Chronic Constipation and Constipation-Predominant IBS: Separate and Distinct Disorders or a Spectrum of Disease?

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Abstract: Rome III diagnostic criteria separate patients with idiopathic chronic constipation into mutually exclusive categories of constipation-predominant irritable bowel syndrome (IBS-C) or functional constipation (FC). However, several experts think that these conditions are not different disorders, but parts of a continuum. To shed light on this issue, we examined studies that compared IBS-C with FC with respect to symptoms, pathophysiologic mechanisms, and treatment response. When the Rome III requirement that patients meeting criteria for IBS cannot also be given a diagnosis of FC is suspended, most patients meet criteria for both, and, contrary to expectation, IBS-C patients have more symptoms of constipation than patients with FC. No symptoms reliably separate IBS-C from FC. Physiologic tests are not reliably associated with diagnosis, but visceral pain hypersensitivity tends to be more strongly associated with IBS-C than with FC, and delayed colonic transit tends to be more common in FC. Although some treatments are effective for both IBS-C and FC, such as prosecretory agents, other treatments are specific to IBS-C (eg, antidepressants, antispasmodics, cognitive behavior therapy) or FC (eg, prucalopride, biofeedback). Future studies should permit IBS-C and FC diagnoses to overlap. Physiologic tests comparing these disorders should include visceral pain sensitivity, colonic transit time, time to evacuate a water-filled balloon, and anal pressures or electromyographic activity from the anal canal. To date, differential responses to treatment provide the strongest evidence that IBS-C and FC may be different disorders, rather than parts of a spectrum.

Irritable bowel syndrome (IBS) is characterized by abdominal pain associated with defecation or with changes in stool frequency or consistency, and many patients with IBS often complain of constipation.1 Rome III criteria define IBS with predominant constipation (IBS-C) as a subtype of IBS. However, the authors of the Rome III criteria realized that the symptoms of functional constipation (FC) are similar to those of IBS-C, making...
it difficult to distinguish between the 2 disorders; the authors solved this dilemma artificially by stating that a patient who meets the criteria for IBS cannot be classified as having FC. This rule assigns priority to the presence of abdominal pain for distinguishing IBS-C from FC.

Multiple authors have questioned the validity of treating IBS-C and FC as distinct disorders. These authors suggest that IBS-C and FC may be parts of a continuum, with differences based upon symptom severity. Other authors divide FC into subtypes based upon the presence or absence of abdominal pain.

This paper reviews whether IBS-C and FC are distinct disorders, or the same disorder at different points of a severity spectrum or different time points in a progression. Also explored are the implications and consequences of these different concepts for diagnosis and management.

**Symptom Overlap**

The Rome III diagnostic criteria for IBS and FC imply that clear differences should exist between the symptoms of IBS-C and FC. The diagnosis of IBS requires the presence of abdominal pain or discomfort, whereas FC is diagnosed based upon the presence of at least 2 of 6 symptoms (passage of hard stools, infrequent stools, straining, feeling of incomplete emptying, feeling of obstructed defecation, and need for digital facilitation of stool evacuation), none of which refer to pain or discomfort. One would expect from these differences in diagnostic criteria that the presence of abdominal pain would separate IBS-C from FC, and that patients with FC would report more of the 6 symptoms of constipation compared with patients with IBS-C. The pivotal studies that address this issue are summarized below.

Wong and colleagues described a longitudinal follow-up study in 1615 primary care patients in a large health maintenance organization in the United States. At enrollment, 231 patients met Rome III criteria for FC and 201 met Rome III criteria for IBS-C. When the Rome III requirement stating that FC cannot be diagnosed in a patient who meets the criteria for IBS was suspended, the FC group expanded to 411 patients, and 89.5% of the IBS-C group also fulfilled the criteria for FC. The observational studies previously described support the hypothesis that IBS-C patients experience more abdominal pain, bloating, and discomfort compared with FC patients, although there is a substantial overlap, with the majority of patients with FC also reporting abdominal pain and discomfort. The differences appear to be more quantitative than qualitative. Moreover, the complementary hypothesis that patients with FC should have more constipation symptoms than patients with IBS-C has been consistently disconfirmed, which suggests that IBS-C and FC cannot be reliably distinguished based upon symptoms alone.

The possibility that IBS-C and FC are different points on the same spectrum of symptoms receives further support from studies comparing the 2 disorders on quality of life, disease burden, and psychological symptom scales.
Wong and colleagues showed that IBS-C patients experience greater impairment than FC patients in quality of life on the Patient Assessment of Constipation Quality-of-Life questionnaire, and Drossman and colleagues reported similar findings on the Sickness Impact Profile. However, Zhao and colleagues found no significant difference between IBS-C and FC on quality-of-life and symptom severity instruments. In several studies, IBS-C patients were found to have significantly more anxiety and depression compared with FC patients. IBS-C patients were also more likely than FC patients to seek health care. Additionally, FC patients with abdominal pain missed more work days per month compared with FC patients without pain.

Pathophysiologic Mechanisms

Pathophysiologic mechanisms (physiologic tests) might discriminate between IBS-C and FC better than symptoms alone. Several different pathophysiologic mechanisms have been described for FC, including delayed whole-gut transit due to decreased numbers of high amplitude propagating contractions in the colon, paradoxical contraction or failure to relax pelvic floor muscles during attempts to evacuate (also called dyssynergic defecation), and inadequate rectal propulsive force during attempted defecation (also called inadequate rectal propulsion). The balloon evacuation test, which assesses the ability to evacuate a 50-mL water-filled balloon from the rectum within 1 to 2 minutes, is also useful for identifying patients with outlet dysfunction, although it does not directly measure any specific physiologic process. Gastroenterologists regard these tests as biomarkers for groups of patients with FC, and classify chronic constipation patients as having slow transit constipation or disordered defecation based upon these presumed pathophysiologic mechanisms. However, the majority of patients with symptoms consistent with FC do not have delayed whole-gut transit or pelvic floor dysfunction despite persistent symptoms of constipation; they are designated as having normal transit constipation.

Unlike FC, there is little consensus on the mechanisms responsible for symptoms of IBS-C. Commonly discussed mechanisms include visceral pain hypersensitivity due to peripheral or central nervous system mechanisms; abnormalities in the phasic motility of the small or large intestine; immune mechanisms related to increased numbers of mast cells, increased levels of proinflammatory cytokines, altered levels of microbiota in the intestines, and/or increased mucosal permeability; effects of stress hormones on the gut; and dysregulation of the bidirectional signaling between the gut and the brain that modulates visceral pain perception. The visceral pain/discomfort threshold is most frequently cited as a physiologic measure that can identify IBS-C patients, even though only approximately two-thirds of patients with a clinical diagnosis of IBS-C have abnormally low pain thresholds.

The hypothesis we would like to address in this section is that physiologic measures such as those listed above can distinguish IBS-C patients from those with FC more accurately than symptom criteria. However, there is no standard for classifying patients as IBS-C or FC other than symptoms, and symptom criteria identify overlapping groups and are likely imprecise, as the aforementioned studies have shown. Consequently, some overlap in physiologic markers should be expected when comparing groups of patients classified as IBS-C and FC by symptom criteria.

Very few published studies have investigated the underlying mechanistic differences between IBS-C and FC using a parallel group design (Table 1). In the earliest study to compare these groups, Suttor and colleagues compared the prevalence of dyssynergia and failure to evacuate a water-filled balloon in 25 FC patients vs 25 non-diarrhea-predominant IBS patients. However, because the investigators were specifically looking for evidence of dyssynergia in patients with non–diarrhea-predominant IBS, they included only non–diarrhea-predominant IBS patients who had at least 2 of 4 symptoms believed to be associated with disordered defecation (ie, straining, feeling of incomplete emptying, feeling of blocked evacuation, and use of digital assistance to evacuate). These non–diarrhea-predominant IBS patients were significantly less likely to exhibit paradoxical contraction; however, failure to evacuate a water-filled balloon was significantly more prevalent in the non–diarrhea-predominant IBS group than in the FC group. Transit time was not measured. This study shows that outlet dysfunction is prevalent in a subset of non–diarrhea-predominant IBS patients who have symptoms of outlet dysfunction in at least 25% of their bowel movements, but it is unclear how representative these patients are of all patients with non–diarrhea-predominant IBS.

In a subsequent study carried out in India, where transit times may be more rapid due to differences in diet, Ansari and colleagues compared whole-gut transit time via the Sitzmark technique in 50 patients with FC and 50 patients with IBS-C. Whole-gut transit time tended to be slower in patients with FC (52.2 ± 35.5 hours) compared with patients with IBS-C (41.2 ± 31.6 hours), but the difference was not statistically significant (P=.10). Rectosigmoid transit time was significantly slower in FC patients (19.9 ± 15.5 hours) compared with IBS-C patients (11.9 ± 10.6 hours; P=.003). In another study, 23 patients with IBS-C were compared with 11 patients with FC and 23 healthy volunteers. Dependent measures were plasma levels of serotonin, sensitivity to rectal distention, orocecal (small intestinal) transit time, and colonic transit.
anal canal pressures during straining, and anal electromyography (EMG) during straining in 131 patients with refractory constipation. 

The authors noted that 82% of their patients also satisfied (older) Rome II criteria for IBS-C. Owing to significant overlap between IBS-C and FC in this study, the primary interest was whether physiologic measures that were characteristic of IBS-C (ie, visceral pain hypersensitivity) were negatively correlated with physiologic measures that were characteristic of FC (ie, delayed colonic transit and/or dyssynergic defecation). Colonic transit was delayed in 47% of patients, visceral hypersensitivity was present in 58%, and paradoxical anal contraction (present on both pressure and EMG) was present in 59%. The authors reported that there were no significant correlations, either positive or negative, among these physiology-dependent measures. However, a possible limitation of the study was the unusually high rate of findings of dyssynergia; the authors treated failure to relax anal canal pressures as a normal finding yet found evidence of paradoxical contraction by either anal pressure measurements or EMG in approximately 82% of the patients.

Table 1. Physiologic Differences Between Constipation-Predominant IBS and Functional Constipation

<table>
<thead>
<tr>
<th>Study</th>
<th>Population Studied</th>
<th>Measures</th>
<th>Results</th>
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<tbody>
<tr>
<td>Suttor et al17</td>
<td>25 FC patients vs 25 non–diarrhea-predominant IBS patients</td>
<td>DYS, BET</td>
<td>DYS was more prevalent in FC patients than IBS patients. Abnormal BET was more prevalent in IBS patients than FC patients.</td>
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<td>Ansari et al18</td>
<td>50 FC patients vs 50 IBS-C patients</td>
<td>CTT (Sitzmark technique), segmental transit time</td>
<td>CTT was 52.2 hours in FC patients vs 41.2 hours in IBS-C patients (P&lt;.01). Rectosigmoid transit was 19.9 hours in FC patients vs 11.9 hours in IBS-C patients (P=.003).</td>
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<tr>
<td>Shekhar et al4</td>
<td>11 FC patients vs 23 IBS-C patients; 23 HVs</td>
<td>5-HT levels in serum, SBTT, CTT, PainTh</td>
<td>5-HT levels were similar in FC patients and HVs, with both having higher levels than IBS-C patients. SBTT was similar in all groups. CTT was similar in FC patients and IBS-C patients, with both having longer CTT than HVs. PainTh was similar in FC patients and HVs, with lower thresholds in IBS-C patients.</td>
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<tr>
<td>Manabe et al19</td>
<td>287 IBS patients, including 118 IBS-C patients</td>
<td>CTT (scintigraphic technique). Abnormal is &lt;10th percentile for HVs.</td>
<td>22.9% of IBS-C patients had delayed transit at 48 hours vs 10.0% of HVs.</td>
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<tr>
<td>Torblom et al20</td>
<td>359 IBS patients, including 100 IBS-C patients</td>
<td>CTT (Sitzmark technique)</td>
<td>CTT was delayed in 12% of IBS-C patients.</td>
</tr>
<tr>
<td>Mertz et al21</td>
<td>131 FC patients (82% also met the criteria for IBS-C)</td>
<td>CTT, DYS, PainTh</td>
<td>CTT was delayed in 47%. DYS was present in 59%. PainTh was abnormal in 58% and was uncorrelated with CTT or DYS.</td>
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5-HT, 5-hydroxytryptamine; BET, balloon evacuation test; CTT, colonic transit time; DYS, dyssynergic defecation; FC, functional constipation; IBS, irritable bowel syndrome; IBS-C, constipation-predominant irritable bowel syndrome; HVs, healthy volunteers; PainTh, rectal threshold pressure or volume for pain or discomfort; SBTT, small bowel transit time.

In 2 studies, colonic transit time was measured in patients with IBS-C but without a comparison group of patients with FC.19,20 If there is no difference in the pathophysiology of IBS-C vs FC, one might expect to find that a high proportion of IBS-C patients have delayed colonic transit; however, the proportion with delayed transit was relatively low in both studies. One study reported a delay in colonic transit time, measured by the scintigraphic method, in 22.9% of 118 IBS-C patients,19 and when transit time was measured by the Sitzmark technique, colonic transit was delayed in 12% of 100 IBS-C patients (Table 2).20

Mertz and colleagues examined the correlations between visceral sensory thresholds, colonic transit time, anal canal pressures during straining, and anal electromyography (EMG) during straining in 131 patients with refractory constipation.21 The authors noted that 82% of their patients also satisfied (older) Rome II criteria for IBS-C. Owing to significant overlap between IBS-C and FC in this study, the primary interest was whether physiologic measures that were characteristic of IBS-C (ie, visceral pain hypersensitivity) were negatively correlated with physiologic measures that were characteristic of FC (ie, delayed colonic transit and/or dyssynergic defecation). Colonic transit was delayed in 47% of patients, visceral hypersensitivity was present in 58%, and paradoxical anal contraction (present on both pressure and EMG) was present in 59%. The authors reported that there were no significant correlations, either positive or negative, among these physiology-dependent measures. However, a possible limitation of the study was the unusually high rate of findings of dyssynergia; the authors treated failure to relax anal canal pressures as a normal finding yet found evidence of paradoxical contraction by either anal pressure measurements or EMG in approximately 82% of the patients.
Chiarioni and colleagues described a study in which a physical examination, whole-gut transit study (Sitzmark technique), anorectal manometry, balloon evacuation test, and, in select patients, a defecography were used to classify 238 chronically constipated patients into subtypes. Outlet obstruction was diagnosed in 26 patients based upon failure to evacuate a 50-mL water-filled balloon in 2 minutes, normal relaxation of pelvic floor muscles when pushing to evacuate, and findings of rectocele or rectal prolapse on physical examination or defecography. Disordered defecation was diagnosed in 113 patients based upon failure to evacuate the balloon, anorectal manometry showing paradoxical contraction of pelvic floor muscles when pushing to evacuate or inadequate rectal propulsive force, and no evidence of mechanical obstruction. Slow transit constipation was diagnosed in 31 patients based upon delayed transit combined with normal balloon evacuation, normal anorectal manometry, and no significant findings on physical examination or defecography. A gastroenterologist independently assessed all patients for the presence of comorbid IBS-C based upon Rome III criteria and clinical history. An IBS-C diagnosis was present in 52% of the normal transit constipation group, 31% of the outlet obstruction group, 20% of the disordered defecation group, and 6% of the slow transit constipation group. This study suggests that transit time, anorectal manometry/EMG, and the balloon evacuation test identify distinct subgroups of patients with FC, most of which do not overlap with IBS-C, and that patients with normal transit constipation (ie, absence of these biomarkers for constipation) are more likely to have comorbid IBS-C.

**Treatment**

Treatments that have been shown to be effective for IBS-C and/or FC are summarized in Table 2. It is notable...
that many of the pharmacologic treatments approved by
the US Food and Drug Administration specifically for the
treatment of IBS-C were also approved for the treatment
of FC. These treatments include the prosecretory agents
lubiprostone (Amitiza, Takeda) and linaclotide (Linzess,
Actavis and Ironwood) and the older 5-hydroxytryptamine
receptor 4 (5-HT4) agonist tegaserod. This observation has been interpreted as supporting the concept that
IBS-C and FC are not distinct disorders with different
pathophysiologies.2 However, Table 2 also shows that
some treatments are unique to IBS-C (eg, antidepressants,
cognitive behavioral therapy, antispasmodics), while other
treatments are unique to FC (eg, prucalopride, pelvic floor biofeedback). The differences between these classes of
therapy are logically related to presumed differences in
pathophysiology; drugs, diets, or psychological interventions
that specifically target reductions in pain or bloating are more likely to benefit patients with IBS-C than
patients with FC, whereas treatments that target transit
time or motility (eg, 5-HT4 agonists such as prucalo-
pride) or pelvic floor biofeedback to target dyssynergic
defecation are more likely to benefit patients with FC
than patients with IBS-C. Pelvic floor biofeedback is an
example of a treatment that has very specific indications
for a subtype of FC called dyssynergic defecation; studies
have shown that the presence of dyssynergic defecation is highly predictive of the success of pelvic floor biofeedback
for patients with FC.22,23

Discussion

This review does not permit a definitive answer to the
question of whether FC and IBS-C are qualitatively dif-
ferent disorders or parts of a spectrum. Rome III symp-
tom criteria for IBS-C and FC do not identify distinct
groups of patients; the Rome III criteria classify patients
with symptoms of constipation into mutually exclusive
categories by requiring that a patient cannot be classified
with FC if they meet symptom criteria for IBS. However,
when this rule is removed, the overwhelming majority of
patients meet criteria for both disorders, and when the
rule of mutual exclusion is reinstated, a significant num-
ber of patients change from 1 diagnosis to the other over
a 1-year period. Specific symptoms of constipation do not
reliably separate IBS-C from FC.

Physiologic studies also do not provide robust sup-
port for the hypothesis that different pathophysiologic
mechanisms are involved in IBS-C vs FC. Visceral hyper-
sensitivity was more common in IBS-C than in FC in the
only study2 where this was measured in both groups
(Table 1). Delayed transit was somewhat more common
in FC compared with IBS-C. Dyssynergic defecation, which
would appear to be uniquely associated with FC,
was actually more prevalent in the IBS-C group in the
only study to compare the groups on this measure.17 Some
of the lack of specificity in physiologic test data may be
due to the large overlap between IBS-C and FC when
diagnosed by symptoms. Findings from the study by
Chiarioni and colleagues17 are consistent with this inter-
pretation; the overlap of IBS diagnosis with FC was great-
est in the subgroup of chronically constipated patients
who had no delay in colonic transit, no dyssynergia on
manometry, and normal balloon evacuation. This group
of patients with normal transit constipation may have a
shared pathophysiology with IBS-C.

The most persuasive evidence that there may be
important differences between IBS-C and FC comes from
the response to treatment. Although there are some treat-
ments that appear to be effective in both groups, there are
other treatments that appear to be more effective for 1
group than the other. Pain-specific treatments such as anti-
depressants and cognitive behavioral therapy, for example,
are more effective for IBS-C than for FC, whereas pru-
calopride and pelvic floor biofeedback are more effective
for FC. Differential responses to treatment, if shown to
be related to physiologic deficits found in patients with
FC and/or IBS-C, will likely provide the most compelling
evidence that FC and IBS-C are distinct disorders.

The currently available data do not allow an answer
to whether IBS-C and FC are distinct disorders or parts of
a spectrum of disease because of the large overlap in symp-
toms and in pathophysiologic mechanisms. However, we
are persuaded by the evidence for differential response to
some treatments to believe that it will eventually be pos-
sible to identify different pathophysiologic mechanisms
for these symptoms, which will enable physicians to select
the most effective treatments for their patients. These dif-
ferent pathophysiologic mechanisms are not expected to
be parts of a single continuum, although current studies
do not permit the rejection of this possibility. New stud-
ies should better characterize the relationship between
pathophysiologic mechanisms and differential responses
to treatments.

The studies reviewed above have several limitations.
Many of the studies are small and may not be adequately
powered to detect differences. Additionally, the inclusion
criteria may have influenced the outcome; for example, in
the study by Sutter and colleagues,17 IBS-C patients were
enrolled only if they endorsed symptoms that are usually
linked to dyssynergic defecation, such as straining, feeling
of incomplete evacuation, feeling of blocked evacuation,
and use of digital maneuvers to defecate. Use of these
inclusion criteria could have led to an overestimation of
the prevalence of dyssynergic defecation in the IBS-C
group. Furthermore, studies that have compared IBS-C
with FC have not used all of the most relevant physiologic
tests available. An important omission is that only one of the studies summarized in Table 1 included the balloon evacuation test, even though it is a highly reproducible test that appears sensitive and specific for a subset of patients with FC.12

Future Research

This review underscores the importance of a few guidelines for future research. Overlapping diagnoses of IBS-C and FC should be permitted when symptom-based diagnostic criteria are used. In addition, the physiologic tests used to characterize patients with chronic constipation should include, at minimum, rectal pain thresholds, colonic transit time, anal canal pressures or EMG to detect dysynergia, and a test of the ability to evacuate a water-filled balloon. Finally, study designs that test whether these physiologic measures predict response to specific treatments may be preferable to studies of whether physiologic tests are concordant with symptom-based diagnostic groups.

Summary

This review addressed the question of whether IBS-C and FC are different disorders or parts of a spectrum by comparing patients with these diagnoses with respect to symptom overlap, pathophysiologic mechanisms for symptoms, and response to different classes of treatment. A definitive answer to this question does not seem possible based upon published evidence to date. However, the following conclusions can be made: (1) IBS-C and FC cannot be reliably distinguished on the basis of current symptom criteria; (2) there are inadequate data on physiologic differences between the 2 disorders (few studies, small samples, selective tests) to judge whether they are different disorders; and (3) different responses to specific treatment (ie, treatments that target pain for IBS-C and treatments that target motility or pelvic floor dysfunction for FC) suggest that these disorders will eventually be shown to have distinct pathophysiologic mechanisms. New studies are needed to guide clinical practice.

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References