Colonic Transit Time and IBS Symptoms: What's the Link?

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OBJECTIVES: **The relevance of colonic transit alterations for the overall symptom pattern in irritable bowel syndrome (IBS) is incompletely understood. The aim of this study was to assess the total and segmental colonic transit time (CTT) and their relationship to symptoms and subgroups in a large sample of IBS patients.**

METHODS: **Total and segmental CTT was assessed using radiopaque markers in 359 patients with IBS (279 females). These results were compared with existing normal values for healthy men and women without gastrointestinal (GI) symptoms. Stool frequency and consistency (Bristol Stool Form (BSF) scale), and the perceived severity of three GI symptoms (bloating, flatulence, and abdominal pain) were noted in a daily diary during the measurement week. Patients could be classified by the BSF scale characteristics into Rome III subtypes ($n=338$), or by use of the Rome II modular questionnaire into Rome II subtypes ($n=143$).**

RESULTS: **CTT was normal in 287 patients (80%), whereas 53 (15%) had accelerated and 19 (5%) had delayed CTT. Transit abnormalities in relation to gender-specific reference values were more common in males (30.0%) than in females (17.2%; $P<0.05$). IBS subgrouping according to Rome III ($P<0.0001$) and Rome II criteria ($P<0.001$) was associated with the presence of abnormal CTT. Stool form ($r=-0.40$; $P<0.0001$) and stool frequency ($r=-0.30$; $P<0.0001$) were moderately and negatively correlated to total CTT. No correlations of clinical significance were found between transit data and the three GI symptoms.**

CONCLUSIONS: **Total and segmental colonic transit alterations are of importance for the abnormal bowel habit seen in men and women with IBS, but of no or minor importance for other IBS symptoms.**

Am J Gastroenterol advance online publication, 14 February 2012; doi:10.1038/ajg.2012.5

INTRODUCTION

Irritable bowel syndrome (IBS) is common worldwide (1–5) and is often considered a troublesome diagnosis in many respects: for the patient (6), the doctor (7), and the society in terms of direct and indirect costs (2,8). Even though our knowledge regarding pathophysiological mechanisms, such as gastrointestinal (GI) dysmotility, visceral hypersensitivity, and psychosocial factors, (9) is steadily improving, it remains difficult to use them as predictors of outcome regarding any treatment presumably directed toward one or more of these factors. A major reason for initiating the ongoing Rome process (10) was to define and validate diagnostic criteria for functional GI disorders, and to create a more robust understanding of the underlying pathophysiology, leading to more effective treatment decisions. Much has been gained by this work, but still most of the treatment algorithms in functional GI disorders continue to be based upon predominant symptoms without thorough knowledge of the underlying pathophysiological mechanism.

Complaints about symptoms related to defecation are one of the most common reasons to consult a gastroenterologist. If the defecatory symptom is part of an IBS diagnosis, abdominal pain or discomfort is also included (11). The relevance of transit alterations for the overall symptom pattern in this clinical situation is incompletely understood. Stool form expressed by the Bristol Stool Form (BSF) scale seems to have a fair correlation to bowel transit (12–14), where loose and hard stools predict accelerated

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Received 21 September 2011; accepted 20 December 2011

and delayed transit, respectively, reasonably well. Stool frequency has been reported both as a less reliable (15) and a good predictor (16) of bowel transit. However, most studies are weakened by a small sample size and they rarely assess stool habits in relation to other GI symptoms (17). As transit abnormalities were recently reported to be a highly prevalent pathophysiological mechanism in IBS and functional constipation (18), a thorough investigation assessing relationships between gut transit and a wider array of GI symptoms in a large group of IBS subjects seems warranted.

As the group of patients that may benefit from a transit assessment is huge, the method used has to be widely accessible, not too expensive and harmless. For the moment there are three validated methods available; radio-opaque markers (ROMs), scintigraphy, and the wireless motility capsule (19). Of these, the ROM method is the most widely available, and easy to set up in most hospital environments without a significant investment in technology. The results obtained by a ROM study have also been shown to correlate well with scintigraphy (20). However, its major drawback is the lack of standardization between centers.

With this as a background, the primary aim of this study was to assess total and segmental colonic transit time (CTT) and their relationship to GI symptoms and subgroups in a large sample of IBS patients.

METHODS

Patients

During the time period November 2002 until May 2010, consecutive patients admitted to a combined clinical and research tertiary care outpatient clinic, fulfilling criteria for IBS according to Rome II (21) and later Rome III criteria (11), were enrolled into studies characterizing different aspects of GI pathophysiology, symptoms, and treatment options in IBS. The diagnosis of IBS was based on a typical clinical presentation, and additional technical investigations if considered necessary. As this is a tertiary care population, most patients had already undergone additional examinations such as blood biochemistry, endoscopic, and radiological investigations.

All patients were given study-specific verbal and written information before giving their written consent to participate in the studies. The Regional Ethical Review Board and the radiation safety committee at the University of Gothenburg had approved each of the studies included in this manuscript before the start of patient inclusion.

Colonic transit study

For the CTT measurement, the subjects ingested 10 radiopaque rings every morning for 5 days. On the 6th day they ingested five radiopaque rings at 0800 hours and five radiopaque rings at 2000 hours in order to better define patients with accelerated transit. On the morning of the 7th day the radiopaque rings still present in the bowel were counted upon arrival at the laboratory, using fluoroscopy (Exposcop 7000 Compact, Ziehm GmbH, Nüremberg, Germany). The position of the rings was noted in relation to ileal and colorectal anatomic segments (terminal ileum, ceacum, ascending, transverse, descending, sigmoid colon, and rectum). CTT and segmental transit expressed in days was calculated by dividing the number of retained radiopaque rings by the daily dose number; i.e., 10. The sum of the ceacal and ascending region was considered as right colonic transit, the transverse colon transit assessed on its own, and the anatomic regions distal to the splenic flexure considered as left colonic transit. Different fluoroscopy projections (posterior, lateral, and oblique) were used when needed for optimal localization. During the CTT study, no medications that could affect GI motility were allowed. The protocol has been extensively described and validated previously (22–24), including reference values for gender-specific normal ranges, based on measurements in 139 healthy subjects (mean age 33.4 (18–70) years; 76 females) without GI symptoms investigated at our unit (22,25). On the basis of this previous work, a normal transit time for men is defined as 0.7–2.2 days and for women 0.9–4.2 days. All patients and healthy control subjects were investigated using the same method.

Questionnaires

Patients were asked to complete Rome II ($n=143$) and later Rome III ($n=216$) diagnostic questionnaires for IBS, to confirm that they fulfilled current diagnostic criteria for IBS at the time of the investigation. During the 6 days that the CTT measurement was done, all bowel movements were registered in a diary by the patient and the stool form characterized according to the BSF scale (12). A majority ($n=344$) of patients could be classified by the BSF scale characteristics into Rome III subtypes, i.e., IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed IBS, or unsubtyped IBS (11). Those patients ending up being classified as unsubtyped IBS or mixed IBS by the Rome III criteria were treated as one group (IBS-nonCnonD) in the statistical analysis and the presentation of data. The Rome II Modular Questionnaire (26) was used for Rome II subtyping ($n=143$) into diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C) or alternating type IBS (IBS-A). The perceived severity of three GI symptoms, bloating, flatulence, and abdominal pain, was assessed by the patient on a daily basis in the diaries and scored on a Likert scale with severity scores between 0 and 3 (0 = absent, 1 = mild and easily ignored, 2 = moderate and with a negative impact on daily activities, and 3 = severe and disabling, profoundly interfering with daily activities).

Data analysis

Statistical analysis was performed with the software package IBM SPSS Statistics version 18 (IBM Corporation, Armonk, NY).

Data are presented as mean±s.d. or as proportions (%). Means were compared between two groups using the Students *t*-test, whereas nominal data were compared by use of the Pearson χ^2 test. Correlations were calculated using Spearman's correlation coefficients. Comparison of the mean values between multiple groups was done by analysis of variance, with *post-hoc* group differences corrected for multiple comparisons (the Bonferroni correction). In order to test if the relationship between CTT

and GI symptoms differs significantly between men and women, general linear models were used with each GI symptom as the dependent variable and transit and gender as independent variables including a transit-by-gender interaction. For the ease of interpretation of the main effects, the interaction effect will only be reported when significant. Receiver operating characteristics (ROC) curves were used to assess the specificity and sensitivity of stool form and stool frequency for discriminating patients with abnormal transit from those with normal transit. An area under the ROC curve (AUROC) of >0.7 is considered fair, >0.8 good, and >0.9 as having excellent discriminating ability. The level of statistical significance was set at a *P*-value <0.05.

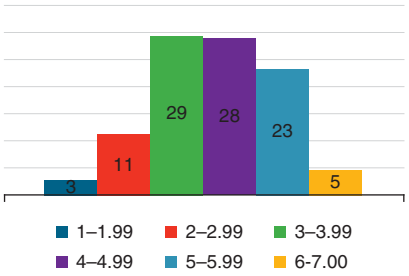

Figure 1. Distribution of mean stool form among 338 IBS patients according to BSF scale (%). BSF, Bristol Stool Form; IBS, irritable bowel syndrome.

RESULTS

Patient characteristics

The total study cohort consisted of 359 patients (279 females) with a mean age of 38±12.9 years (range 18–69 years). The distribution of IBS subgroups according to the Rome II criteria were; IBS-C 18%, IBS-D 35%, and IBS-A 47%, and according to the Rome III criteria; IBS-C 26%, IBS-D 39%, and IBS-nonCnonD 35%. The average stool form according to the BSF scale was 4.2±1.2 and the average stool frequency was 2.2±1.0 stools/day. The distribution of mean stool form on an individual basis is summarized in **Figure 1**. The mean individual symptom scores were mild or moderate for 78% of patients regarding bloating, 75% of patients for flatulence, and 66% of patients for abdominal pain. Only 16% (bloating), 10% (flatulence), and 15% (abdominal pain) of patients reported severe symptom scores (mean >2).

Transit data: descriptive statistics and role of gender

A normal CTT was found in 287 patients (80%), whereas 53 patients (15%) had accelerated and 19 patients (5%) had delayed CTT. Transit abnormalities in relation to gender-specific reference values were more common in males (30.0%) than in females (16.2%; $\chi^2=7.50$, df=2, $P=0.024$). CTT was significantly ($P<0.0001$) shorter in males (1.3±0.8 days) compared with females (1.8±1.1 days) but this was not reflected by any difference regarding stool frequency (2.3±1.3 vs. 2.1±1.3 times/day; $P=0.27$), or stool form expressed by the BSF scale (4.3±1.2 vs. 4.2±1.2; $P=0.39$). Age had a weak positive correlation to CTT ($\rho=0.11$; $P=0.04$). Transit characteristics are summarized in **Table 1**.

Table 1. CTT, bowel habits and symptom characteristics (s.d.)

	Total	Females	Males	*P* values
Age (years)	38 (12.9)	37.3 (12.9)	40.2 (12.8)	0.08
CTT (days)		*n*=279	*n*=80	
Total	1.7 (1.0)	1.8 (1.1)	1.3 (0.8)	<0.0001
Right	0.5 (0.3)	0.5 (0.4)	0.4 (0.2)	<0.01
Transverse	0.25 (0.3)	0.3 (0.4)	0.2 (0.2)	0.31
Left	0.8 (0.8)	0.9 (0.8)	0.6 (0.5)	0.001
Transit group		*n*=279	*n*=80	
Normal	80%	84%	70%	
Accelerated	15%	13%	20%	
Delayed	5%	3%	10%	
Stool habits		*n*=267	*n*=75	
Frequency/day	2.2 (1.3)	2.1 (1.3)	2.3 (1.3)	0.27
Stool form (BSF)	4.2 (1.2)	4.2 (1.2)	4.3 (1.2)	0.28
Symptoms		*n*=264	*n*=70	
Abdominal pain	1.1 (0.9)	1.1 (0.8)	1.1 (0.9)	0.96
Bloating	1.4 (0.7)	1.4 (0.7)	1.3 (0.8)	0.12
Flatulence	1.3 (0.6)	1.3 (0.6)	1.3 (0.7)	0.80

BSF, Bristol Stool Form; CTT, colonic transit time.

Transit data: Rome subgroups

IBS subgrouping according to the Rome III criteria was associated with the presence of abnormal CTT ($\chi^2 = 41.0$, df = 4, $P < 0.0001$). Accelerated CTT was found in 27% of patients with IBS-D and delayed CTT in 11.5% of those with IBS-C. Conversely, the proportion of patients with IBS-D having delayed transit was 0.8%, and in IBS-C accelerated transit was seen in 2.3% (**Figure 2**). When analyzing transit data using the Rome II subgroups a significant association to abnormal CTT was still present ($\chi^2 = 19.2$, df = 4, $P = 0.001$), but the group of 37 patients (26%) ending up with a transit abnormality was in absolute numbers small. Accelerated CTT was found in 36% of subjects classified as IBS-D and delayed CTT in 15% with IBS-C.

Total and segmental transit time, bowel habits, and GI symptoms

Segmental transit time (right colon, transverse, and left colon) had a positive correlation to total CTT, being most pronounced in the left colon ($\rho = 0.78$; $P < 0.0001$), but also with a good correlation to right ($\rho = 0.46$; $P < 0.0001$) and transverse ($\rho = 0.50$; $P < 0.0001$) segmental transit time. The strengths of these correlations were similar in men and women, though somewhat stronger in men.

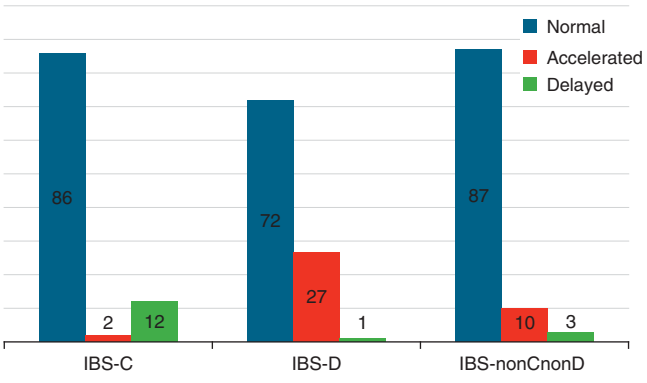

Figure 2. Proportion of patients (%) with normal and abnormal colonic transit in relation to IBS subgroups according to the Rome III criteria. IBS, irritable bowel syndrome.

Both stool form ($\rho = -0.41$; $P < 0.0001$) and stool frequency ($\rho = -0.37$; $P < 0.0001$) were moderately and negatively correlated to total CTT, with correlations being generally stronger for left colonic transit than for right and transverse transit times (**Table 2**). In general linear model analysis, stool frequency was found to be significantly associated with total CTT ($\beta = -0.36 \pm 0.06$, $P < 0.0001$), but not with gender ($P = 0.99$). The CTT-by-gender interaction effect was not significant (data not shown). For stool form, on the contrary, a significant CTT-by-gender interaction effect was found, in addition to a main effect of CTT and a trend for gender (**Table 3**). The interaction effect indicates that, although CTT has a significant effect on stool form in both genders, its effect is significantly stronger in men compared with women. Similar results were found for stool frequency and stool form when left colonic transit rather than total CTT was used as independent variable.

Both stool form and stool frequency had a fair discriminative validity to positively identify patients with accelerated or delayed total CTT. Stool form had an AUROC of 0.76 for both accelerated ($P < 0.0001$) and delayed ($P = 0.0002$) transit, and stool frequency an AUROC of 0.78 for delayed transit ($P < 0.0001$) and 0.7 ($P < 0.0001$) for accelerated transit (**Figure 3**). The best cutoff value to identify accelerated transit was >2.1/day for stool frequency, with a sensitivity of 68% (95% CI 53–80%) and a specificity of 64% (95% CI 58–69%), and >4.5 for stool form, with a sensitivity of 78% (95% CI 64–88%) and a specificity of 64% (95% CI 59–70%). The best cutoff values for identification of delayed transit was <1.2/day for stool frequency with a sensitivity of 78% (95% CI 73–82%) and a specificity of 72% (95% CI 47–90%), and <3.5 for stool form, with a sensitivity of 72% (95% CI 47–90%) and a specificity of 70% (95% CI 65–75%).

Assessing the results from the three GI symptoms, abdominal pain showed weak though significant negative correlations with total CTT ($\rho = -0.14$; $P = 0.013$) and left CTT ($\rho = -0.16$, $P = 0.004$; **Table 2**). The association between total CTT and abdominal pain remains significant in general linear model analysis ($\beta = -0.09 \pm 0.05$, $P = 0.045$) including gender ($P = 0.74$). The CTT-by-gender interaction effect was not significant (data not shown). Again, a similar result was found for abdominal pain when left colonic transit rather than total CTT was used as independent variable.

Table 2. Correlations between CTT, segmental transit and stool habits and GI symptoms

	CTT (*r*)	Right (*r*)	Transverse (*r*)	Left (*r*)
Stool form	−0.40****	−0.20****	−0.16**	−0.38****
Stool frequency	−0.30****	−0.15**	−0.15**	−0.26****
Abdominal pain	−0.11*	0.04	−0.02	−0.14**
Bloating	−0.04	0.06	−0.03	−0.07
Flatulence	−0.02	0.03	0.01	−0.02

CTT, colonic transit time; GI, gastrointestinal.
*$P<0.05$; **$P<0.01$; ****$P<0.0001$.

Table 3. General linear model analysis with stool form as the dependent variable

	Estimate (β)	s.e.	*P*-value
Intercept	5.39	0.25	<0.0001
CTT	−0.86	0.17	<0.0001
Gender[a]	−0.49	0.27	0.0741
CTT[a] Gender[b]	0.45	0.18	0.0120

CTT, colonic transit time.
Model $F_{4,339}$=1385.8, P<0.0001, R^2=0.18.
[a]Dummy variable, reference category, men.
[b]The significant interaction effect indicates that the strength of the relationship between CTT and stool form significantly differs between men and women: the significant main effect of CTT shown in the table applies to men only (β=−0.86±0.17, P<0.0001), whereas the effect of CTT in women is less strong, though still significant (β=−0.40±0.06, P<0.0001).

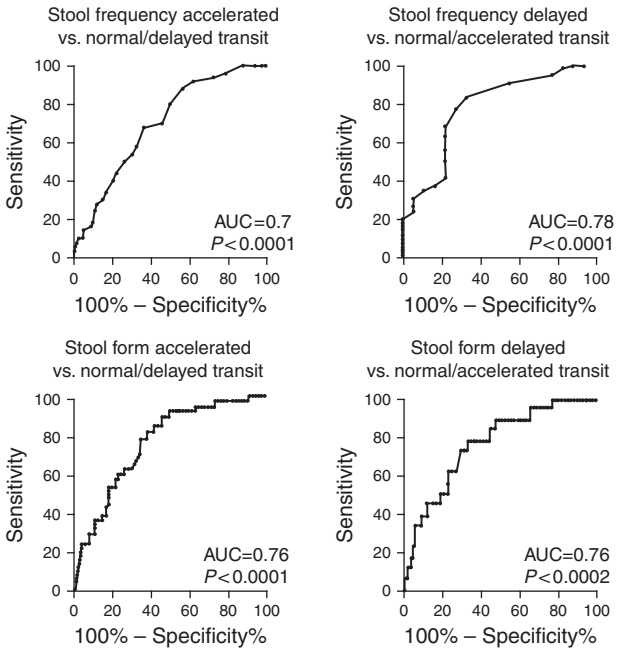

Figure 3. ROC curves analysis were performed to assess the specificity and sensitivity of stool frequency and stool form discriminating patients with accelerated and delayed CTT from the respective remaining patient group. AUROC curve of >0.7 is considered as having a fair discriminative value. AUROC, area under the ROC; CTT, colonic transit time; ROC, reciever operating characteristics.

DISCUSSION

This study is, to the best of our knowledge, the first to assess the association between total and segmental CTT, stool habits, and GI symptoms in a large cohort of IBS patients. In line with our previous, smaller study assessing the relationship between transit and GI symptoms in IBS (17), total and segmental CTT alterations were found to be significantly associated with the abnormal bowel habits seen in men and women with IBS. However, the majority of IBS patients included in this study had a CTT within the normal range for their age and gender; only one in five had pathological values (22,25). The proportion of patients with an abnormal CTT was higher in men than in women with IBS, but the wider range of normality in females also affects this finding. In those with abnormal transit times, accelerated CTT dominates, but most IBS-D patients still have a normal CTT. A significant negative correlation was found between CTT and stool form and frequency, and consequently IBS-C and IBS-D, defined by the Rome II and III criteria, are associated with delayed and accelerated CTT, respectively. The symptoms of bloating, flatulence, and abdominal pain correlate poorly or not at all with CTT.

One strength of this study is the use of an identical transit investigation and symptom registration in all patients. The method with ROMs as used here has been under continuous validation during a long time period at our motility lab, resulting in a thorough knowledge with no major pitfalls in the standard of the procedure (22,24,27). Simplicity and safety, both for the patient and the investigator, are important factors to take into account. The symptom registration did not use a formally validated questionnaire, but the same type of scale has been used in other settings (28–30) with good exploratory evaluation properties. Our outpatient clinic represents a tertiary referral center, but as the majority of patients are referred directly from their general practitioner to our research projects, we believe they are reasonably representative for IBS in general. However, one indication that there is probably a slight referral bias is the observation of a higher proportion of IBS-D in this study relative to community samples (31).

Recently, a large study assessing colonic transit by scintigraphy in a cohort of patients with lower functional bowel disorders concluded that an underlying motor disorder could be found in about 30% (18). This is a somewhat higher proportion of patients with an objectively identifiable transit alteration compared with our study. A difference of importance is a wider inclusion of patients with different functional bowel disorders, such as IBS, functional constipation, and functional diarrhea, defined by the Rome II criteria (21) in the study from the Mayo group, potentially contributing to the higher proportion of patients with transit alterations. Another recent study investigated colonic transit with the use of both the wireless motility capsule and the ROM together with registration of stool form and frequency in 46 constipated patients and 64 healthy controls (14). These authors come to a similar conclusion as we did in our study, namely that stool form can reasonably well predict CTT. Their correlation coefficient with both the wireless motility capsule (r = −0.61), and ROM (r = −0.45) was more convincing than what we found, but they included a more homogenous patient group, potentially explaining this discrepancy. As others have found before us, we also found stool frequency to be a less reliable surrogate marker for colonic transit than stool form.

Studies addressing whether other GI symptoms than alterations in bowel habits are also associated with a colonic transit abnormality, have not been performed in IBS, to the best of our knowledge. In our previous study, we found an association between some

GI symptoms, including stool frequency and form, and colonic transit, but in that study the symptoms were not assessed during, but the week before, the transit measurement (17). One previous study, which included a large number of IBS patients, used a well-validated scintigraphic method for gut transit but restricted their analysis to segmental transit time clusters, and only IBS patients with normal total transit time were finally investigated (32). They concluded that differences in segmental transit time existed in normal transit IBS compared with healthy controls, but did not actually correlate to the individual symptoms comprising the basis for the IBS diagnosis. The lack of a meaningful association of CTT with other GI symptoms than the stool habits, as described in our current study, is important. Even if GI motility since long is recognized as one of the key features in IBS pathophysiology (33), its central role can be questioned when it comes to symptom generation other than for stool form, and, to a lesser degree, frequency. It is reasonable to believe that a visceral sensory dysfunction (34) and altered central processing of sensory information from the gut (35) may be of more importance in the majority of IBS patients, and that at least IBS-related abdominal pain cannot in a simple way be associated with the bowel habits per se as has been previously pointed out (36). This observation may also be relevant for drug development and efficacy evaluation in IBS. Several pharmacological agents with well-defined motility effects in the GI tract have recently been developed for the treatment of IBS, with the overall impression that they were most efficacious in their action on stool consistency, and were at best moderately effective in improving other symptoms such as abdominal pain, discomfort, or bloating (37).

From a clinical point of view, our study can be used both as a pro and con argument regarding the use of CTT measurements in patients diagnosed with IBS. The finding that most of them have a normal CTT advocates a restrictive use, and it is also known that about one quarter of IBS patients change their predominant bowel pattern, at least once within a year (38), risking a short "best-before" date for a CTT study. On the other hand, a more liberal use of CTT studies could be advocated to increase our chances of using laxatives and anti-diarrheals in the right patients, and especially when considering using new drugs, which mainly affect GI transit. In those patients with troublesome bowel disturbance, not responding to laxatives or anti-diarrheals, a transit study still adds clinically relevant information and may enhance confidence in choosing which treatment option to recommend. As CTT and stool form are closely correlated, a stool diary based upon the BSF scale and stool frequency may be sufficient in most clinical settings, and CTT could be restricted to cases that are difficult to evaluate just by symptom registration. Studies evaluating the impact of transit studies in IBS management and outcome seem warranted. If deciding to do a transit study, a ROM based one is the most widely available method and for the moment more cost-effective than scintigraphy and the wireless motility capsule. In our hands it has been shown to be accurate and reliable, exposing patients to a low radiation dose (17,22,24).

In conclusion, in this large study we have demonstrated that abnormal colonic motility, indirectly measured as total and segmental CTT, are of importance for the altered bowel habits seen in both men and women with IBS, but seems to be of no or minor importance for the other key IBS symptoms.

CONFLICT OF INTEREST

Guarantor of the article: Magnus Simrén, MD, PhD.
Specific author contributions: Hans Törnblom: study design, data analysis and statistics, and manuscript preparation. Lukas Van Oudenhove: data analysis and statistic and manuscript preparation. Riadh Sadik: patient inclusion and critical review of manuscript. Hasse Abrahamsson: study design and critical review of manuscript. Jan Tack: data analysis and critical review of manuscript. Magnus Simrén: study design, patient inclusion, data collection, data analysis and statistics, and manuscript preparation.
Potential competing interests: Jan Tack has given scientific advise to: Almirall, AstraZeneca, Danone, Menarini, Novartis, Nycomed, Ocera, Ono pharma, Shire, SK Life Sciences, Theravance, Tranzyme, Xenoport, and Zeria Pharmaceuticals, and has been a member of the Speaker bureau for: Abbott, Almirall, AlfaWasserman, AstraZeneca, Janssen, Menarini, Novartis, Nycomed, Shire, and Zeria. Magnus Simrén has received unrestricted research Grants from Danone and AstraZeneca, and served as a Consultant/Advisory Board member for Danone, Novartis, Boehringer-Ingelheim, and Shire/Movetis. The rest of the authors declare no potential competing interests.
Financial Support: This work is funded by the Swedish Medical Research Council (Grants 13409, 21691, and 21692). The Marianne and Marcus Wallenberg Foundation, Sahlgrenska Academy, University of Gothenburg, Centre for Person-Centred Care (GPCC), University of Gothenburg and by the Faculty of Medicine, University of Gothenburg. Lukas Van Oudenhove is a postdoctoral research fellow of the Research Foundation—Flanders (FWO-Vlaanderen). Jan Tack is supported by a Methusalem grant from Leuven University.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Gastrointestinal dysmotility is a pathophysiological mechanism in irritable bowel syndrome (IBS).
- ✓ The relevance of colonic transit alterations for the different IBS symptoms is incompletely understood.

WHAT IS NEW HERE

- ✓ Colonic transit is abnormal in only 20 % of IBS patients.
- ✓ Colonic transit affects bowel habits in IBS, in particular stool form, but seems to be of little or no importance for other IBS symptoms such as abdominal pain, bloating, and flatulence.

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