data revealed a significant increase in LCA (p=0.034) and decrease in the proportion of the secretory BA, DCA (p=0.027), in patients with IBS-C compared to healthy volunteers. This difference in individual BA proportions has been replicated in other studies.[12] In constipated children, there was no difference in the proportion of DCA, but there was increased sulfonated CDCA. The sulfonation removes the active secretory component of the BA.[26]

There are two plausible hypotheses regarding constipation and fecal BA measurements. First, decreased proportion of secretory fecal BAs results in constipation. At face value, our data would support this hypothesis in up to 15% of patients with IBS-C because they had low total fecal BA and DCA excretion. A second hypothesis is that increased colonic transit time in constipation results in increased passive absorption of fecal BAs and, hence, lower excretion of secretory BAs such as DCA. The precise contribution of colonic transit to the fecal excretion of individual BAs has been the subject of few previous papers. Within the colon, there is passive absorption of unconjugated, di-hydroxy BAs, which include DCA (3,12 di-α hydroxylated) and UDCA (3α, 7β di-hydroxylated).[27] When constipated patients were given senna to accelerate colonic transit, it was observed that the biliary DCA (which must have been reabsorbed through the colonic mucosa) was decreased.[27] Conversely, healthy volunteers who received loperamide to decelerate colonic transit had increased biliary DCA.[28] Similarly, in patients with acromegaly, octreotide retarded colonic transit, yielding an increase in serum DCA.[29]

CONCLUSION

The current data are consistent with the hypothesis that a subset of patients with IBS-C has decreased total fecal BAs and percentage of fecal secretory BAs, which is significantly correlated to a decrease in colonic transit. The serum biomarkers, C4 and FGF19, were not

always concordant with total fecal BAs. Based on our data, we believe 48-hour total and percentage of fecal secretory BAs will be considered the gold standard until further studies are completed. Given the potential limitations of a retrospective analysis, future studies are planned to confirm these findings in a prospective cohort of patients with functional constipation and IBS-C.

Acknowledgments

Abbreviations

BA	Bile Acid
BAM	Bile Acid Malabsorption
BMI	Body Mass Index
C4	7α-hydroxy-4-cholesten-3-one
CDCA	chenodeoxycholic acid
CA	cholic acid
DCA	deoxycholic acid
ELISA	Enzyme-Linked Immunosorbent Assay
FGF19	Fibroblast Growth Factor 19
GC	geometric center
GPBAR1 (TGR5)	G protein-coupled bile acid receptor 1
HV	Healthy volunteers
HPLC	High Performance Liquid Chromatography
IBAT	Ileal bile acid transporter
IBS-C	irritable bowel syndrome with constipation
IBS-D	irritable bowel syndrome with diarrhea
In	Indium
LCA	Lithocholic Acid
LC-MS/MS	Liquid chromatography tandem-mass spectrometry
SD	Standard Deviation

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184 HV

184 with C4

50 with FGF19

46 with fecal BA

25 with individual fecal BA

45 pts with IBS-C

45 pts with C4
43 pts with FGF19

39 pts with fecal BA

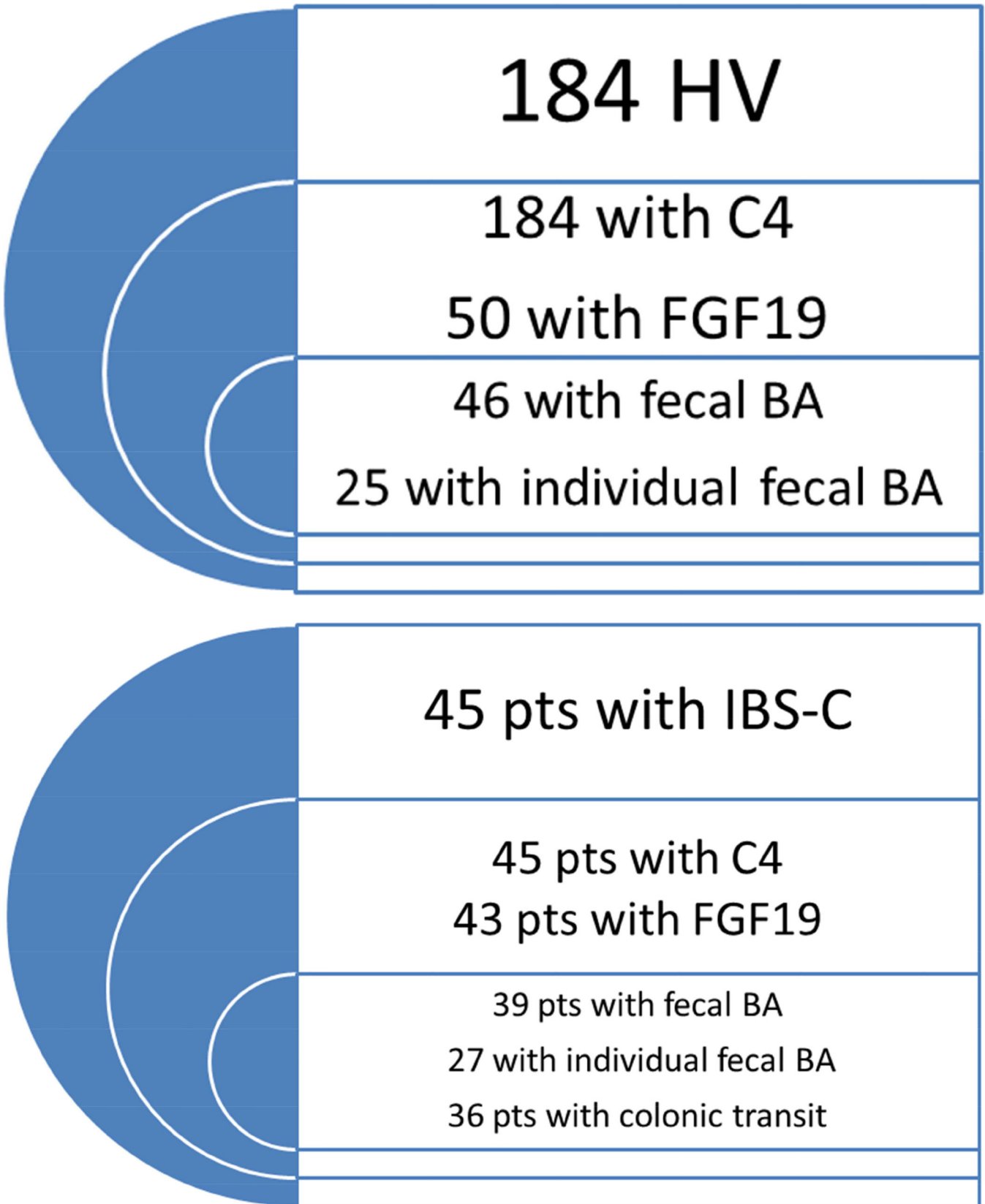27 with individual fecal BA

36 pts with colonic transit

Figure 1.
Number of bile acid biomarkers and colonic transit measurements available for review in healthy volunteers (HV, left panel) and patients with IBS-C (right panel)
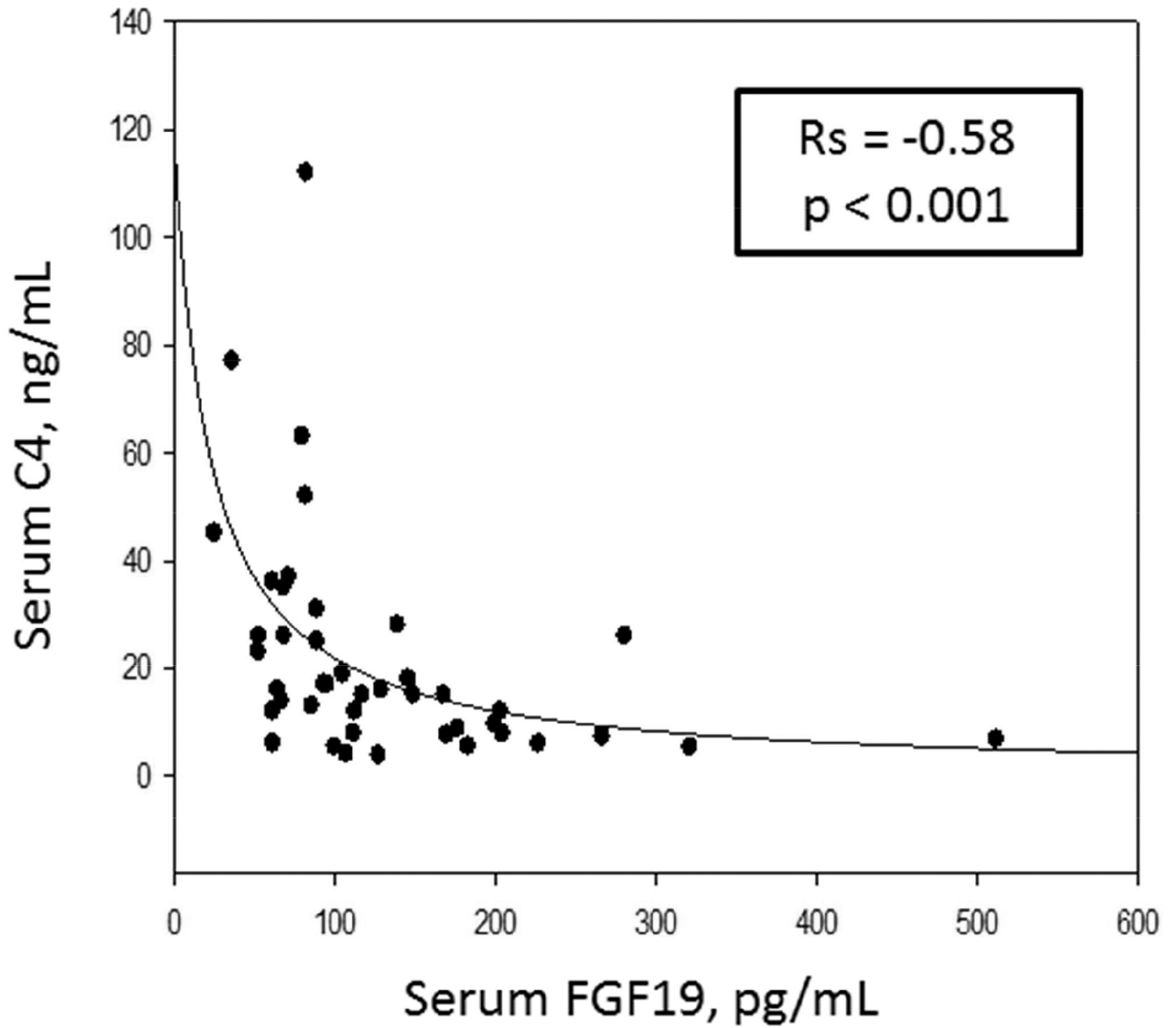
Figure 2.
Inverse relationship between fasting serum C4 and FGF19 in patients with IBS-C. Graph represents a 2-parameter hyperbolic decay: Y=ab/(b+x).
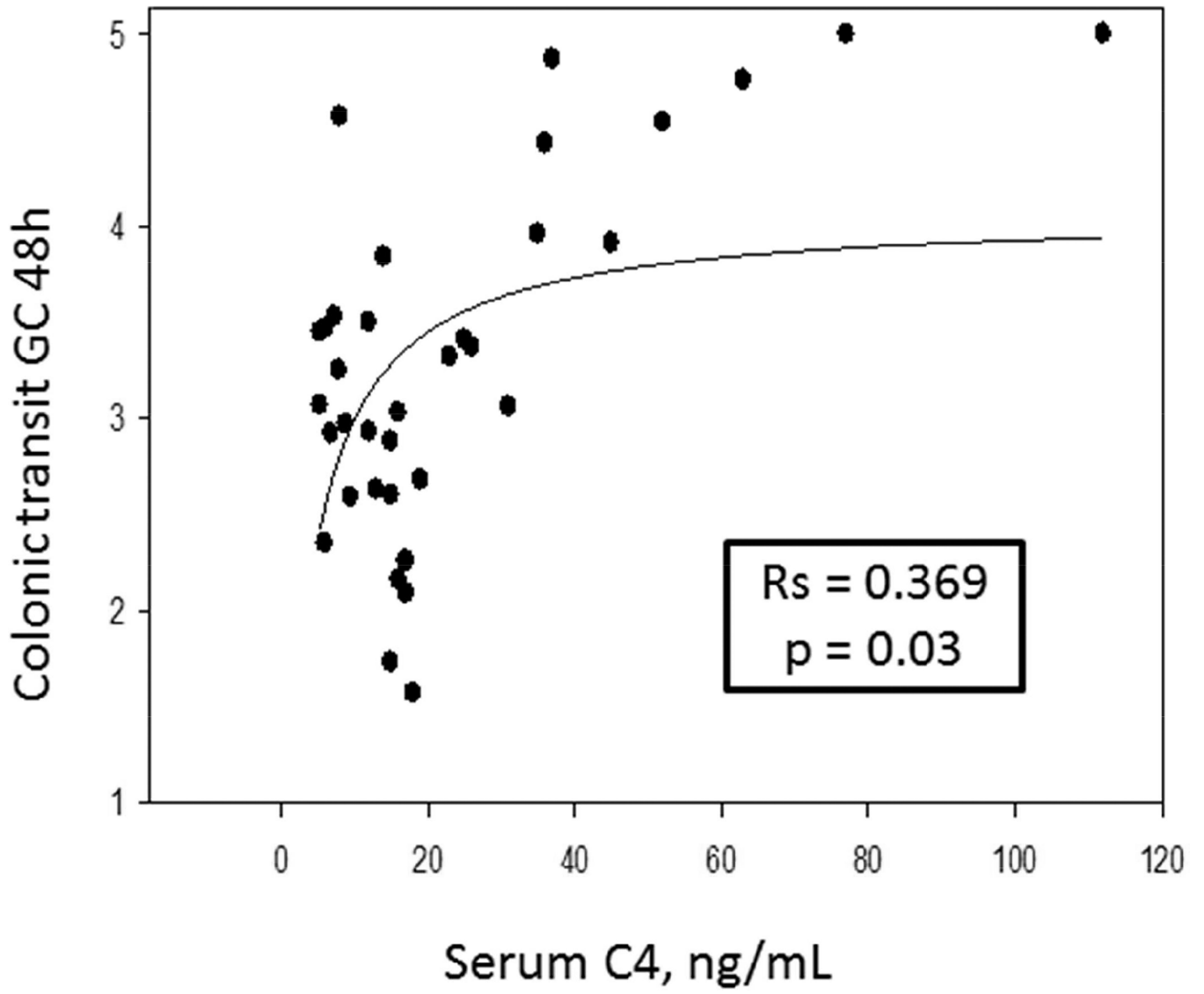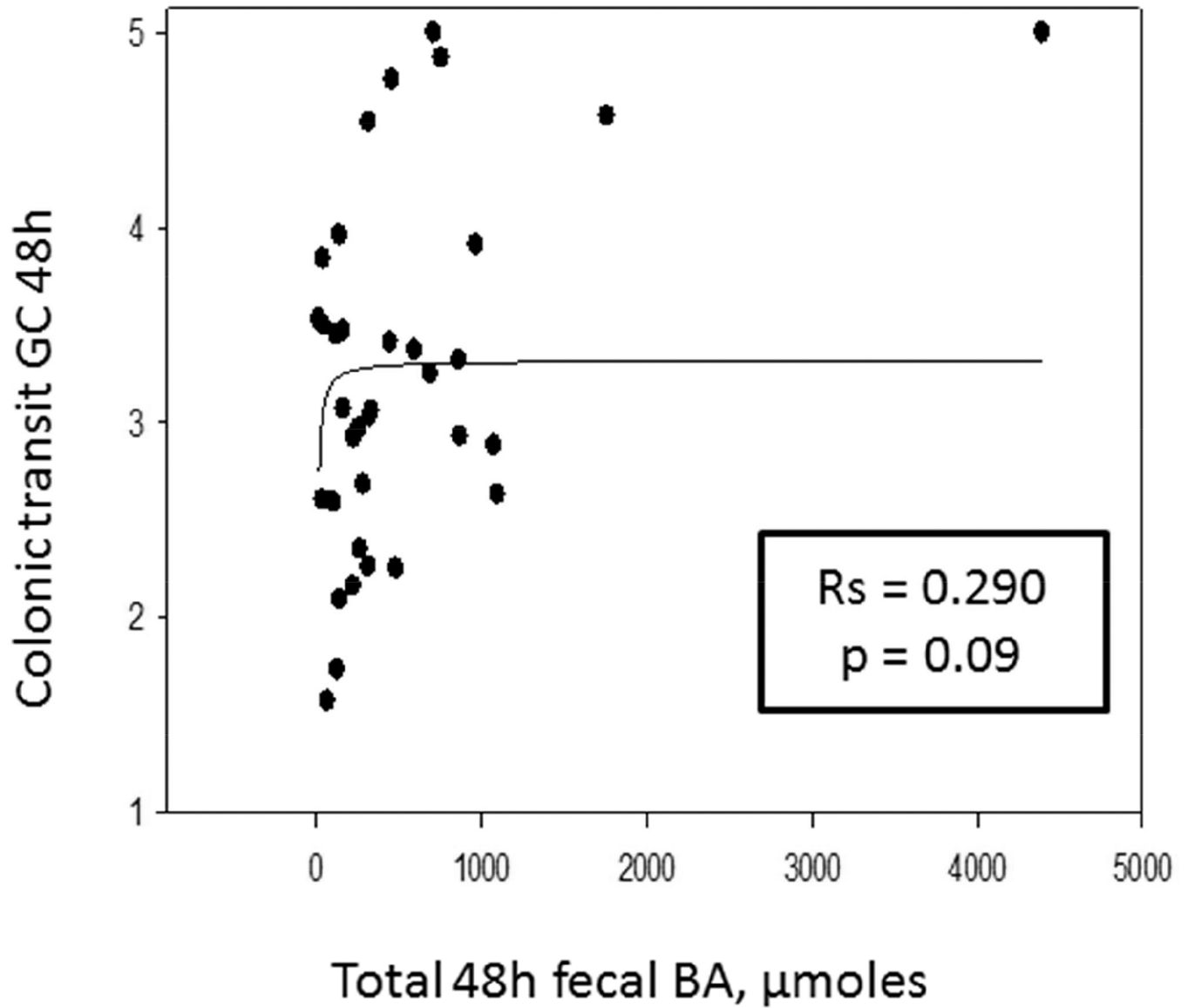
Figure 3.
Direct correlation of serum C4 (left panel) and fecal BA excretion (right panel) and colonic transit (geometric center, GC) at 48 hours. Graphs represent 2-parameter rectangular hyperbola: y=ax/(b+x).
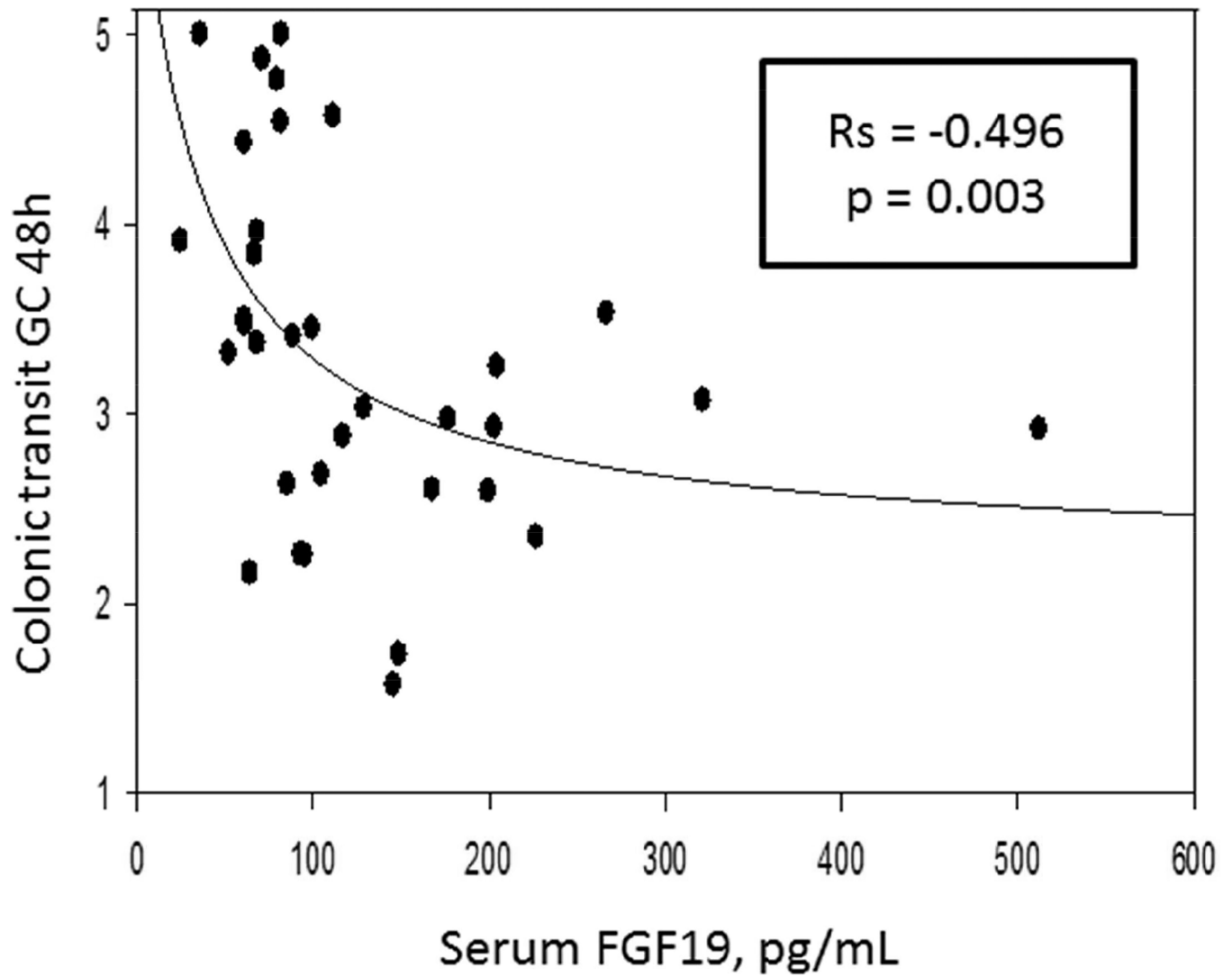
Figure 4.
Inverse relationship between fasting serum FGF19 and colonic transit (geometric center, GC) at 48 hours. Graphs represent a 3-parameter hyperbolic decay: $y = y_0 + ab/(b+x)$.

Table 1

Proportion of total fecal BAs excreted and absolute values for individual BAs excreted in 48 hours (data show mean ± SD)

Individual BA (% or μmol/48h)	Healthy volunteers (n=25)	IBS-C (n=27)	Wilcoxon Rank Sum test
% LCA	39 ± 14	51 ± 19	Z= 2.12, p = 0.0337*
% CDCA	0.0 ± 1.0	1.0 ± 1.3	Z= −1.84, p = 0.07
% DCA	59 ± 14	48 ± 19	Z= −2.22, p = 0.027*
% UDCA	1.0 ± 2.0	0.0 ± 0.2	Z= −0.81, p = 0.42
% CA	1.0 ± 1.0	1.0 ± 2.7	Z= −0.30, p = 0.76
LCA μmol/48h	297.7 ± 291.4	204.8 ± 188.2	Z = −1.23, p = 0.22
CDCA μmol/48h	5.56 ± 10.13	1.89 ± 4.0	Z = −1.88, p = 0.06
DCA μmol/48h	500.81 ± 564.3	354.9 ± 691.1	Z= −1.8, p = 0.07
UDCA μmol/48h	9.04 ± 23.11	0.46 ± 0.9	Z = −1.49, p = 0.14
CA μmol/48h	6.02 ± 10.82	3.77 ± 8.5	Z = −1.12, p = 0.26

Table 2

Spearman correlations between the serum and fecal biomarkers and colonic transit

	GC24	GC48	Fecal BA	FGF19
C4	Rs = 0.363, p=0.03 [*]	Rs = 0.369, p=0.03 [*]	Rs = 0.362, p = 0.02 [*]	Rs = −0.58, p<0.001 [*]
FGF19	Rs = −0.267, p=0.126	Rs = −0.496, p=0.003 [*]	Rs = −0.235, p=0.16	
Fecal BAs	Rs = 0.357, p = 0.036 [*]	Rs = 0.290, p = 0.09		Rs = −0.235, p=0.160

[*]
significant correlations