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Irritable Bowel Syndrome

Diagnostic Symptom Criteria
and Impact of Rectal Distensions on
Cortisol and Electrodermal Activity

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To Bent and Fridolf

ABSTRACT

In a population prevalence questionnaire study we demonstrated that constipation and fecal incontinence are common problems in the general Swedish population with a similar magnitude as in other Western countries. 95.6% of the population had between three bowel movements per day and three per week. Constipation was mostly defined by “hard stools” and “the need of using laxatives”.

Irritable Bowel Syndrome (IBS) is characterized by abdominal pain/discomfort and abnormal bowel habits. The diagnostic criteria of IBS are based on clinical symptoms. Division of IBS patients into symptom subgroups appears important as their bowel symptoms are characterized by heterogeneity. International criteria to subgroup IBS (Rome II) are based on expert consensus and not on evidence. We investigated the variation of stool consistency and defecatory symptoms in 135 IBS patients by symptom diary cards. Most patients had alternating stool consistency. When subgroups were based on stool consistency, all kinds of defecatory symptoms (straining, urgency, and feeling of incomplete evacuations) were frequently present in all subgroups. Stool frequency was in the normal range in the majority of patients. We propose that IBS subgroups should be based on stool consistency. We suggest that Rome II supportive criteria must be reconsidered as the determination of presence or absence of specific symptoms does not work as an instrument for categorization of IBS patients into diarrhoea-and constipation-predominant. We also propose that abnormal stool frequency should be excluded to define subgroups of IBS. Alternating stool consistency and presence of different defecatory symptoms, regardless of stool consistency should be included as criteria for IBS.

Stress is known to play an important role in the onset and modulation of IBS symptoms. From experimental studies there is evidence for a stress-dependent alteration of visceral sensitivity. The biological mechanisms responsible for the causal link between stress and IBS symptoms are not completely understood, but the hypothalamic-pituitary-adrenocortical axis and the autonomous nervous system seem to play a prominent role in the pathophysiology of IBS. We investigated visceral sensitivity and the effect of repeated maximal tolerable rectal distensions on salivary cortisol levels and skin conductance in patients with IBS, chronic constipation and healthy volunteers.

We found that the expectancy of the experimental situation *per se* (provocation of bowel symptoms by rectal distensions) compared to non-experimental days at home measured as salivary cortisol had a high impact on the level of arousal in IBS. IBS patients had higher skin conductance values than controls in the beginning of distension series and lower rectal thresholds for first sensation, urge and discomfort than healthy controls and constipation patients. IBS patients demonstrated habituation to repeated subjective maximal tolerable rectal distensions according to sympathetic activity although patients continued to rate their discomfort as maximal. Constipation patients had lower sympathetic activity than IBS patients before and during repeated rectal distensions. None of the groups demonstrated a significant increase in cortisol after repetitive rectal distensions.

We conclude that Rome II supportive criteria for IBS should be reconsidered according to our findings. IBS patients are more sensitive to pre-experimental stress than healthy controls and patients with constipation. This should be considered in the design of experimental IBS studies. IBS patients habituated to subjective maximal tolerable, repetitive rectal distensions with decreasing sympathetic activity. Since responses to repeated stimuli of close-to-pain intensities are resistant to habituation this finding could be caused by psychological influences on perception, that is, perceptual response bias.

PAPERS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

- I. A population-based study on bowel habits in a Swedish community: prevalence of faecal incontinence and constipation
Walter S, Hallböök O, Gotthard R, Bergmark M, Sjö Dahl R
Scand J Gastroenterol. 2002 Aug;37(8):911-6.
- II. Subgroups of irritable bowel syndrome: a new approach
Walter SA, Skagerström E, Bodemar G
Eur J Gastroenterol Hepatol. 2004 Oct;16(10):991-4.
- III. New criteria for irritable bowel syndrome based on prospective symptom evaluation
Walter SA, Ragnarsson G, Bodemar G
Am J Gastroenterol. 2005 Nov;100(11):2598-9.
- IV. Pre-experimental stress in patients with irritable bowel syndrome: high cortisol values already before symptom provocation with rectal distensions
Walter SA, Aardal-Eriksson E, Thorell L-H, Bodemar G, Hallböök O
Neurogastroenterol & Motil. 2006; (18): 1069- 1077
- V. Sympathetic activity during repeated maximal rectal distensions in patients with irritable bowel syndrome and constipation
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INTRODUCTION

Normal bowel habits

There have been several attempts to study what are “normal” bowel habits.^{1 2 3 4 5 6 7 8 9 10} In 1965 Connell et al. found that 99.3% of people had between three bowel movements per day and three per week.¹ This was confirmed in a later study by Drossman et al.³ Today a stool frequency within this range is still considered to be normal.¹¹ Ragnarsson and Bodemar found that the majority of patients with irritable bowel syndrome (IBS) had a bowel movement frequency within this “normal” range.¹² Obviously, normal bowel frequency does not exclude bowel disturbances. Heaton et al. found, in a prospective diary card study, that only 40% of men and 33% of women had a regular 24-hour bowel habit cycle⁵ and concluded that normal bowel function is experienced by less than half of the population. Bowel habits are reported to be influenced by several factors such as gender,^{4 5, 13 14 15} age,^{5 16} race,^{4 13} diet,^{17 18} stress,³ or physical activity⁴ and may therefore differ between different cultures and countries. It seems to be somewhat unclear how to interpret the term “normal bowel habits”. It may also be difficult to translate the results of international population prevalence studies of bowel habits to Swedish conditions. A better understanding of bowel function in the general population would be useful to evaluate patients with gastrointestinal complaints.

The prevalence of self-reported constipation

One common gastrointestinal complaint is constipation. In North American population prevalence studies, constipation ranged from 1.9% to 27.2%, with most estimates from 12% to 19%.¹⁹ Everhart and co-workers found in a population sample by face-to-face interview that 20.8% of women and 8.0% of men reported constipation.⁴ In the same study 9.1 % of women and 3.2% of men reported three or fewer bowel movements per week. People thus consider low stool frequency as one among other symptoms when they consider themselves constipated. Most epidemiological studies have relied upon self-reported constipation, in which the subjects have simply been asked whether they are constipated or not.²⁰ The concept of constipation is complicated by disagreement among patients and doctors about its nature.¹¹ The value of self-reported constipation has been questioned as it cannot reliably differ between functional constipation and bowel outlet delay.²⁰ Moreover, there is an overlap of subjects reporting constipation and having IBS. Mearin et al. found that 66% of patients with IBS who fulfilled symptom criteria for IBS according to expert consensus (Rome I²¹) and 57% who fulfilled symptom criteria for IBS according to expert consensus (Rome II²²) considered themselves to have constipation.²³ In conclusion, results of constipation prevalence studies have to be interpreted carefully with respect to how subjects define constipation. Moreover, there seems to be a large overlap between self-reported constipation and IBS.

The prevalence of fecal incontinence

Another gastrointestinal problem that is common and may have a devastating impact on quality of life is fecal incontinence.^{24 25 26 27 28} The prevalence of fecal incontinence is estimated to be between 11-15%.²⁹ Prevalence figures heavily rely on the definition of severity and frequency of leakage events. Unfortunately only 5%-27% of patients with this condition consult their doctors about this problem^{30 31} and consequently physicians should ask about the symptoms.³² However, Nelson et al. found by telephone interview that 2.2% of an American population had anal incontinence including soiling and incontinence of gas.³³ This could be an underestimation because of people's reluctance to report these symptoms. The overall prevalence in another American study was as high as 18.4%.³⁴ The prevalence of fecal incontinence is higher in older than in younger people.³⁵ Functional bowel disorders including IBS may account for a large portion of fecal incontinence, although evidence data are limited.^{36 37} Other risk factors for fecal incontinence are diarrhoea, diabetes, older age, neurological disorders, high body mass index, obstetric anal sphincter injury, poor overall health and previous hysterectomy.³² On this background there are probably large international differences in the prevalence of fecal incontinence.

The prevalence of irritable bowel syndrome (IBS)

Population prevalence rates of IBS vary widely. Mearin et al. showed that the stricter the criteria, the lower the prevalence of IBS.³⁸ The IBS prevalence varied between 2.1% (according to Rome II³⁹) and 12.1% (according to Manning⁴⁰) in the same population dependent on the criteria used. But even if the same criteria are used (Rome II), the IBS prevalence still can vary between different population prevalence studies, from 3.3% in Spain³⁸ to 35% in Mexico⁴¹ (Table 1).

To study whether the international differences are real or apparent, Hungin et al. studied IBS prevalence in eight European countries, using the Manning, Rome I and Rome II criteria. The overall prevalence of current IBS symptoms across Europe was 9.6 % with a range from 6.2% in the Netherlands to 12% in UK and Italy.¹⁵ The prevalence of subjects who had a formal diagnosed IBS varied from 1.7% in Germany to 11.5% in Italy. In the same study the highest overall prevalence rate was obtained with the Manning criteria (6.5%) followed by the Rome I (4.2%) and the Rome II criteria (2.9%). They also found that IBS seems to be more common in women, even if different criteria are used.

IBS is a disorder with a chronic relapsing course.³⁹ In a follow-up study using Rome II criteria, Williams et al. found that 52% no longer met the IBS criteria two years after the first survey.⁴² They concluded that Rome II criteria are limited in capturing fluctuations of disease over time. Ragnarsson and Bodemar studied IBS patients in a follow-up after seven years⁴³ using diary cards. Although there was a general decrease in pain and straining and increase of normal stools, they found that the abdominal symptoms remained fairly unchanged. However, 35% of patients (n=20) did not take part in the follow-up study, limiting the conclusions that may be drawn from the results.

In conclusion, the epidemiology of IBS depends on the criteria used to classify it; the stricter the criteria, the lower the prevalence of the disease.⁴⁴ However, there are still large international differences even when the same criteria (Rome II) are used. It remains an open question to what extent these international differences are real, dependent on cultural factors or study designs. One common major factor of these epidemiologic studies is the use of questionnaires, which leads to recall bias,⁴⁵ and the absence of prospective documentation of symptoms on diary cards.

Table 1: Epidemiologic prevalence studies for irritable bowel syndrome

Author	Year	Country	Sample	Method	IBS prevalence	IBS criteria
Thompson et al. ²	1980	Great Britain	301 apparently healthy subjects	Questionnaire	13.6%	Manning criteria
Drossman et al. ³	1982	United States	789 students and hospital employees	Questionnaire	17.1%	Manning criteria
Jones et al. ⁴⁶	1992	Great Britain	Random sample 2280 subjects	Questionnaire	Ca 25%	Manning criteria
Agreus et al. ⁴⁷	1995	Sweden	Population sample 1290 subjects	Questionnaire	12.5%	
Talley et al. ⁴⁸	2001	New Zealand	Cohort of Young adults n= 1290	Questionnaire	12.7% 4.3%	Manning Rome II
Mearin et al. ²³	2001	Spain	2000 subjects	Personal interviews	3.3%	Rome II
Bommelaer et al. ⁴⁹	2002	France	11 131 subjects	Questionnaire & interview	4%	Rome I
Icks et al. ⁵⁰	2002	Germany	Random sample 2400 subjects	Questionnaire	12.5%	
Kwan et al. ⁵¹	2002	Hong Kong	Random sample 1000 subjects	Telephone interview	6.6%	Rome II
Hungin et al. ¹⁵	2003	Europe (eight countries)	40 000 subjects	Telephone interview	11.5%	Manning, Rome I or Rome II

Table 1 (continuation)

Author	Year	Country	Sample	Method	IBS prevalence	IBS criteria
Lu et al. ⁵²	2003	Taiwan	2865 subjects receiving a health check	Questionnaire	22.1%	Rome II
Tan et al. ⁵³	2003	Malaysia	533 healthy students	Questionnaire	15.8%	Rome I
Hoseini-Asl et al. ⁵⁴	2003	Iran	Random sample 5492 subjects	Questionnaire	5.8%	Rome II
Gwee et al. ⁵⁵	2004	Singapore	Random sample 3000 households	Face-to-face interview	8.6%	Rome II
Celebi et al. ⁵⁶	2004	Turkey	Random sample 1900 subjects	Face-to-face interview with questionnaire	6.3%	Rome II
Bommelaer et al. ⁵⁷	2004	France	8221 subjects	Questionnaire	1.1%	Rome II
Wilson et al. ⁵⁸	2004	Great Britain	Random sample 4807 subjects	Questionnaire	10.5%	Rome II
Hungin et al. ⁵⁹	2005	United States	Random sample 5009 subjects	Screening telephone interview	14.1%	Manning, Rome I or Rome II
Yilmaz et al. ⁶⁰	2005	Turkey	Random selection 3000 subjects	Face-to-face interview	10.2%	Rome II
Wigington et al. ⁶¹	2005	United States	990 subjects	Questionnaire	9.6%	Rome II
Sperber et al. ⁶²	2005	Israeli Bedouin society	737 rural subjects 1018 urban subjects	Interview	5.8% 9.4%	Rome II
Schmulson et al. ⁴¹	2006	Mexico City	324 healthy volunteers	Questionnaire	35%	Rome II
Vandvik et al. ⁶³	2006	Norway	4622 subjects	Questionnaire	8.4%	Rome II
Boyce et al. ⁶⁴	2006	Australia	1225 subjects	Questionnaire	8.9%	Rome I Rome II

Diagnostic symptom criteria for IBS

Manning criteria

The diagnosis of IBS is based on clinical symptoms. The first attempt to find unifying criteria was in 1978 when Manning and co-workers⁴⁰ studied 109 unselected patients who were referred to gastroenterology or surgery clinics with abdominal pain and/or change in bowel habit. Thirty-two of them got the diagnosis IBS. Based on a questionnaire with 15 questions about bowel symptoms, they found that four symptoms were more common in IBS patients than in patients with organic diseases:

- pain eased after bowel movement
- looser stools at onset of pain
- more frequent bowel movements at onset of pain
- abdominal distension

Later the Manning criteria were criticized as they apply to women and were not considered of diagnostic value for men.^{65 66} Moreover, only one of the four Manning criteria (abdominal distension) distinguished patients with IBS from patients with inflammatory bowel disease.⁶⁷

Kruis et al. criteria

In another attempt, Kruis and co-workers⁶⁸ compared 108 patients with IBS and 299 patients with organic disease. The following symptoms, evaluated by questionnaire, were more common in IBS:

- abdominal pain
- flatulence
- bowel irregularity
- the presence of symptoms for more than two years
- diarrhoea alternating with constipation

Rome I criteria

Rome I criteria²¹ were largely drawn from the Manning and Kruis data.⁶⁵ (Table 2)

Table 2: Rome 1 criteria for IBS²¹

Continuous or recurrent symptoms of:

- 1) Abdominal pain relieved by defecation or associated with a change in frequency or consistency of stools, and/or
- 2) Disturbed defecation (two or more of):
 - Altered stool frequency
 - Altered stool form
 - Altered stool passage (straining, urgency, or feeling of incomplete evacuation)
 - Passage of mucus
 - Usually with bloating or feeling of incomplete distension

Rome II criteria

In 1998 an expert consensus called “the Rome Working Team” changed the definition and diagnostic criteria for IBS with the intention to improve clarity and international consistency, based on existing evidence. The Rome II criteria are presented in Table 3. The studies to support the changes of the criteria according to the consensus document³⁹ are listed in Table 5. Beside the study of Manning there are two more patient studies with 104⁶⁹ and 156⁷⁰ patients, respectively, that have explored the symptoms of IBS patients. Both studies as well as the other studies are based on questionnaires, not on prospective recording of symptoms on diary cards.

Rome II supportive criteria

Because of the heterogeneity of the symptoms in IBS,⁷¹ subgrouping appears meaningful. Subgroups of patients with irritable bowel syndrome (IBS) are likely to respond differently to existing and evolving therapies.⁷² Rome II supportive criteria (Table 4) recommend the use of specific symptoms to classify patients into diarrhoea- or constipation-predominant IBS. They propose that patients with diarrhoea-predominant IBS should have more than three bowel movements a day or loose stools or urgency and that patients with constipation-predominant IBS should have fewer than three bowel movements a week or hard or lumpy stools or straining during a bowel movement. Patients belonging to one subgroup should not have any of the items present in the other subgroup.

Rome II supportive criteria are based on expert opinions, not on evidence. Our clinical impression was that IBS patients often have an alternating stool consistency. Criteria for an IBS subgroup with alternating stool consistency are missing in Rome II. Furthermore, our clinical impression and results obtained in trials was that almost all patients with IBS have some proportions of all defecatory symptoms and stool frequency seemed to be independent of stool consistency.

Results of earlier IBS symptoms studies from Linköping

Paper II and III of the present thesis is the continuation of the work of Ragnarsson and Bodemar.^{43 73} Ragnarsson and Bodemar showed that pain is temporally related to eating but not to defecation in IBS patients.⁷⁴ Patients define constipation and diarrhoea on the basis of stool consistency, not frequency, which is in the normal range in the majority of patients.¹² Patients can be divided into subgroups and the symptoms remain fairly unchanged over time.⁴³ Compared with controls, the patients are distinguished by pain, bloating and stools with straining and feeling of incomplete evacuation.⁷⁵

General aspects of symptom records

IBS is a diagnosis based on symptom reports. Heterogeneity of symptoms in IBS is a well known problem. Symptom evaluation by diary card is superior to questionnaires and minimizes the phenomena of recall.⁴⁵ Moreover, IBS patients might have a peculiar confirmatory bias for negative material⁷⁶ leading to bias when grading their symptoms retrospectively. In a majority of clinical studies, inclusion of IBS patients are performed by symptom questionnaires. Usually a description of patients' symptoms is absent with a reference that patient inclusion fulfils defined criteria (Manning, Rome I or Rome II). Unfortunately those criteria are not sufficiently evidence-based and criticism of them is growing.

Table 3: Rome II diagnostic criteria* for IBS²²

At least 12 weeks or more, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features:

- (1) Relieved with defecation; and/or
- (2) Onset associated with a change in frequency of stool; and or
- (3) Onset associated with a change in form (appearance) of stool.

Symptoms that cumulatively support the diagnosis of Irritable Bowel Syndrome

- Abnormal stool frequency (for research purposes “abnormal” may be defined as greater than three bowel movements per day and less than three bowel movements per week);
- Abnormal stool form (lumpy/hard or loose/watery stool);
- Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation);
- Passage of mucus;
- Bloating or feeling of abdominal distension.

* In the absence of structural or metabolic abnormalities to explain the symptoms

Table 4: Rome II Supportive Symptoms of IBS to subclassify IBS original* and additional criteria from the revised version **⁶⁵

- (1) Fewer than three bowel movements a week
- (2) More than three bowel movements a day
- (3) Hard or lumpy stool
- (4) Loose (mushy) or watery stools
- (5) Straining during a bowel movement
- (6) Urgency (having a rush to have a bowel movement)
- (7) Feeling of incomplete bowel movement
- (8) Passing mucus (white material) during a bowel movement
- (9) Abdominal fullness, bloating or swelling

Diarrhoea-predominant

1 or more of 2, 4, or 6 and none of 1, 3, or 5;*

or: 2 or more of 2, 4, or 6 and one of 1 or 5. (3. Hard or lumpy stools do not qualify)**

Constipation-predominant

1 or more of 1, 3, or 5 and none of 2, 4, or 6;*

or: 2 or more of 1, 3, or 5 and one of 2, 4, or 6.**

Table 5: Rome II criteria for IBS is based on studies given in the table, according to the Rome II Multinational Consensus Document ³⁹

Author	Year	Journal	Study Type	Subjects	Inclusion criteria	Method
Manning et al. ⁴⁰	1978	British Medical Journal	Patient study	109 unselected patients, 32 of them got the diagnosis IBS	Patients referred to gastroenterology or surgery clinics with abdominal pain and/or change in bowel habit	Questionnaire
Harvey et al. ⁶⁹	1987	Lancet	Long-term follow-up study on patients	104 IBS patients	Manning criteria	Questionnaire
Whitehead et al. ⁷⁷	1990	Gastroenterology	Factor analysis on non-patients	Two samples (n=351, n=149) of female adults	Women consulting for contraception and women belonging to church women's society were invited	Questionnaire
Taub et al. ⁷⁸	1995	Digestive Diseases and Sciences	Factor analysis on non-patients	1344 male and female adults	Female and male African-Americans and Caucasians	Questionnaire
Thompson et al. ⁷⁰	1997	European Journal of Gastroenterology	Patient study	156 IBS patients	Patients with diagnosis IBS not based on specific criteria	Questionnaire
Longstreth et al. ⁷⁹	1997	Digestive Diseases and Sciences	Review			

Pathophysiological aspects of IBS

The current view on the pathophysiology of IBS is that of interactions between different biological and psychological factors. Visceral hyperalgesia, altered motility, disturbances of the brain-gut axis, abnormal central processing, autonomic and hormonal events, genetic and environmental factors, postinfectious sequels, and psychological disturbances such as dysfunctional coping, stress and psychiatric disorders are variably involved in IBS.¹¹ In the present study we focus on visceral hypersensitivity, cortisol and sympathetic activity.

Visceral hypersensitivity

In 1973, Ritchie was the first to show that IBS patients report pain at lower volume when a balloon was inflated in the lumen of the bowel.^{80 81} Later studies demonstrated that IBS patients in general perceive pain at lower rectal pressures or volumes than healthy controls.^{51 82 83 84 51, 85 86 87 88} However some studies have not been able to show significant differences between patients and controls according to thresholds for pain or discomfort and for non-painful rectal distensions.^{81 89, 90} Differences of visceral sensitivity between subgroups of IBS have been reported but with inconsistent results.^{91 92 93 94 95} In IBS patients visceral hypersensitivity has also been measured in the esophagus.⁹⁶ In a recent study it was found that visceral intolerance to distension appears organ-specific in patients exhibiting a specific site of symptoms.⁹⁷ IBS patients do not have a general hypersensitivity to pain apart from visceral hypersensitivity.⁹⁸ At least half of IBS patients perceive stimuli over wider referral areas of the abdomen than healthy subjects⁹⁹ and lidocaine application into the rectum before barostat procedure reduces the visceral hyperalgesia.¹⁰⁰

Several factors can influence the visceral sensitivity. IBS patients often have postprandial abdominal symptoms.^{101 102} An increased sensitivity of the rectum after a meal is seen in IBS patients but also in healthy volunteers.^{75 103} A fatty meal can increase rectal sensitivity in both controls and IBS patients¹⁰⁴ and lipid administration in the duodenum leads to a marked reduction in colonic perception thresholds in IBS patients compared to controls.¹⁰⁵ Rectal hypersensitivity in IBS patients can also be induced by repetitive sigmoid stimulation.^{94 106} Psychological factors, including stress, influence pain thresholds in patients with IBS.⁸¹ Hypnotic relaxation increased the distension volume of the bowel required to induce discomfort, while anger reduced this threshold compared with relaxation in healthy controls.^{88 107} Hypnotherapy is effective in the treatment of IBS.¹⁰⁸ Mental stress increases the subjective feeling of pain during sigmoid distensions in healthy volunteers.¹⁰⁹

The cause of visceral hypersensitivity is not completely understood. Studies have shown evidence for abnormalities in afferent neurons,⁸⁴ abnormal peripheral visceral receptors,¹¹⁰ hyperexcitability of spinal nociceptive processes,¹¹¹ abnormal endogenous pain inhibitory mechanisms⁹¹ and a heightened pain sensitivity of the brain-gut axis in IBS.¹¹² There is also evidence for a specific brain activation in patients with IBS not only during noxious rectal distension but also during the anticipation of rectal pain.¹¹³ In functional brain studies IBS patients have shown an augmented activation in the dorsal portion of the anterior cingulate cortex in association with increased subjective pain reports to rectal stimuli. These data do not necessarily indicate a cerebral etiology for visceral hypersensitivity; they could reflect a normal cerebral response to a heightened incoming sensory signal.⁹⁹ Studies of visceral hypersensitivity in IBS patients represent both neural and cognitive functions. A rectal distension causes principally two processes in the brain, that is, registration of the sensory

signal and perception-related cognitive processes.¹¹⁴ Recently, the effect of small and therefore unperceived rectal distensions on brain activity has been tested to minimize the influence of cognitive processes related to the experimental stimulus. IBS patients showed a larger functional Magnetic Resonance Imaging (f-MRI) activity volume in the brain in response to these unperceived rectal distensions, confirming the presence of neural circuitry hypersensitivity.¹¹⁵

Manovolumetry

Manovolumetric investigation methods of reservoir organs were developed in the 1960s and 1970s.^{116 117} The apparatus often used for manovolumetry is called a barostat. The barostat can measure motor functions, such as motility of gastrointestinal reservoirs like the rectum.¹¹⁸ The barostat is also used to estimate the extent of hypersensitivity and to provoke symptoms in IBS.^{119 120, 121 122} It has even been suggested as a diagnostic instrument for IBS.^{82 83 123} The methodology of measuring rectal sensitivity in patients with IBS has been improved in recent years by standardization of distension protocols and technical development of the barostat.^{124 125 126 127} One of these distension protocols is called “tracking technique”. The tracking technique was described by Whitehead et al. in 1997.¹²⁸ It was developed to circumvent the problem of susceptibility to psychological influences.^{81 124} “Nonperceptual factors, such as prior learning and the anticipated consequences of reporting pain, can affect the threshold at which pain is reported. Some subjects may report pain at low intensity of stimulation to insure that they do not experience harm, whereas other subjects may deny pain even at levels of stimulation that cause tissue damage because they want to appeal strong or stoical.”⁸¹ With the tracking technique the distension of the rectum is either increased or kept the same as long as the patient does not report pain or maximal tolerable distension. When the patient reports pain or maximal tolerable distension, the next distension is either decreased or remains the same. Whether the next distension is changed or remains the same is determined by a random process.

Stress

Stress is known to play an important role in the onset and modulation of IBS symptoms.^{129, 130 128 131 132} From experimental studies there is evidence for a stress-dependent alteration of visceral sensitivity.^{133 134 135} The biological mechanisms responsible for the causal link between stress and IBS symptoms are not completely understood, but the hypothalamic-pituitary-adrenocortical axis and the autonomic nervous system seem to play a prominent role in the pathophysiology of IBS.^{99 133 136} In rats, stress by “the neonatal maternal deprivation model” is known to trigger long-term alterations in gut transit-time, colonic epithelial barrier function, and mucosal immunity.¹³⁷ One main finding in these animals was that basal plasma adrenocorticotrophic hormone and corticosterone concentrations were significantly elevated.¹³⁸ Pre-treatment of the separated rats with a corticotrophin-releasing hormone antagonist abolished the stress-induced mucosal changes of the intestine, indicating that neonatal trauma can induce phenotypic changes in adulthood, including enhanced vulnerability of the gut mucosa to stress, via mechanisms involving peripherally located corticotrophin-releasing hormone receptors.¹³⁹ There is also evidence that corticotrophin-releasing hormone receptor activation prevents colorectal-induced visceral pain in rats.¹⁴⁰

Human data also show that corticotrophin-releasing hormone is an important mediator of the central stress response and seems to play an important role for the colonic motility and visceral perception. Fukudo et al. showed that IBS patients had a greater colonic motility than controls after corticotrophin-releasing hormone injection.¹⁴¹ Sagami et al. found that

peripheral administration of a corticotrophin-releasing hormone receptor antagonist improved gastrointestinal motility, visceral perception, and negative mood in response to gut stimulation.¹⁴² Posserud et al. found that basal corticotrophin-releasing hormone levels were lower in IBS patients and increased significantly during stress in patients but not in controls.¹³⁴

Cortisol

Cortisol was first isolated from the adrenal cortex in the 1930s by Kendall¹⁴³ and Reichstein.¹⁴⁴ Cortisol is a corticosteroid hormone produced by the adrenal cortex. The synthesis of cortisol from cholesterol is stimulated by adrenocorticotrophic hormone from the anterior lobe of the pituitary gland. Adrenocorticotrophic hormone is in turn stimulated by corticotropin-releasing hormone released by the hypothalamus. The basal hypothalamic-pituitary-adrenocortical axis activity is regulated by a pulsative corticotrophin-releasing hormone secretion leading to a cortisol peak level before awakening and a decrease throughout the day reaching its nadir in the late evening.¹⁴⁵

Psychological or physiological stress results in increased cortisol secretion from the adrenal cortex within ten minutes of the stress situation.¹⁴⁶ This process requires a normal function of the hypothalamic-pituitary-adrenocortical axis. In response to psychological stress, corticotrophin-releasing hormone release is controlled by central neurotransmitters such as norepinephrine and serotonin and in response to infection corticotrophin-releasing hormone containing neurons respond to proinflammatory cytokines such as interleukin 1, 6 and tumor necrosis factor alfa.¹⁴⁷

Cortisol has a broad spectrum of effects in many tissues to maintain homeostasis under conditions of strain.^{148 149} Changed levels have been observed in connection with psychological stress,^{150 151} fear, pain, depression,¹⁵² posttraumatic stress disorder,¹⁴⁹ physical exertion or physiological conditions such as intake of a meal,¹⁴⁸ hypoglycemia, premenstrual syndrome,¹⁵³ fever, trauma, or surgery.¹⁵⁴ Measurement of salivary free cortisol is widely used in experimental studies to evaluate the activation of the hypothalamic-pituitary-adrenocortical axis.¹⁵⁰

Several studies have reported increased cortisol or an overactivation of the hypothalamic-pituitary-adrenocortical axis in IBS patients.^{147 155 156 157} According to IBS symptom subgroups, there are contradicting results. Elsenbruch and co-workers found elevated cortisol levels in diarrhoea-predominant IBS compared to constipation-predominant IBS¹⁵⁸ and Dinan and co-workers found that cortisol was elevated in all IBS subgroups (diarrhoea-predominant, constipation-predominant and alternators), although the elevation was most marked in the constipation subgroup.¹⁴⁷ Other studies have not found any differences between IBS patients and controls.^{134 159}

In conclusion there is evidence for a dysregulation of the hypothalamic-pituitary-adrenocortical axis in IBS patients both during stress and non-stress conditions.

Autonomic dysfunction

The autonomic nervous system regulates vegetative processes such as heart rate, blood pressure, body temperature and motility of the gut and modulates these homeostatic functions to meet behavioural demands. Dysfunction or imbalance of the autonomic nervous system is associated with gastrointestinal symptoms in IBS,¹⁶⁰ but the results of studies have been inconsistent.^{157 161 162 163 164 165 166 167 168}

Aggarwal et al. demonstrated that patients with constipation-predominant IBS had cholinergic abnormalities, whereas patients with diarrhoea-predominant IBS had adrenergic abnormalities.¹⁶¹ Abnormal cholinergic function in IBS was also demonstrated by other investigators.^{168 169 170} Some investigators found evidence for increased sympathetic activity in IBS patients^{157, 160 165} whereas others did not find any differences in autonomic response.¹⁷¹ Alterations of the autonomic function may increase susceptibility to gastrointestinal symptoms.¹⁷² It is unclear whether the autonomic alterations in IBS are a primary phenomenon or merely reflect dysregulations in the bidirectional interactions of the central and enteric nervous system.⁹⁹

Skin conductance

Afferent neurons from the sympathetic axis of the autonomous nervous system innervate eccrine sweat (sudomotor) glands, and their activity leads to measurable changes in skin conductance, termed electrodermal activity.^{173 174} The palmar and plantar regions are very sensitive to psychological processes such as emotion, alertness and attention.¹⁵² Changes in skin conductance are strongly linearly related to changes in the number of active eccrine sweat glands,¹⁷⁵ changes in sympathetic sudomotor nerve activity upon stimulation¹⁷⁶ and changes in the amount of water evaporation from the skin under skin conductance measurement.¹⁷⁷

Stress and anxiety represent high levels of arousal and emotion-related sympathetic activity, which can be manifested as increased electrodermal activity¹⁷⁸ and electrodermal reactivity to repeated stimulation.¹⁷⁹ This connection enables electrodermal activity to be used as an objective index of emotional behaviour, for example, as an indicator of fear conditioning. By fear conditioning is meant that a neutral stimulus is temporarily paired with an aversive stimulus. The neutral stimulus becomes predictive of the aversive stimulus and will elicit arousal responses that can be measured as increased electrodermal activity.¹⁸⁰ Fear conditioning may occur without conscious awareness.¹⁸¹ The first conditioning experiment performed referred to the gastrointestinal tract, and demonstrated the possibility of producing conditioned autonomic visceral responses to external neutral stimuli.¹⁸² Skin conductance has been measured in IBS patients but studies are few and results have been inconsistent.^{160 169 183 184 185}

Psychosocial aspects

Patients with IBS experience significant impairment of health-related quality of life compared with the general population.^{58 186} Psychological disturbances are generally more common in IBS patients with more severe symptoms who seek medical care.^{187 188 189} Among them, there is a high prevalence of anxiety, mood and somatoform disorders,^{190 191} sleep disturbances,¹⁹² and fatigue.¹⁹³ Psychiatric disorders such as depression and anxiety are not viewed as causes for IBS⁴⁸ but as comorbid factors that may influence the patient's response to symptoms. IBS patients who are not health-care seekers do not show any appreciable differences in psychological disturbances from the general population.¹⁹⁴

AIMS

- To investigate bowel habits in the general Swedish population with focus on constipation and fecal incontinence.
- To investigate the variation of stool consistency and defecatory symptoms in IBS patients with the help of symptom records from diary cards
- To validate the Rome II supportive criteria for IBS and to identify subgroups based on symptom diary card records
- To propose alternative criteria for IBS based on evidence from prospective studies of symptoms with diary cards
- To investigate visceral sensitivity in patients with IBS, chronic constipation and healthy volunteers
- To investigate the effect of maximal tolerable rectal distensions on salivary cortisol levels in patients with IBS, chronic constipation and healthy volunteers
- To investigate whether the expectancy of the experimental situation per se (provocation of bowel symptoms by rectal distensions) has a higher impact on the level of arousal in IBS patients compared to patients with constipation and healthy volunteers.
- To investigate skin conductance activity before and during repetitive rectal distensions at subjective maximal tolerable pressure in patients with irritable bowel syndrome and chronic constipation compared to healthy volunteers
- To investigate if IBS patients habituate or sensitize to repeated rectal maximal distensions, measured with skin conductance during repetitive rectal distensions

SUBJECTS AND METHODS

Paper I

A questionnaire was mailed to a random sample of 2000 residents between the age of 31 and 76 years in the county of Östergötland with mixed rural and urban population. For this the Swedish population register and a random generator were used. The questionnaire had not been validated before. It was coded and reminder letters were sent once to non-responders. The translated questionnaire is given in the Appendix .

Paper II

The symptom diary cards (Figure 1) of 60 IBS patients (22 men), who had kept daily records of their abdominal symptoms during 40 days were analysed. The same diary card recordings were earlier used and validated in a study by Ragnarsson and Bodemar.^{12 74}

Patients were included according to the Rome I criteria and the absence of organic disease. They were referred by primary care physicians to our unit, department of gastroenterology. Each patient underwent an extensive interview and a thorough physical examination. All patients were seen or contacted during a follow-up period of at least two years to ascertain that no organic disease had been subsequently diagnosed.

Patients had been asked to define stool consistency as “loose, normal, hard or very hard stools, with separate hard lumps like nuts” for every bowel movement. Patients had also recorded corresponding defecatory symptoms (urge, straining and feeling of incomplete evacuation) and episodes of pain and bloating.

Figure 1: Symptom diary card (IBS)

Hours:	06	08	10	12	14	16	18	20	22	24	02	04	06
Note meals with X													
Note when you have abdominal pain with: X---X and score the intensity of the pain with number written above the line. (please see below).													
Hours:	06	08	10	12	14	16	18	20	22	24	02	04	06
Note bowel movements with circle (O). Write number inside the circle. (please see below) .													
Did you have to rush to the toilet ? Yes/No													
Did you have to strain passing stool? Yes/No													
Did you have the feeling that you could empty the bowel completely? Yes/No													
Intensity of pain: 1: X---1---X light pain 2: X---2---X intermediate pain that can be disregarded 3: X---3---X intensive, unbearable pain	Stool consistency: 1: loose stool 2: normal stool 3: hard stool 4: very hard stool, with separate hard lumps like nuts												

Paper III

The results of paper III are based on the symptom diary cards of three patient populations. Sixty patients are the same as in study II. Fifty patients are the same as in another earlier study by Ragnarsson and Bodemar ¹⁹⁵ and these patients were also included after getting the diagnosis by a gastroenterologist. They also fulfilled Rome I criteria for IBS. Twenty-five patients and controls are the same as in study IV and V.

The following diary card data were used: Number of stools, number of bowel movements with urgency, straining and feeling of incomplete evacuation, number of stools with loose, normal or hard consistency, pain and bloating (number of episodes or total number of hours of pain and bloating).

We defined subgroups based on stool consistency and associations to defecatory symptoms were investigated. Patients were also classified into subgroups according to Rome II supportive criteria.

Papers IV and V

Subjects

IBS patients

Twenty-seven patients with IBS (4 men, 23 women, mean age 41 years, range 22–73 years) were studied. Patients were referred by primary care physicians working in the primary catchment area of the University Hospital of Linköping. All patients fulfilled Rome 1 criteria for IBS. Exclusion criteria were the presence of additional conditions such as organic abdominal disease, progressive weight loss, medication that could affect the gastrointestinal system, metabolic, neurological and current psychiatric disorders.

Patients were interviewed and examined by a gastroenterologist. Blood samples were taken from all patients for analysis of haemoglobin, leucocytes, platelets, C-reactive protein, alanine aminotransferase, aspartate aminotransferase, albumin, blood glucose, T4, TSH and stool examination for occult blood. All patients underwent sigmoidoscopy or colonoscopy. Other examinations were performed when required to exclude any organic disease.

The IBS patients had had symptoms for median 15 years, range 3–50 years. Two IBS patients remembered that symptoms started after gastroenteritis. Start of symptoms in 17 patients had no connection to gastroenteritis and eight patients did not remember. All IBS patients recorded their bowel symptoms prospectively on diary cards for 14 days before entering the study. During diary card registration any intake of bulking agents was continued but other medication that could affect bowel function was not allowed.

Constipation patients

Thirteen patients with constipation (all women, mean age 50 years, range 32–60 years) were studied. Patients were referred by the primary care physicians in the primary catchment area of the University Hospital of Linköping. Patients were evaluated by a gastroenterologist. All of them fulfilled the Rome II criteria³⁹ for functional constipation (Table 6). Symptoms were recorded on diary cards. Blood samples were taken from all patients for analysis of haemoglobin, leucocytes, platelets, C-reactive protein, alanine aminotransferase, aspartate aminotransferase, albumin, calcium, blood glucose, T4, thyroid stimulating hormone and stool examination for occult blood. All patients had a colonoscopy or barium enema before entry into the study.

Control group

The control group consisted of 18 healthy subjects with no history of gastrointestinal disease (4 men, 14 women, mean age 42 years, range 22–72 years) who were recruited by announcement. Controls were interviewed by a gastroenterologist and recorded their bowel habits on diary cards.

Table 6: The Rome II diagnostic criteria for constipation

At least 12 weeks, which need not be consecutive, in the preceding 12 months of two or more of:

- 1) Straining in $> \frac{1}{4}$ defecations;
- 2) Lumpy or hard stools in $> \frac{1}{4}$ defecations;
- 3) Sensation of incomplete evacuation in $> \frac{1}{4}$ stools;
- 4) Sensation of anorectal obstruction/blockage in $> \frac{1}{4}$ of stools;
- 5) Manual maneuvers to facilitate $> \frac{1}{4}$ defecations;
- 6) < 3 defecations/week

Loose stools are not present, and there are insufficient criteria for IBS

Methods

Psychiatric ratings

The Comprehensive Psychiatric Rating Scale for Self-Assessment is a self-rating scale for affective syndromes containing 19 items covering symptoms of depression, anxiety and obsessive-compulsive syndromes.¹⁹⁶ Each item contains a description of the symptom at four defined levels of severity. Three additional intermediate levels were used, resulting in a seven-point scale. This self-rating scale is an instrument to estimate temporary psychological distress.¹⁹⁷ The questionnaire was sent to the patients between two and three weeks before the experiment, to be filled in at home.

Barostat and manovolumetry

The electronic barostat (Dual Drive Barostat, Distender series II, G&J Electronics Inc., Toronto, Canada) was connected to a computer. Distension protocols were created by using the Protocol Plus Deluxe (V 4.2 R) program. An external computer using the Protocol Plus data scanner (V 1.9) recorded the information. The rectal balloon catheter consisted of a highly compliant polyethylene bag (maximal volume 520 ml) which was attached to a polyethylene tube. Maximal infusion rate was 40 ml/s. The method of rectal manovolumetry is described elsewhere.¹⁹⁸

Distension Protocol

Intermittent phasic stimulations with distension duration of 60 sec were used. The time interval between distensions was 30 sec. Pressure increments were 5 mmHg. The subjects had to grade their sensation 15 sec after start of each distension by using four parameters: 1 = no sensation; 2 = first sensation/some sensation; 3 = urge to defecate; 4 = maximal discomfort/pain.

When the subjects reported maximal discomfort the barostat computer randomly reduced the next distension by 5 mmHg or repeated the same distension level. When subjects had reported maximal discomfort or pain three times at the same pressure level, this level was defined as maximal tolerable distension level (tracking technique).¹²⁴

After the level of maximal tolerable distension had been determined, it was repeated five times with a duration of 30 sec each. The time between each distension was 30 sec. The subjects continued to grade their symptoms. When the subjects had increasing discomfort or pain, the distension series was interrupted.

Salivary cortisol measurements

Because of the non-invasive simple sampling procedure, the analytical simplicity and the stability of the samples, salivary cortisol was chosen as a stress marker. A commercial enzyme, immunoassay, designed for the analysis of salivary cortisol, was used (Salimetrics, Eletrabox). The Salivette test tube (Sarstedt, Nuembrecht, Germany) method for saliva sampling was used. The procedure of saliva collection is described earlier.¹⁹⁹ Pre- and post-experimental cortisol values were calculated in relation to baseline cortisol measured close to the same time of day on a normal day in the subject's usual environment. Cortisol values were evaluated by an independent expert in clinical chemistry (E.A-E).

Assessment of cortisol circadian variation

Patients and controls were instructed to collect saliva at 8 am, 1 pm, 3 pm and 10 pm on a normal day in their usual environment. Samples were sent to our laboratory by mail within four days. The midday samples were taken at 1 pm and 3 pm because the laboratory experiment was performed close to the same times of the day. Subjects were instructed not to eat, drink, or smoke for 60 minutes before sampling.

Skin conductance measurement

The MP100 from BIOPAC Systems Inc., Santa Barbara, California, USA was used for continuous measurement of the skin conductance by a GSR100B amplifier during the whole experiment.

The skin conductance was measured according to a standard method,¹⁷³ i.e. by a constant voltage of 0.5V applied over two Ag-AgCl (Neuroline 70001-A, Medicotest A/S, Ølstykke, Denmark) electrodes on the toe-tips of the second and third toes of the non-dominant foot. The resulting signal is expressed in units of conductance.

The analogue signals from the amplifiers were converted to digital by the A/D converter MP100, sending 16-bit digitalized skin conductance values over a serial port to a computer at a rate of 250Hz per channel and stored on hard disk. Predefined sections of the skin conductance curves were selected visuo-manually off line according to a curve-dependent standard set of rules for scoring skin conductance. These skin conductance curves were then computed automatically by the commercially available standard signal processing programme AcqKnowledge 3.7.3, from BIOPAC Systems Inc. All skin conductance data were analysed without knowledge of subject identity or category.

Scoring skin conductance

Skin conductance measures were expressed in microSiemens (μS). Skin conductance variables are explained and shown in Figure 2. For each of the five repetitive distensions the following variables were derived: (1) The SCL_b : skin conductance baseline level at start of each distension; (2) The SCR_{1a} : the amplitude of the first skin conductance response within a latency window of 2 to 8 sec from the start of rectal pressure increase; and (3) the SCR_{max} : the difference between the maximal skin conductance level (SCL_{max}) and the skin conductance baseline level (SCL_b), provided that this difference emanates from a skin conductance increase that starts within a latency window of 2 to 32 sec from the start of rectal distension,

i.e. during the whole time period of rectal distension. In addition, the SCL_b was also measured before the barostat investigation. The usual latency criterion for a first skin conductance response to a distinct stimulus is 1–4 sec.¹⁷⁴ However, due to the increment time of the balloon distension to target pressure level, this up-to-8-sec wide latency window was applied for the SCR_{1a} of this study.

The definitions of skin conductance response habituation and sensitisation were a statistically significant skin conductance response decrement and increment, respectively, over repeated rectal distensions using Friedman’s non-parametric test for repeated measures.

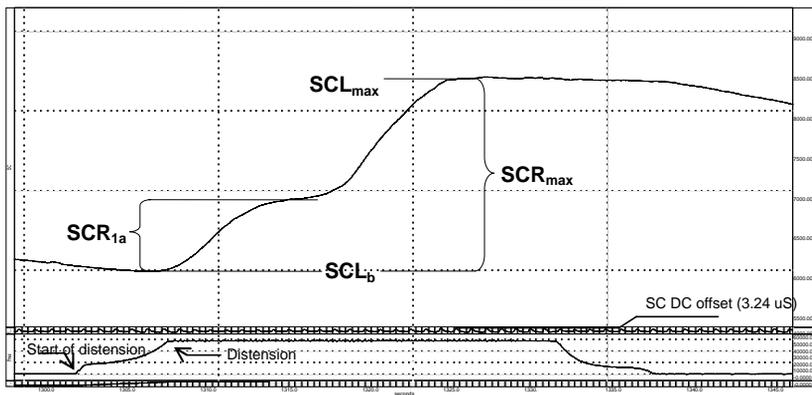


Figure 2: Example of skin conductance reactivity (uS) during a subjective maximal rectal distension. Parameters chosen for analysis of skin conductance are shown. Abbreviations: SCR_{1a} : Amplitude of the initial SC Response within the latency window 1 – 8 s from start of distension; SCL_b : Baseline SC Level at start of SCR_1 or if no SCR_1 , at start of distension; SCL_{max} : Maximal SC level of a SC increase if started within the latency window of 1 to 31 s from start of distension; SCR_{max} : Maximal SC Response, i.e. the SCL_{max} relative to the SCL_b .

Experimental protocol

At midday (at about 1 pm) after a fasting period of four hours, the subjects came to our unit without bowel preparation. After a 15-minute rest in a quiet room, given the possibility to read light literature, salivary samples for cortisol analysis were taken. They were then served 400 ml of a liquid high-calorie nutritional solution (Fortimel Nutricia Nordic) containing 40 g protein, 41.2 g carbohydrate and 8.2 g fat (= 400 kcal).

After finishing their meal, subjects were placed in left lateral position and the balloon catheter was inserted into the rectum. After positioning the balloon the subjects turned around lying on their back in a comfortable position. Then, the electrodes for skin conductance were applied. After initial instructions about the distension protocol, the examiner was always present during the study but communication with the subject was avoided during measurement. An

initial distension of 20 mmHg was performed to unfold the balloon. The subject had no visual or auditory cues to anticipate the magnitude of the distensions. The duration of the barostat procedure was between 25 and 35 minutes. After completion of the distension protocol, salivary samples for cortisol analysis were taken.

Statistical methods

For all studies the statistical significance level was set to $\alpha=0.05$.

Study I: Chi-square tests were used to calculate differences in bowel habits between women and men, older and younger. The Kruskal-Wallis test was used to investigate any association between individual symptoms. Results of study II and III were expressed as mean confidence interval and median and interquartile range. To compare groups, the Kruskal-Wallis test and the Mann-Whitney *U* test were used. Results of studies IV and V were expressed as mean, standard error of mean (SEM), standard deviation (SD), median and interquartile range. Nonparametric tests were used to test differences in each group, to compare day x time interactions between groups (VI), and to compare groups (Wilcoxon's Sign Rank Test, Mann-Whitney *U*-test and Kruskal Wallis test). Repeated measures in paper V were calculated by the Friedman test. Correlations were calculated with the Spearman rank correlation coefficient (ρ). Initial covariance analyses with subject category as factor and age as co-variate were used to evaluate if age was associated with cortisol values or with SC values in paper VI or V, respectively.

Ethics

The studies were carried out in accordance with the Helsinki declaration. The Research Ethics Committee, Faculty of Health Sciences, Linköping University, Sweden approved the studies. Oral informed consent was obtained from each patient. For further details, see separate paper I-V.

RESULTS

Paper I

General results

The overall response rate was 80.5% (69 % answered directly and 11.5% after one reminder letter). Median age was 52 years (range 31-76) and the male-to female ratio was 1:1.12 (male:female). 95.6% had between three bowel movements per day and three per week and this is in accordance with other studies.^{1 3 10} 3.1 % reported to have fewer than three bowel movements per week and 1.4% more than three bowel movements per day. The majority of people (84%) managed to empty their bowels within 15 minutes. For the subjects' opinions about how the bowel function affects general well-being and daily activities see Figures 3-5.

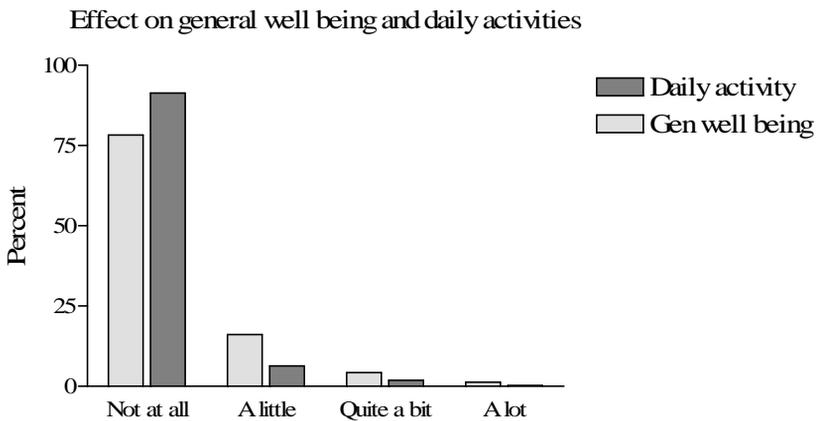


Figure 3: The subjects' opinions about how the bowel function affects general well-being and daily activities. Percentages of the total number of answers are given.



Figure 4: Age and sex distribution of the subjects' opinions that the bowel function affects general well-being "quite a bit" or "a lot". Percentages of the total number of answers in each subgroup are given.

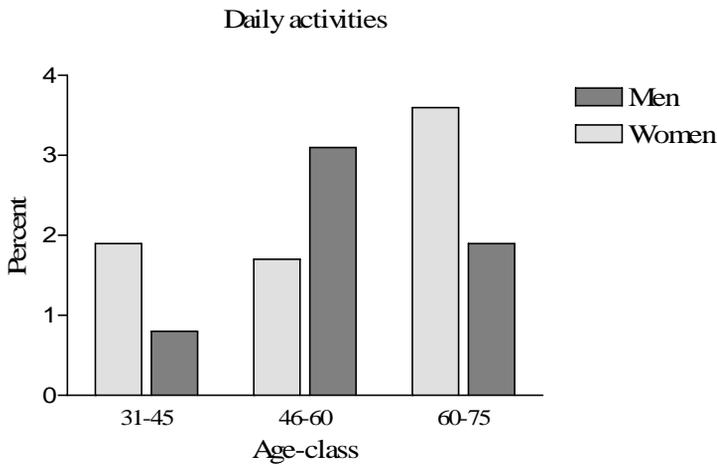


Figure 5: Age and sex distribution of the subjects' opinions that the bowel function affects daily activities "quite a bit" or "a lot". Percentages of the total number of answers in each subgroup are given.

Constipation

In the present study 5.7% of women and 2% of men considered themselves to be constipated “often” or “always”. (Figure 6) For a more detailed age and gender distribution see Table 7. When subjects were included who considered themselves to be constipated “sometimes” the prevalence was 19.8% for women and 8.3% for men.

In the present study subjects’ opinions on what they meant with constipation varied and infrequent bowel movements were in a greater extent by women than by men considered to be a symptom of constipation. Table 8. Self- reported constipation was most often related to hard stools but also to difficulties withstanding the urge to defecate, the need to strain, the use of laxatives and to incontinence for gas and soiling. Self reported constipation had a significantly negative impact on general well-being. Straining at bowel movement (at least 25% of the times) was reported by 53% of the population (women 61.2% and men 43.9 %). Straining at bowel movement at least 50% of times was reported by 5.7% of the population.

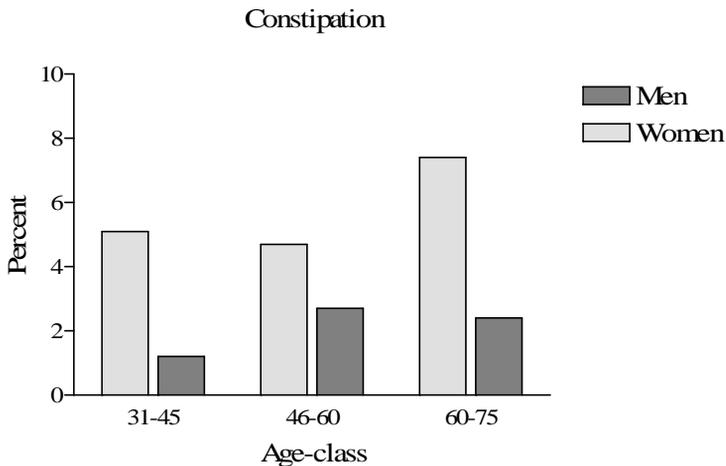


Figure 6: Age and sex distribution of subjects reporting constipation “often” or always”. Percentages of the total number of answers in each subgroup are given.

Table 7: Proportion of bowel habits according to age class and gender. Refers to answers to the questionnaire (Appendix)

	women 31-45 y n=277	women 46-60 y n=300	women 61-76 y n=274	men 31-45 y n=248	men 46-60 y n=297	men 61-76 y n=213	total n=1609
consider themselves to be constipated "often" or "always"	5.1%	4.7%	7.4%	1.2%	2.7%	2.4%	4 %
bowel movements three times or less a week	5.1%	3.1%	4.8%	1.6%	1.6%	1.9%	3,1 %
needing to strain at 50% of bowel movements or more often	7.2%	7.4%	9.5%	2 %	4.1%	3.2%	5.7%
"often" wake up at night time needing to pass a motion.	0.3%	0 %	0 %	0 %	0.3%	0 %	0.1%
"never" or "sometimes" able to empty the bowels in less than 15 minutes	4.7%	2.7%	5.1%	3.6%	3.1%	1 %	3.4%
use of medication to be able to open their bowels at least every fourth time	9.8%	11.1%	22.1%	2.8%	4.7%	8.5%	9.9%
"never" or "sometimes" able to withstand urge to defecate for 15 minutes	18.7%	25.6%	20 %	11.9%	12.1%	17.7%	17.8%
"never" or "sometimes" able to break wind without soiling underclothes	3.3%	2.4%	6.2%	1.6%	2.3%	3.7%	3.3%
involuntary leakage of wind more often than once a week	8.1%	11.5%	22.6%	16.8%	13.3%	13.9%	14.8%
involuntary leakage of solid faeces more often than once a week	0 %	0 %	0.7%	0 %	0.3%	1 %	0.3%
involuntary leakage of loose faeces more often than once a week	0.4%	1.6%	4 %	0.8%	1 %	2 %	1.6%
soiling underclothes more often than once a week	2.6%	5 %	8.9%	6.5%	5.5%	6.6%	5.8%
bowel function affects well-being "quite much" or "a lot"	6.6%	4.4%	9.5%	2.8%	6.1%	3.7%	5.7%
bowel function affects daily activities "quite much" or "a lot"	1.9%	1.7%	3.6%	0.8%	3.1%	1.9%	2.2%

Table 8: Opinions on what men and women mean by the word „constipation“. Percentages of the total number of answers (n=1610). Multiple answers could be given, see Table 1, question 16.

	women	men
hard stools	43.7%	43%
straining in connection with bowel movement	23.8%	24.3%
pain when passing a motion	23.1%	22.4%
Infrequent bowel movements	41%	21%
Needing to use laxatives	58.3%	56.2%

Use of laxatives

9.9% of the population use medication to achieve a bowel movements at least every fourth time. For a more detailed age and gender distribution see Figure 7

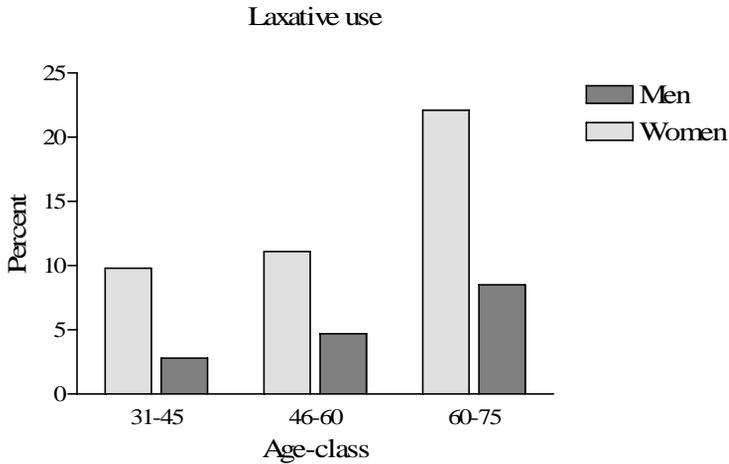


Figure 7: Age and sex distribution of subjects using laxatives at least every fourth time to open the bowels. Percentages of the total number of answers in each subgroup are given.

Fecal incontinence

Among the total population, 10.9% of women and 9.7% of men reported leakage of faeces more often than once a month when the consistency was loose. With solid fecal consistency the rate of leakage was 1.4% and 0.4% for women and men respectively. Soiling occurred significantly more often than once a month in 21.0% of men and 14.5% of women. In the age group 31- 45 years it was 17.8% for men and 9.9% for women (Figure 8). Daily involuntary leakage of gas was found in 5.9% of men and 4.9% of women (Figure 9). Overall 10% sometimes woke up during night time by the need of passing a motion and 4.5% could never withstand the urge to pass a motion longer than 15 minutes.

For differences in bowel habits and symptoms between younger and older men and women also see Table 7

All types of incontinence (for gas, soiling, loose stool and solid stool) had a significantly negative impact on general well-being. Incontinence (all types) was also related to difficulties in withstanding the urge to defecate. Incontinence for gas and soiling was related to constipation but incontinence for loose and solid faeces was not.

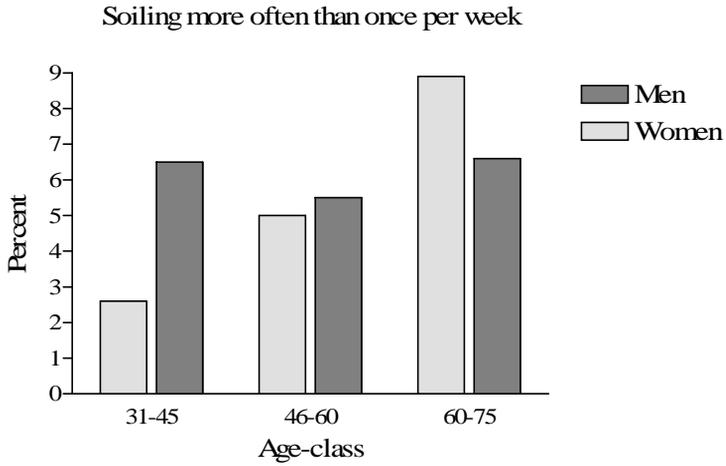


Figure 8: Age and sex distribution of subjects having soiling more often than once per week. Percentages of the total number of answers in each subgroup are given.

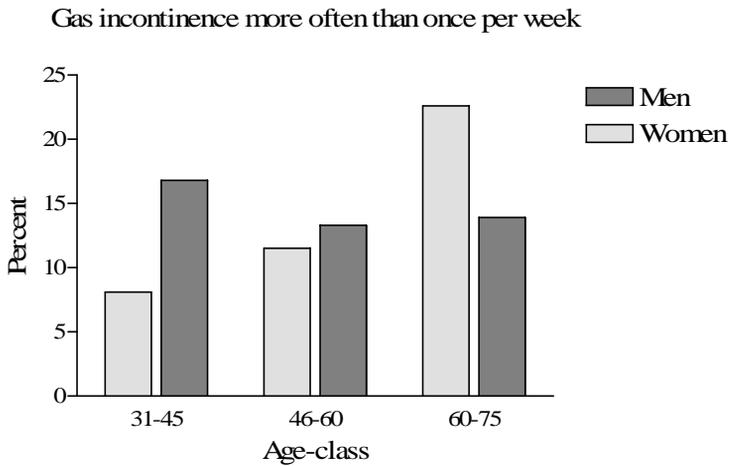


Figure 9: Age and sex distribution of subjects having gas incontinence more often than once per week. Percentages of the total number of answers in each subgroup are given.

Papers II and III

The results of the 60 IBS patients from paper II are included in the results of the 135 patients in paper III; therefore we mainly report the results of study III.

All patients, but no control subjects, suffered from abdominal pain and/or discomfort and almost all patients had bloating or abdominal distension. Symptoms of abdominal pain and bloating are shown in Table 9.

114 patients had between three bowel movements per day and three per week. Eighteen patients had more than 21 stools per week and three patients less than three stools per week. This means that 84,4 % had between three bowel movements per day and three per week with no major differences in stool frequencies between subgroups (Table 10).

The main subgroup according to stool form consisted of 51 patients with alternating loose, normal and hard stools, more than 10% of each kind. Other subgroups (for definition see Table 10) were loose-stool predominant, hard-stool predominant, loose-normal, hard-normal and normal. Our results show that almost all patients had alternating stool consistency. All kinds of defecatory symptoms (urgency, straining and feeling of incomplete evacuation) occurred in all subgroups (Table 10, Figures 10-13). The degree of pain and bloating was unrelated to subgroup.

In this study only 12 out of 135 patients could be classified into subgroups according to Rome II supportive criteria (original Rome II supportive criteria, Table 4), as the majority of patients had urgency combined with hard stools or straining even if stools were loose.

Table 9: IBS patients of study II-V. Episodes and hours of pain and bloating are shown.

	Subjects (n)	Days of symptom recording (n)	Pain episodes median (range)	Hours of pain median (range)	Hours of bloating median (range)	Bloating episodes median (range)
IBS patients study II and III	60	40	23 (0-86)	92 (0-960)		22 (0-81)
IBS patients study III	50	7	7 (0-22)	21 (0-153)	21 (0-105)	
IBS patients study III, IV and V	25	14	15 (0-54)	47 (1-173)	47 (0-209)	12 (0-58)
Controls study IV and V	18	14	0	0	0	0

Table 10: IBS Subgroups based on stool consistency

Stool consistency	Loose-normal-hard	Loose stool Predominant	Hard stool predominant	Loose-normal	Hard-Normal	Normal Stools	Controls
Subgroup Definition	>10% hard and >10% loose stools	≥50% loose and <10% hard stools	≥50% hard and <10% loose stools	10-50% loose, <10% hard and ≥50% normal stools	10-50% hard, <10% loose and ≥50% normal stools	<10% loose, <10% hard stools	
Subjects (n)	51	43	10	19	8	4	18
Bowel movements n/week *	11 (1-36)	14 (7-58)	8 (1-35)	11 (5-20)	9 (3-21)	11 (8-15)	7 (4-16)
% loose stools**	32.7 (21.6-52.4)	75.0 (62.2-96.1)	0 (0-3.9)	30.0 (24.5-37.0)	5.9 (0-7.1)	1.0	6.5 (0-21.7)
% normal stools**	33.3 (17.0-44.2)	20.0 (4.5-37.5)	37.2 (3.0-42.0)	65.0 (61.8-73.7)	71.4 (63.3-78.9)	93.6	90.8 (66.7-100)
% hard stools**	27.3 (16.1-38.2)	0 (0-2.3)	62.8 (51.9-95.0)	0 (0-5.3)	24.8 (18.5-32.2)	2.0	0 (0-10.8)
% stools with urge**	33.3 (21.8-62.5)	53.6 (17.2-74.5)	50.0 (4.0-98.5)	17.0 (1.0-34.9)	7.7 (0-18.0)	8.5	0 (0-17.8)
% stools with straining**	40.0 (22.5-64.0)	37.5 (4.3-65.5)	77.9 (55.0-96.2)	23.0 (12.6-57.3)	40.4 (21.6-83.0)	70.0	8.7 (0-34.4)
% stools with incomplete evacuation**	58.0 (35.7-83.5)	38.8 (14.2-74.5)	78.4 (65.5-92.0)	38.9 (10.1-61.5)	25.6 (14.4-52.7)	37.3	0 (0-2.7)

* Number of bowel movements per week is expressed in median (range)

**Data expressed in median of percentages (25-75 percentile range)

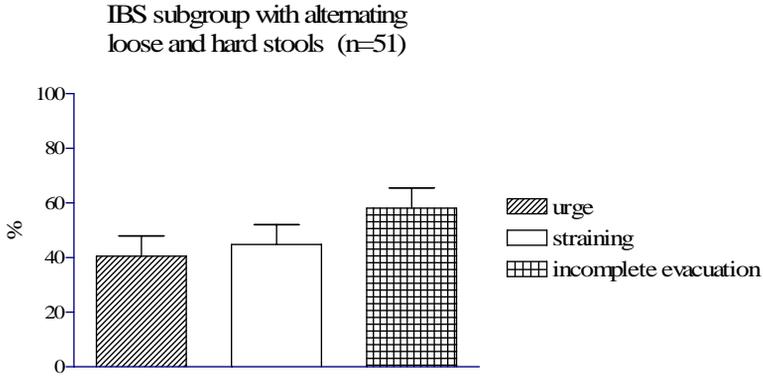


Figure 10: Proportions of defecatory symptoms in IBS patients with more than 10% hard stools and more than 10% loose stools. Mean values and 95% confidence intervals are shown.

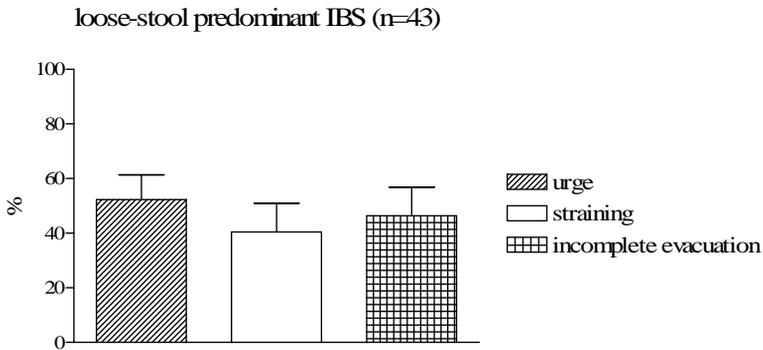


Figure 11: Proportions of defecatory symptoms in IBS patients with less than 10% hard stools and more than 50% loose stools. Mean values and 95% confidence intervals are shown.

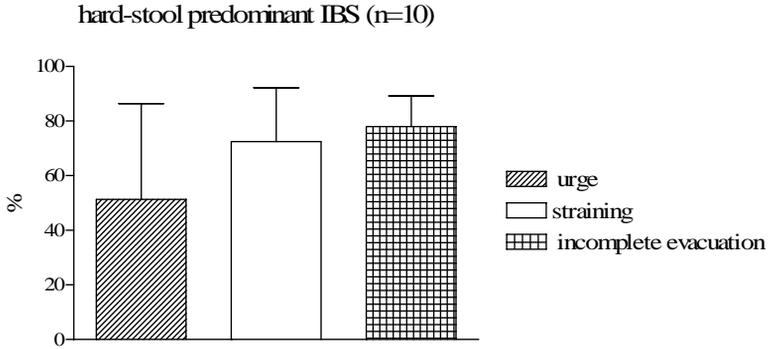


Figure 12: Proportions of defecatory symptoms in IBS patients with more than 50% hard stools and less than 10% loose stools. Mean values and 95% confidence intervals are shown.

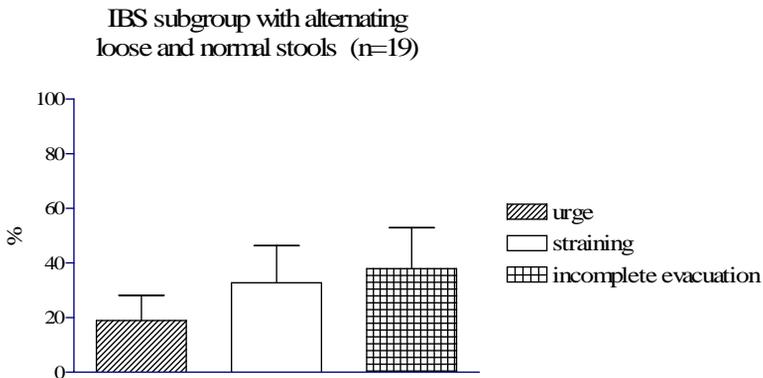


Figure 13: Proportions of defecatory symptoms in IBS patients with less than 10% hard stools, more than 10% loose stools and 50% normal stools. Mean values and 95% confidence intervals are shown.

Papers IV and V

Symptoms

For bowel habits and abdominal symptoms see Table 11. One IBS diary card registration was lost during the study. All IBS patients had episodes of abdominal pain during diary card recording. Their bowel habits were highly disturbed, with alternating stool consistency in combination with defecatory symptoms. Five constipation patients completed their diary card recordings following the instructions given. Diary cards of six constipation patients could not be evaluated because of daily use of laxatives: Two patients used water enemas, two patients bisacodyl, one patient lactulose and one patient large doses of macrogol. Two constipation patients did not complete their recordings.

Table 11: Bowel symptoms according to the diary card recording during 14 days. Stools forms and defaecatory symptoms are expressed in proportions of the total number of bowel movements.

Median (range)	IBS (n=26)	Controls (n= 18)	Constipation (n=5)*
Stools <i>per week</i>	11 (3-29.5)	7.5 (3.5-16)	2.5 (1-13.5)
Loose stools %	36 (0-96)	6 (0-50)	0 (0-0)
Hard stools %	21 (0-81)	0 (0-22)	80 (0-100)
Normal stools %	36 (0-93)	91 (50-100)	20 (0-27)
Urgency %	39 (0-100)	0 (0-37)	0 (0-20)
Straining %	36 (0-91)	9 (0-74)	100 (60-100)
Feeling of incomplete evacuation %	57 (0-100)	0 (0-58)	47 (0-100)
Episodes of abdominal pain <i>per week</i>	7.5 (0.5-27)	0	0.5 (0-7)
Hours of pain <i>per week</i>	23.5 (0.5-86.5)	0	2.5 (0-120)
Episodes of bloating <i>per week</i>	5.5 (0-8)	0	1 (0-8)
Hours of bloating <i>per week</i>	23.5 (0-104.5)	0	4 (0-150)
Days without bowel movement <i>per week</i>	0.5 (0-3)	0.75 (0-3.5)	4.5 (0-6)

*Patients using laxatives and/or enemas constantly during diary card recording were excluded in this table.

Psychiatric ratings

The IBS and constipation patients had significantly higher “Comprehensive Psychiatric Rating Scale for Self-Assessment” scores for depression ($p < 0.0001$ and $p = 0.007$), anxiety ($p < 0.0001$ and $p = 0.005$), physical disability ($p < 0.0001$ and $p = 0.03$) and obsessional compulsive symptoms ($p = 0.003$ and $p = 0.008$) than controls, respectively (Figure 14 a-d). There was no significant correlation between rating scores and skin conductance measures or bowel symptoms in any of the groups. In IBS patients the ratings (anxiety, depression and obsessive compulsive symptoms) were all significantly positively intercorrelated ($\rho = 0.45$ – 0.78).

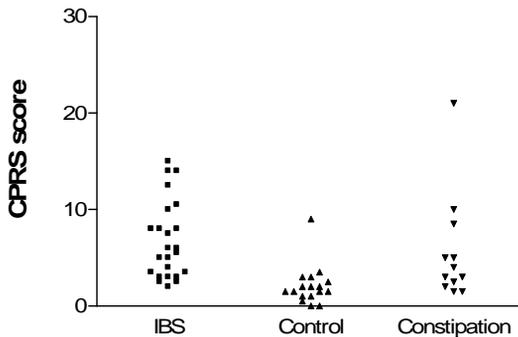


Figure 14 a: Depression: IBS patients and constipation patients had significantly higher Comprehensive Psychiatric Rating Scale for Self-Assessment (CPRS-SA) scores for depression than controls ($p < 0.0001$ and $p = 0.007$) (Mann-Whitney U -test).

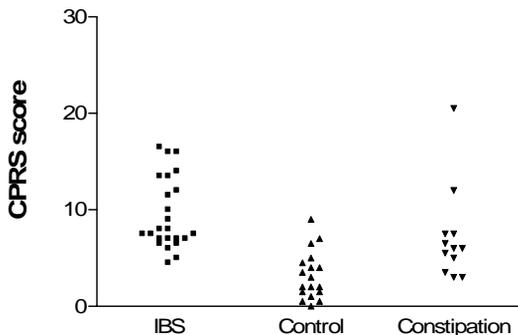


Figure 14 b: Anxiety: IBS patients had significantly higher CPRS-SA scores for anxiety than patients with constipation ($p = 0.02$) and controls ($p < 0.0001$). Patients with constipation had significantly higher anxiety scores than controls ($p = 0.005$) (Mann-Whitney U -test).

Rectal Manovolumetry

Distension protocol 1

Mean maximal tolerable rectal distension pressure for IBS patients was 38 mmHg (SD 8.3), for controls 55 mmHg (SD 6.4), and for patients with constipation 53 mmHg (SD 10.1).

The IBS patients had lower rectal distension pressure thresholds for first sensation, urge and maximal tolerable distension than the patients with constipation ($p=0.0164$, $p=0.0023$, $p=0.0003$) and the controls ($p=0.0366$, $p=0.0008$, $p<0.0001$), as shown in Figure 15. There was no significant difference in sensation thresholds between patients with constipation and controls. IBS patients had significantly lower rectal volumes than the two other groups at first sensation, urge and maximal tolerable distension (Figure 16). IBS patients had significantly lower rectal compliance than patients with constipation and controls ($p<0.05$).

Nine healthy volunteers, two patients with IBS and three with constipation did not reach maximal tolerable pressure in distension protocol 1 due to the safety level of the barostat device, which allowed pressures up to 60 mmHg. These subjects continued distension protocol 2 with “submaximal tolerable pressure”, i.e. 60 mmHg. The exclusion of subjects with submaximal pressure levels from the statistical analyses did not change the conclusions about differences between groups.

Distension protocol 2

Most patients and controls continued to grade their rectal symptoms as maximal tolerable except for one constipation patient who discontinued because of increasing discomfort. There was no significant change of symptoms in any of the groups. There was a significant increase in rectal volumes in all groups from distensions 1–5 ($p<0.0001$) (Friedman).

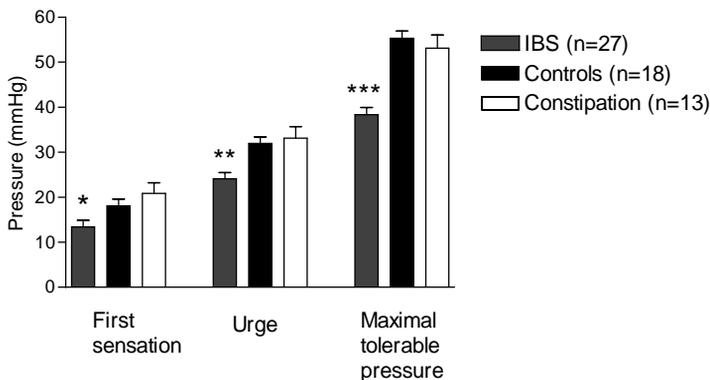


Figure 15: Mean rectal thresholds for first sensation, urge and maximal tolerable pressure. The standard error of mean is shown in the bars. IBS patients had significantly lower thresholds (first sensation, urge, maximal tolerable pressure) compared to patients with constipation ($p= 0.0164$, $p= 0.0023$, $p= 0.0003$) and controls ($p= 0.0366$, $p= 0.0008$, $p< 0.0001$) (Mann-Whitney *U*-test). There was no significant difference between patients with constipation and controls.

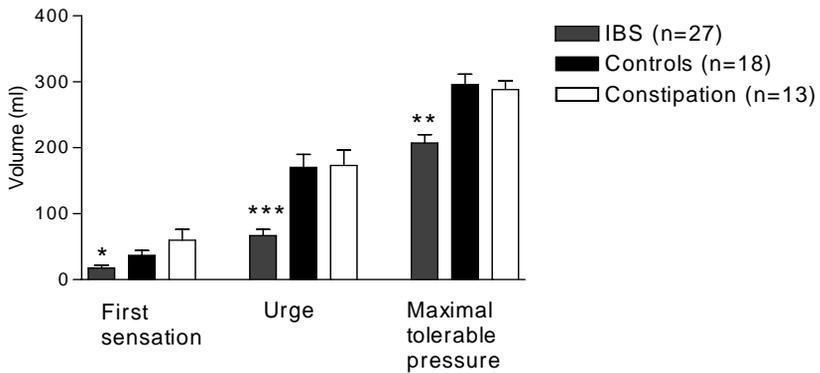


Figure 16: Mean rectal volumes at first sensation, urge and maximal tolerable pressure. The standard error of mean is shown in the bars. IBS patients had significantly lower volumes at first sensation, urge and maximal tolerable pressure compared to patients with constipation ($p= 0.0170$, $p= 0.0005$, $p= 0.0004$) and controls ($p= 0.015$, $p< 0.0001$, $p= 0.0002$) (Mann-Whitney U -test). There was no significant difference between patients with constipation and controls.

Cortisol

Cortisol data from two IBS patients, five constipation patients and three controls were incomplete because of non-compliance when taking saliva samples at home or because of lost samples. One IBS patient was excluded because of very high salivary cortisol values but further examination could not verify high cortisol values or any endocrinological abnormality. All calculations according to cortisol analysis were based on those subjects that had complete cortisol data, i.e. 24 IBS patients, 15 controls and 8 patients with constipation.

Initial covariance analyses with subject category as factor and age as co-variate showed that age did not statistically significantly explain differences in cortisol values. Therefore variations in age were not taken into account in subsequent statistical analyses of cortisol values.

IBS patients, but not constipation patients and controls, had significantly higher cortisol concentrations during the afternoon when the barostat experiment was performed (before and after barostat procedure) compared to similar times (1 pm: $p=0.0034$; 3 pm: $p=0.0002$) on an ordinary day in their usual environment Figure 17, (Table 12). There was no significant difference in salivary cortisol levels before compared to after rectal distensions in patients or in controls (Figure 17). The cortisol level changes from pre-experimentally to post-experimentally did not differ significantly from the change from 1 pm to 3 pm between the groups. There was no statistically significant difference between the groups according to salivary cortisol values at 8 am, 1 pm, 3 pm and 10 pm, measured at home (Table 12). There was no significant correlation within the groups between bowel symptoms, cortisol values, barostat measurements or psychometric testing results.

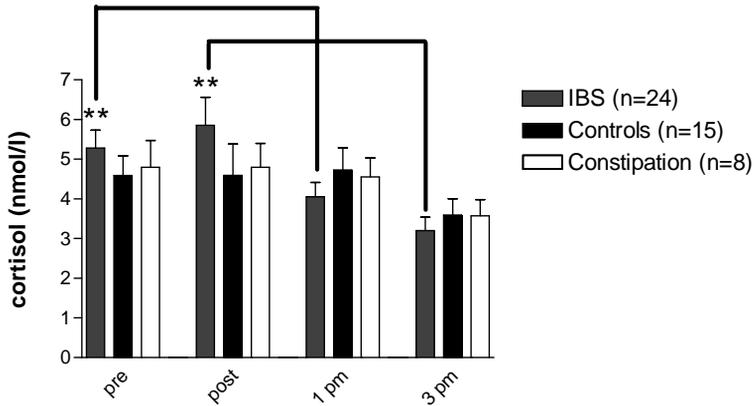


Figure 17: Salivary cortisol levels pre-experimentally (pre), post-experimentally (post) and in their usual environment at similar times (1 pm) and (3 pm). IBS patients had higher salivary cortisol values pre-experimentally ($p=0.0034$) and post-experimentally ($p=0.0002$) than at similar times (1 and 3 pm) in their usual environment (Wilcoxon Sign Rank test). Mean values and standard error are shown.

Table 12: Means (standard deviations) of salivary cortisol at 8 am, 1 pm, 3 pm and 10 pm at home on an ordinary day. There were no significant differences between IBS patients and controls.

Salivary cortisol (nmol/l)	IBS	Control	Constipation
8 am	8.26 (3.70)	7.84 (3.03)	8.36 (3.13)
1 pm	4.05 (1.77)	4.73 (2.17)	4.55 (1.36)
3 pm	3.20 (1.65)	3.59 (1.60)	3.57 (1.15)
10 pm	2.32 (2.09)	2.47 (3.09)	2.47 (2.23)
Pre-experimental	5.28 (2.21)	4.59 (1.92)	4.80 (1.92)
Post-experimental	5.85 (3.47)	4.59 (3.06)	4.80 (1.69)

Skin conductance during repetitive maximal rectal distensions

Skin conductance data of one IBS patient, two controls and two patients with constipation could not be analysed because of data collection artefacts. Initial covariance analyses with subject category as factor and age as covariate showed that age did not statistically significantly explain group differences in skin conductance measures. There was no statistical difference between men and women according to skin conductance values in the IBS and control group. Consequently, variations in age and gender were not taken into account in subsequent statistical analyses.

IBS patients had consistently significantly higher baseline skin conductance (SCL_b) than the patients with constipation before the start of the barostat examination ($p=0.014$), and before the five rectal repetitive distensions ($p=0.0008$; $p=0.0014$; $p=0.0013$; $p=0.0007$; $p=0.0004$); see Figure 18. Patients with constipation had significantly lower baseline skin conductance (SCL_b) than controls before the first ($p=0.048$), fourth ($p=0.034$) and fifth ($p=0.034$) distensions. This difference persisted after excluding men from analysis. There was no significant difference in SCL_b between patients with IBS and controls. There was no statistically significant increase or decrease in baseline skin conductance in any of the groups over the course of the distensions. The exclusion of subjects who did not reach maximal tolerable rectal pressure levels from the statistical analyses did not change the conclusions about differences between groups.

The IBS patients had significantly higher maximal skin conductance response (SCR_{max}) than patients with constipation at the second ($p=0.039$), third ($p=0.04$) and fourth ($p=0.014$) distension (Figure 19). There was no significant difference in SCR_{max} between the IBS and controls, nor was there any difference in SCR_{max} between the constipation and the control groups.

The IBS patients had significantly higher values of initial skin conductance response (SCR_{1a}) than patients with constipation and controls at the second rectal distension ($p=0.022$ and $p=0.046$, respectively). There was no significant difference between patients with constipation and controls. There was a significant SCR_{1a} decrement over the distensions 1–5 within the IBS group and within the constipation group, but not within the control group (Figure 20). When individuals with submaximal distension thresholds were excluded from analysis there was still a significant SCR_{1a} decrement over distensions 1–5 within the IBS patients ($p=0.0015$), but not within the constipation or control groups.

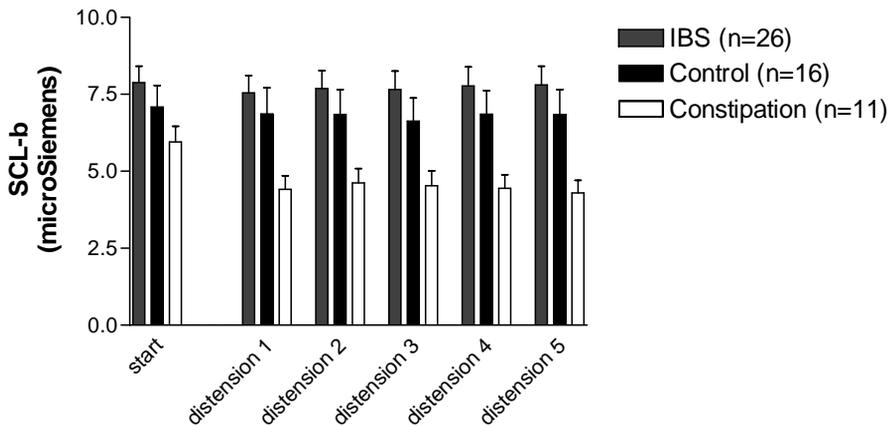


Figure 18: Mean skin conductance (SC) at start of the barostat examination and baseline values (SCL_b) between the five repetitive rectal distensions. The standard error of mean is shown in the bars. The IBS patients had significantly higher SC levels overall than patients with constipation ($p=0.014$ (start); $p=0.0008$; $p=0.0014$; $p=0.0013$; $p=0.0007$; $p=0.0004$ (distensions 1-5)) (Mann-Whitney U -test). Patients with constipation had significantly lower values than controls before first ($p=0.048$), fourth ($p=0.034$) and fifth ($p=0.034$) distension (Mann-Whitney U -test). There was no significant difference between patients with IBS and controls. The Friedman test for repeated measures was not significant in any of the groups for distensions 1-5.

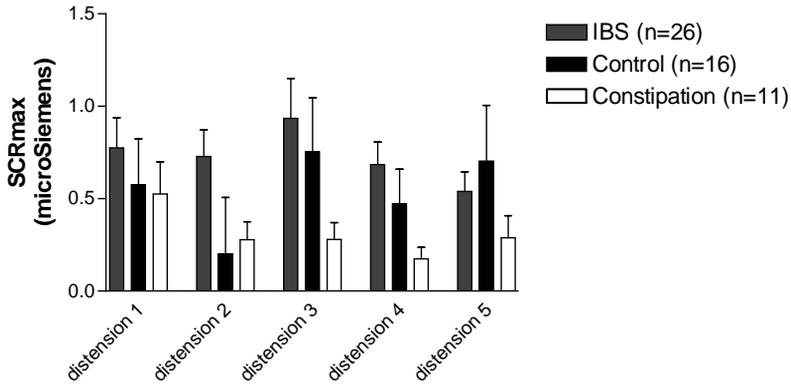


Figure 19: Amplitude of the maximal skin conductance (SC) responses to the repetitive rectal distensions 1-5, (SCR_{max} 1-5). The standard error of mean is shown in the bars. The IBS patients had significantly higher values than patients with constipation at the second ($p=0.039$), third ($p=0.04$) and fourth ($p=0.014$) distension (Mann-Whitney U-test). There was no significant difference between controls and IBS patients and between controls and constipation patients. The Friedman test for repeated measures was not significant in any of the groups for distensions 1-5.

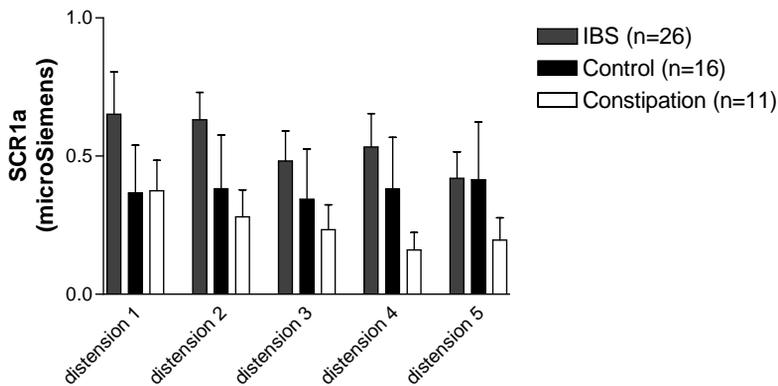


Figure 20: Mean skin conductance (SC) first response amplitude to the repetitive rectal distensions 1-5, (SCR_{1a} 1-5). The standard error of mean is shown in the bars. The IBS patients had higher values than patients with constipation and controls at the second distension ($p=0.022$ and $p=0.046$ respectively) (Mann-Whitney U-test). There was no significant difference between patients with constipation and controls. The Friedman test for repeated measures showed a significant decrease of SC values from distension 1 to 5 for IBS patients ($p<0.0001$) and patients with constipation ($p=0.019$) but not for controls.

GENERAL DISCUSSION

Population prevalence study

Constipation

We have shown that self-reported constipation is a common gastrointestinal complaint in the Swedish population. 19.8% of women and 8.3% of men considered themselves to be constipated “sometimes”, “often” or “always”. This is in accordance with an American study by Everhart et al. which found that 20.1% of women and 8.0% of men reported constipation.⁴

In an Australian study the prevalence of self-reported constipation was about 10% higher than in the present study, that is, 26.6% in middle-aged (45-50 years) and 27.0% in older women (70-75 years).²⁰⁰ This might be a true difference as both studies used similar questions about constipation.

Most results of constipation prevalence studies cannot be compared with each other since different definitions, symptom criteria and study designs are used. In a Canadian study the overall prevalence of self-reported constipation was 27.2% but only 16.7% and 14.9% had functional constipation according to Rome I and II criteria, respectively. For all three definitions, the rate for women was close to twice that for men.²⁰¹ Also in the present study the prevalence of constipation, in accordance with some earlier reports, was highest in elderly women.^{22 202 203}

Probert and co-workers studied the constipation prevalence according to self-reported constipation, slow colonic transit and Rome-I criteria for constipation. They found that the constipation prevalence by each definition was about 8% but overlap between those three definitions was only 2%.²⁰⁴ Harari et al. found that 5.7% of older persons (>60 years) reported constipation “always or mostly” and 38% “sometimes or rarely”. They also found that self-reported constipation was highly related to straining, hard stool consistency and fewer than three stools per week but feeling of incomplete evacuation, bloating and pain were less strongly associated.²⁰³ In a study of young people not seeking healthcare, Sandler et al. found that 7.3% of subjects reported constipation greater than 25% of the time and they most commonly defined constipation as straining and hard stools.¹³ Apart from the need to take laxatives, most subjects in the present study defined constipation as hard stools, 43.7% of women and 43% of men. Infrequent bowel movements were considered a constipation symptom by 41% of women and 21% of men and straining was considered a symptom of constipation by 24% of women and men.

According to our study the prevalence of self-reported constipation is high, 19.8% for women and 8.3% for men. 5.7% of women and 2.0% of men considered themselves constipated “often” or “always”.

Straining at bowel movement

Straining at bowel movement (at least 25% of the time) was reported by 53% of the population (women 61.2% and men 43.9%) and straining at bowel movement at least 50% of times was reported by 5.7% of the population. Straining >1/4 of defecations is one of six criteria of functional constipation according to Rome II criteria.³⁹

In our study the majority of people reported “straining” >1/4 of defecations but in the same population the self-reported prevalence of constipation (often or always) was only 4%.

In a study of Bellini et al. 5% of women and 1% of men recorded straining at 25% of the bowel movements or more often.¹⁰ The corresponding data of the present study were 61.2% for women and 43.9% for men. Bellini and co-workers used a four-week daily diary instead of questionnaire. This may be a more valid method than questionnaire and indicates that subjects in the present study may have overreported their straining symptoms. However, the subjects in Bellini’s study were not from a random sample of the population and the sample size was smaller (n=204) than in the present study. Moreover, subjects were recruited as persons who perceived their bowel function as normal. Thompson et al. found in a questionnaire survey that overall 10.3% of subjects had to strain greater than a quarter of bowel movement occasions.² Also their subjects did not come from a random sample of the population and the sample size was only 301.

Fecal incontinence

The present study shows that fecal incontinence is a common problem in the population. This is in accordance with other studies, even if results can vary depending on study design and criteria used.^{6 30 33 34} One striking finding in the present study was the gender difference in prevalence of soiling, especially in the younger age group. Soiling occurred more often than once a month in 21.0% of men between 31 and 45 years although this group is expected to have the best anal sphincter function.

General aspects

One limitation of paper I is that the analysis relied on questionnaires and diary cards were not used. Another limitation is that we did not investigate confounding factors such as gastrointestinal disease or surgical procedures. On the other hand, this study is strictly population-based with a high response rate. The high response rate was probable due to our decision not to include very old and young people among whom we expected a lower response rate. We used the Swedish population register which is unique, without bias of socio-economic status, thus allowing valid epidemiological studies. We chose a population area with mixed rural and urban components.

Diary card symptom studies of IBS patients

In paper II and III all patients suffered from abdominal pain and/or discomfort and almost all patients had bloating or abdominal distension. Chronic or recurrent abdominal pain and discomfort are the key features of IBS^{11 39 40} in combination with disturbed bowel habits and in absence of organic disease. The present prospective diary card studies have been performed to characterize these key features in detail. One main finding of the present study was that IBS patients had straining even with loose stools and urgency with hard stools. Therefore only 12 out of 135 patients could be classified into subgroups according to Rome II supportive

criteria. This erratic relationship between defecatory symptoms and stool consistency has also been described in IBS patients by Heaton et al.⁷¹ We suggest that IBS subgroups should be based either on stool consistency or defecatory symptom but not on both.

In the present study the majority of patients with IBS had varying stool forms although the degree of variation differed. The patients of the largest subgroup had often loose, hard and normal stools and therefore the largest degree of variation. The patients of the other subgroups had one dominating type of stool form but still had some degree of variation. Therefore we consider that alternating stool consistency should be a major criterion for IBS. The existence of an alternating subgroup is supported by many studies.^{59 205 206} Several researchers have included IBS patients with alternating IBS with reference to the Rome criteria although specific criteria for alternating IBS are missing.^{93 134 160} Since both specific criteria for and symptom description of patients with alternating IBS are missing in Rome II, the validity of those studies could be questioned. This phenomenon has also been addressed by Drossman et al. who state that not fulfilling Rome criteria for diarrhoea-predominant IBS or constipation-predominant IBS does not necessarily mean it is an alternating stool pattern.²⁰⁷

Rome II supportive criteria uses stool frequency as an item to subgroup patients into diarrhoea or constipation-predominant IBS. In our study of 135 patients with IBS who daily recorded their symptoms prospectively on diary cards, the majority of patients (84.4%) had between three bowel movements per day and three per week with no major differences in stool frequencies between subgroups (Table 11). This range of bowel movements is considered normal in the general population. Earlier Ragnarsson and Bodemar demonstrated that IBS patients define constipation (hard stools) and diarrhoea (loose stools) on the basis of stool consistency, not frequency.¹²

According to our data (Table 11), the great majority of IBS patients has alternating stool consistency during registration. Subgroups should be formed by proportions of stool consistency and data should be collected by prospective symptom registration on diary cards. The 51 of 135 patients who had mixed loose, normal and hard stools clinicians would consider to have mixed stool pattern. The 43 patients with mostly loose stools could be called diarrhoea-predominant and the 10 patients with mostly hard stools constipation-predominant. The remaining 31 patients who had predominantly normal stools would probably be considered as diarrhoea-like or constipation-like as they still have some proportion of either loose or hard stools. We do not suggest that our single centre study should be the basis for subgroup definition for IBS, but we argue that stool consistency should be the basis for subgrouping and diary cards should be the basis to collect this information at least in studies. Symptom evaluation in research must be as carefully performed as the very extensive pathophysiologic examination now reported in IBS patients.

Ragnarsson and Bodemar showed earlier that pain is temporally related to eating but not to defecation in IBS patients.⁷⁴ The symptom "pain relieved by defecation" was not among those typical for IBS in a study of Kay & Jørgensen either,²⁰⁸ who studied an unselected population to define common abdominal symptom clusters in the population. They defined an IBS symptom cluster with presence of abdominal pain and distension combined with borborygmi or alternating stool consistency or both.

In conclusion, we propose that symptom criteria for IBS should be changed according to the present evidence (see Table 13). Moreover, symptom subgroups should be based on stool consistency.

Table 13: Proposed symptom criteria for irritable bowel syndrome based on prospective daily symptom records of 135 IBS patients.

Chronic or recurrent symptoms of abdominal discomfort or pain combined with disturbed bowel habits:

- (1) Alternating stool consistency and/or
- (2) Some degree of defecatory symptoms of urgency, straining and feeling of incomplete evacuation regardless of proportions of stools with loose, hard or normal consistency.

Supportive criteria for IBS

- Postprandial onset or worsening of pain and /or discomfort
- Bloating and/or feeling of abdominal distension
- Most IBS patients will have a normal stool frequency (< 3 / day and > 3 / week).

Comments on newly published Rome III criteria

Recently revised Rome III symptom criteria for IBS¹¹ (Table 14) are supported by the findings of the present studies. The Rome committees now recommend that diarrhoea, constipation and mixed IBS subtypes should be based on a simple classification derived from stool consistency and not anymore from defecatory symptoms or frequency. Changes in Rome III criteria compared to Rome II criteria are apart from the results of Ragnarsson and Bodemar^{12, 74} mainly based on three trials.^{23 206, 207}

Table 14: Rome III diagnostic criteria for IBS ¹¹

Rome III diagnostic criteria* for IBS ¹¹

Recurrent abdominal pain or discomfort ** at least three days per month in the last three months associated with two or more of the following:

1. Improved with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

* Criteria fulfilled for the last three months with symptom onset at least six months prior to diagnosis

** Discomfort means an uncomfortable sensation not described as pain. In pathophysiology research and clinical trials, a pain/discomfort frequency of at least two days a week during screening evaluation for subject eligibility.

Rome III: Subtyping IBS by Predominant Stool Pattern

1. IBS with constipation (IBS-C) — hard or lumpy stools $\geq 25\%$ and loose (mushy) or watery stools $< 25\%$ of bowel movements.
2. IBS with diarrhoea (IBS-D) — loose (mushy) or watery stools $\geq 25\%$ and hard or lumpy stools $< 25\%$ of bowel movements.
3. Mixed IBS (IBS-M) — hard or lumpy stools $\geq 25\%$ and loose (mushy) or watery stools $\geq 25\%$ of bowel movements.
4. Unsubtyped IBS — insufficient abnormality of stool consistency to meet criteria for IBS-C, D or M.

Impact of repetitive rectal distensions on salivary cortisol and skin conductance

We investigated visceral sensitivity and the effect of maximal tolerable rectal distensions on salivary cortisol levels and skin conductance (measure of sympathetic activity) in patients with IBS, chronic constipation, and healthy volunteers.

Patients with IBS

The IBS patients demonstrated (a) pre-experimental stress according to increased salivary levels of cortisol which was not found in patients with constipation or controls; (b) habituation to repeated subjective maximal tolerable rectal distensions according to decreasing skin conductance values, although patients continued to rate their discomfort as maximal; (c) higher skin conductance values than controls in the beginning of distension series; (d) higher skin conductance values than constipation patients before and during repeated rectal distensions; (e) lower rectal distension thresholds for first sensation, urge and discomfort than healthy controls and constipation patients; and (f) no further significant increase in cortisol after repetitive rectal distensions.

The pre-experimentally high cortisol level indicates that IBS patients were more stressed in relation to their “normal” state of arousal at home than controls and constipation patients before start of the rectal distensions. This higher level of stress is also mirrored by larger initial skin conductance baseline values and response to rectal distensions in the beginning of the repetitive rectal distension series. We think that this higher degree of arousal in IBS compared to controls represents a higher degree of discomfort, anxiety or hypervigilance, probably due to aversive feelings prior to the experiment.

Other investigators have also shown that IBS patients are more stressed than controls just before start of an experiment. Murray and his group studied the effect of acute psychological and physical stress on autonomic activity and visceral sensitivity in IBS patients. Patients reported significantly higher levels of stress than controls already before onset of experimental stress and they also demonstrated a visceral hypersensitivity.¹³³ Heightened pre-experimental arousal was also measured by Dickhaus et al.¹⁵⁹ and Posserud et al.¹³⁴ who found increased norepinephrine values before the experiment with rectal distensions.

Skin conductance activity is closely linked to distinct brain regions with distinct anatomical contributions to the control of this electrodermal activity. The ventromedial prefrontal cortex is involved in anticipatory electrodermal activity responses, whereas the amygdala is implicated in electrodermal activity response to learned associations between stimuli and reinforcement such as fear conditioning.¹⁸⁰ The amygdala is known to play a critical role in linking external stimuli to defence networks.²⁰⁹ Mayer et al. demonstrated recently that IBS patients show greater activation of the amygdala during rectal distensions than patients with ulcerative colitis.²¹⁰

Lower visceral pain thresholds in IBS could be caused, at least in part, by psychological influences on perception, that is, perceptual response bias. To circumvent this problem, manovolumetry techniques such as the tracking technique used in this study have been developed.¹²⁴ In the present study we found low rectal distension thresholds for both non-painful stimuli and maximal discomfort in IBS patients. This finding would support a

biological basis for visceral hypersensitivity so far as the tracking technique really is able to circumvent perceptual response bias.

The fact that the electrodermal response to distension habituated, indicates that there is a psychophysiological mechanism behind the visceral hypersensitivity. From earlier studies we know that sympathetic responses, such as electrodermal activity, to stimuli of moderate intensity habituate, while responses to repeated stimuli of close to pain intensities are resistant to habituation.²¹¹ Perhaps IBS patients in the present study unintentionally may have chosen lower pre-pain rectal pressures as maximally tolerable. This might be the result of conditioning by earlier painful rectal examinations or colonoscopies.

Emotional experience of pain could set up a memory loop which may be activated by the anorectal test situation.²¹² The habituation of skin conductance represents a decrease of the arousal response in IBS patients during repeated distensions. Probably the healthy controls do not habituate because their maximal tolerable rectal distension thresholds are close to pain.

This interpretation is supported by the results of Naliboff et al., who studied the effect of several repeated rectal distension assessments on perceptual responses in IBS patients over 12 months.²¹³ In the beginning and in the end of this period a positron emission tomography was performed to study regional brain activation. IBS patients had a gradual increase (normalisation) of discomfort thresholds over time although their bowel symptoms during the year remained steady. Anticipation of an aversive rectal stimulus was seen in the first positron emission tomography session but not in the last. While brain activity in the sensory processing areas of the brain remained unchanged, activation of limbic and paralimbic circuits related to vigilance and arousal for aversive events showed significant changes. This occurred during both actual rectal distension and anticipation of distension, suggesting a decrease in visceral hypervigilance as a primary underlying factor for the perceptual change. Probably their results were due to a habituation process with a decrease in hypervigilance to the repeated rectal distensions over time. However, as autonomous responses were not recorded during their study, they have no objective measure of arousal to confirm the hypothesis of habituation. Our study of skin conductance as a measure of sympathetic activity was able to study the level of arousal. During repetitive rectal distensions we found a decrease of sympathetic reactivity. This supports the findings of Naliboff et al. that visceral hypersensitivity is not a constant feature in IBS patients and indeed habituation may lead to normalization of the visceral perceptual response over time.²¹⁴

In the present study the IBS patients had higher scores in psychological ratings than controls and there were correlations between anxiety, depression and obsessive compulsive symptoms, indicating a non-specific psychological characteristic of the IBS patients. Cortisol levels or SC values were not related to any of the specific psychological items among the IBS patients. Because of the two to three-week time span between the ratings of possibly temporary psychological variables and the experiment, a conclusion of absence of relationship between rated anxiety and cortisol levels should be considered as tentative.

Patients with constipation

The main findings for constipation patients were: (1) the constipation patients had significantly lower mean baseline SC compared to both the IBS patients and controls; (2) the maximal SC response to rectal distensions did not differ significantly between constipation patients and controls, but constipation patients had significantly lower values than IBS

patients; and (3) the amplitude of the initial SC response decreased successively over the five repetitive distensions in patients with constipation but not in controls.

The significant habituation of the SC response and significantly lower SC baseline levels in the constipation group when compared with controls suggest that the constipation patients were not stressed by the barostat investigation *per se*, and that the stimuli were perceived as moderate despite choosing similar maximal pressures as controls. These results suggest that the constipation group is not as sympathetically active and reactive as healthy controls and IBS patients.

Emmanuel and co-workers found that patients with idiopathic constipation had a reduction in rectal mucosal blood flow. They conclude that this would provide evidence for a decreased sympathetic drive affecting both colonic transit and mucosal blood flow, or a deficit in the normal cholinergic drive.²¹⁵ Our findings support the theory of an inhibition of the sympathetic drive in constipated subjects.

The significantly lower skin conductance baseline levels in the constipation group, as compared to the normal and the IBS groups, indicates a physiological and maybe also psychological state in constipation patients which has to be explained. In any case, our results support the necessity for differentiation between IBS and constipation patients in scientific research and strongly argue for careful assessment of symptoms to categorize patients correctly.

CONCLUSIONS

Paper I: In the Swedish population the prevalence of self-reported constipation and fecal incontinence was high with a similar magnitude as in other Western countries. 95.6% of the population had between three bowel movements per day and three per week. Constipation was mostly defined by “hard stools” and “the need of using laxatives”.

Paper II and III: Alternating stool consistency and presence of different defecatory symptoms regardless of stool consistency should be included as criteria for IBS. IBS subgroups should be based on stool consistency. Rome II supportive criteria should be reconsidered as the determination of presence or absence of specific symptoms does not work as an instrument for categorization of IBS patients into diarrhoea- and constipation-predominant. Moreover abnormal stool frequency should be excluded to define subgroups of IBS.

Papers IV and V: The expectancy of the experimental situation *per se* (provocation of bowel symptoms by rectal distensions) compared to non-experimental days at home measured as cortisol had a high impact on the level of arousal in IBS. IBS patients are more sensitive to pre-experimental stress than healthy controls and patients with constipation. This should be considered in the design of experimental IBS studies.

IBS patients had higher skin conductance values than controls in the beginning of distension series. IBS patients had visceral hypersensitivity both according to maximal and sub-maximal rectal distension pressures. IBS patients habituated to subjective maximal tolerable, repetitive rectal distension with decreasing sympathetic activity. Since responses to repeated stimuli of close-to-pain intensities are resistant to habituation this finding could be caused by psychological influences on perception, that is, perceptual response bias.

APPENDIX

Questionnaire

1. Do you consider yourself constipated?
 - a) Never, or very rarely
 - b) Yes, sometimes
 - c) Yes, often
 - d) Yes, always

2. How often do you move your bowels?
 - a) More than three times a day
 - b) Approximately two to three times a day
 - c) Approximately once a day
 - d) Approximately three times a week
 - e) Approximately once every five days
 - f) Less often

3. Do you wake up at night time needing to move your bowels?
 - a) No, never
 - b) Yes, sometimes
 - c) Yes, often
 - d) Yes, every night

4. Do you need to strain when moving your bowels?
 - a) Rarely (less than every fourth time)
 - b) Sometimes (at least every fourth but not as much as every second time)
 - c) Often (at least half of the time but not every time)
 - d) Always (every or at least nearly every time)

5. Can you manage to empty your bowels in less than 15 minutes?
 - a) Yes, always
 - b) Yes, often
 - c) Yes, sometimes
 - d) No, never

6. Do you need medication to be able to open your bowels?
 - a) No, never or nearly never
 - b) Yes, sometimes (at least every fourth but not every second time)
 - c) Yes, often (at least every second but not every time)
 - d) Yes, always (or nearly every time)

7. What kind of medication? Please specify:

8. Can you withstand the urge to pass a motion longer than 15 minutes?
- a) Yes, always
 - b) Yes, often
 - c) Yes, sometimes
 - d) No, never
9. Can you break wind without soiling your underclothes?
- a) Yes, always
 - b) Yes, often
 - c) Yes, sometimes
 - d) No, never
10. Does it happen that you break wind involuntarily?
- a) No, never
 - b) Yes, between once a month and once a week
 - c) Yes, between once a week and once a day
 - d) Yes, daily
11. Does it happen that you leak when the motion is loose?
- a) No, never
 - b) Yes, between once a month and once a week
 - c) Yes, between once a week and once a day
 - d) Yes, daily
12. Does it happen that you have a leakage even if the motion is not loose?
- a) No, never
 - b) Yes, between once a month and once a week
 - c) Yes, between once a week and once a day
 - d) Yes, daily
13. Do you have problems with soiling your underclothes?
- a) No, never
 - b) Yes, between once a month and once a week
 - c) Yes, between once a week and once a day
 - d) Yes, daily
14. Does your bowel function adversely affect your general well-being?
- a) Not at all
 - b) A little
 - c) Quite a bit
 - d) A lot

15. Does your bowel function adversely affect your daily activities?

- a) Not at all
- b) A little
- c) Quite a bit
- d) A lot

16. There is a variety of concepts of what it means to be constipated. What does constipation mean to you? Multiple answers may be given.

- a) Hard stools
- b) Straining in connection with bowel movement
- c) Pain when passing a motion
- d) Infrequent bowel movements
- e) Needing to use laxatives

SAMMANFATTNING PÅ SVENSKA

Arbete I är en enkätundersökning som mäter förekomsten av förstoppning och avföringsinkontinens i befolkningen. Ett frågeformulär med 16 frågor om tarmtömningsvanor har skickats till 2000 kvinnor och män i åldrarna 31-76 år, slumpvis utvalda via befolkningsregistret i Östergötland. I frågeformuläret ingick även två frågor om hur tarmfunktionen påverkar livskvaliteten och dagliga aktiviteter. Svarefrekvensen var 80.5%. Resultaten visade att 95.6% av befolkningen har mellan tre tarmtömningsvanor per dag och tre per vecka. 5.7% av kvinnorna och 2% av männen upplever sig ofta eller alltid förstoppade. De flesta definierar förstoppning som hård avföringskonsistens och/eller behovet av att använda laxermedel. 10.9% av kvinnorna och 9.7% av männen har avföringsläckage om avföringskonsistensen är lös. Ofrivillig gasavgång förekommer hos 14.8% av befolkningen. Kvinnor i åldergruppen 61-76 har oftare avföringsinkontinens än yngre kvinnor och män. 6.5% av männen och 2.6% av kvinnorna i åldergruppen 31-45 år har besvär med fuktläckage från ändtarmen minst varje vecka

Sammanfattningsvis är både förstoppning och avföringsinkontinens vanliga problem i befolkningen. Vi visade också att tarmsymptomen har en negativ effekt på det allmänna välbefinnandet och dagliga aktiviteter.

Irritable Bowel Syndrome (IBS) kännetecknas av buksmärta/obehag och avvikande tarmvanor.

IBS är en funktionell gastrointestinal störning och kan för närvarande inte förklaras av anatomiska eller biokemiska avvikelser. Diagnosen baseras uteslutande på symptom som är mycket varierande i karaktär. Försök har gjorts att dela in patienter med IBS i undergrupper med avseende på symptom för att lättare kunna standardisera inklusionskriterier till studier och behandlingar. "Rome II supportive criteria" är ett sådant försök som baseras på åsikter i en expertgrupp.

I arbete II och III har "Rome II supportive criteria" validerats med hjälp av magdagböcker där 135 IBS patienter i detalj har registrerat sina symptom. IBS patienterna inkluderades utifrån klassiska IBS kriterier (Rome I). Majoriteten kunde inte klassificeras i undergrupper enligt dessa nya "supportive criteria" då patienterna hade alla typer av symptom vid tarmtömning (trängning, krystning, känsla av ofullständig tömning) oberoende av avföringskonsistens. Undergruppering föreslås istället vara baserad på avföringskonsistens. Baserat på detta och tidigare Linköpingsstudier föreslås i rapporten att nya symptomkriterier för IBS bör ersätta de idag använda Rome II kriterierna.

Vid IBS finns samverkan mellan stress och debut eller försämring av mag-tarmsymptom. I experimentella studier har man sett samband mellan en ändrad känslighet i tarmen, mätt med rektalballong, och utsöndring av stresshormoner. Det är dock oklart om själva undersökningssituationen på laboratoriet kan påverka och därmed vara en "confounding factor" för IBS patienter avseende stresspåslag. I arbete IV mättes saliv-kortisol, som ett mått på stress, före och efter maximala rektala ballongdistensioner hos patienter med IBS, kronisk förstoppning och friska kontrollpersoner. För att studera hur själva laboratoriesituationen påverkade patienterna genomfördes även basala saliv-kortisol mätningar i hemmiljö. Jämfört med mätningar som utförts i deras hemmiljö visade mätningarna i sjukhusmiljö att endast IBS patienterna var mer stressade före undersökningen. Ballongdistensionerna ledde inte till någon signifikant stegring av stresshormon i någon av grupperna. IBS patienterna hade känslighetströsklar för distension av rektum som var lägre än patienterna med förstoppning och kontroller. Slutsatsen blev att man bör ta hänsyn till IBS patienternas högre stressnivå vid bedömningen av jämförelser med andra patientgrupper.

IBS är associerat till en dysfunktion i det autonoma nervsystemet. Förändringar i hudkonduktans är direkt korrelerade till svettkörtel- och sympatikusaktivitet. I en tidigare studie har man funnit att IBS patienter har ett generellt ökat hudkonduktanssvar (skin conductance response) vid upprepade distensioner i sigmoideum men det framgår inte hur sympatikussvaret mera specifikt ter sig vid upprepning av stimulus. För att bättre karakterisera den överkänsligheten i tarmen mättes i arbete V den initiala hudkonduktansen och den maximala hudkonduktansen för varje rektaldistension. Dessutom mättes basalvärdet före varje distension. IBS patienter hade en högre basal sympatikusaktivitet än förstoppningspatienter samt habituerade avseende sympatikusaktivitet till upprepade subjektivt maximala rektaldistensioner. Detta betyder att IBS patienter hade ett större stresspåslag i samband med undersökningen än förstoppningspatienter och det troligen finns en psykologisk komponent som påverkar känsligheten i tarmen hos IBS patienter.

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