

## VISCERAL PERCEPTION

# Pathophysiology of functional dyspepsia

M Thumshirn

Gut 2002;51(Suppl 1):i63–i66

Functional dyspepsia is a symptom complex characterised by postprandial upper abdominal discomfort or pain, early satiety, nausea, vomiting, abdominal distension, bloating, and anorexia in the absence of organic disease. Gastrointestinal motor abnormalities, altered visceral sensation, and psychosocial factors have all been identified as major pathophysiological mechanisms. This perspective has now replaced the earlier view that the condition was the result of a sole motor or sensory disorder of the stomach. Future therapeutic strategies should be aimed at reducing nociception as well as enhancing the accommodation response.

nisms interact to generate the symptoms. This perspective has now replaced the earlier view that the condition was the result of a sole motor or sensory disorder of the stomach.

### ALTERATIONS IN MOTILITY

Gastrointestinal motor abnormalities such as delayed emptying,<sup>2,3</sup> impaired initial distribution of a meal within the stomach,<sup>4</sup> impaired accommodation to a meal,<sup>5-7</sup> antral hypomotility,<sup>8</sup> gastric dysrhythmias (tachygastrias, bradygastrias, and mixed dysrhythmias),<sup>9,10</sup> and altered duodenojejunal motility have all been identified in subgroups of patients with functional dyspepsia. The onset of dyspeptic symptoms after food digestion suggests a disturbance of postprandial gastric motility leading to slowed gastric emptying accompanied by feelings of prolonged gastric distension, bloating, and nausea.

Delayed gastric emptying has been reported to occur in between 30% and 70% of patients with functional dyspepsia. The presence of antral hypomotility has been shown by manometric techniques,<sup>8</sup> and is sometimes accompanied by disordered intestinal motility.<sup>11</sup> Even though antral hypomotility and delayed gastric emptying are frequent in patients with functional dyspepsia, the clinical importance of these findings remains uncertain as they do not always correlate with symptoms.

The suggestion that patients with functional dyspepsia may have abnormal motor function of the proximal stomach was initially made by Coffin *et al* who documented hyporeactivity or reduced reflex fundic relaxation in response to duodenal distension.<sup>12</sup> Normally, the proximal stomach relaxes in response to meal ingestion in order to act as a reservoir and to enable an increase in gastric volume without a significant increase in gastric pressure. Impaired accommodation, which is a disturbance of “diastolic” function of the stomach, has recently been shown to be a frequent finding in patients with functional dyspepsia.<sup>5-7</sup>

The underlying mechanism for impaired gastric motor function is uncertain. Studies suggest abnormal gastrointestinal parasympathetic or sympathetic function in a small number of patients with gastroparesis, as well as in some patients with normal emptying,<sup>2</sup> or antral hypomotility.<sup>13</sup> However, our data failed to find confirmatory evidence of a role for vagal dysfunction in patients with functional dyspepsia.<sup>5</sup> Furthermore, although altered motility is frequent in functional dyspepsia, a relationship between these disorders and dyspeptic symptoms

### SUMMARY

The major pathophysiological mechanisms responsible for functional dyspepsia include psychosocial factors and alterations in motility and visceral sensation. Approximately 50% of patients with functional dyspepsia have motor disorders, such as impaired fundic relaxation, antral dilation and/or hypomotility, gastroparesis, small bowel dysmotility, or abnormal duodenogastric reflexes. Patients typically present with gastric hypersensitivity resulting from abnormal afferent function. The role of *Helicobacter pylori* in functional dyspepsia is difficult to define. Meta-analysis of seven controlled studies reported a non-significant odds ratio in favour of *H pylori* therapy in patients with functional dyspepsia. Impaired accommodation is a frequent pathophysiological disturbance among patients with and without *H pylori* infection. In terms of symptoms, impaired accommodation is significantly correlated with early satiety, and hypersensitivity is significantly correlated with pain and belching. Patients with delayed gastric emptying generally complain of predominant discomfort. Future therapeutic strategies should be aimed at reducing nociception as well as enhancing the accommodation response.

### INTRODUCTION

Functional dyspepsia is a symptom complex characterised by postprandial upper abdominal discomfort or pain, early satiety, nausea, vomiting, abdominal distension, bloating, and anorexia in the absence of organic disease. Gastrointestinal motor abnormalities, altered visceral sensation, and psychosocial factors have all been identified as major pathophysiological mechanisms. In recent years it has become evident that functional dyspepsia is a biopsychosocial disorder<sup>1</sup> in which these three major pathophysiological mecha-

Correspondence to:  
Dr M Thumshirn,  
Department of  
Gastroenterology,  
University Hospital Zurich,  
Raemistrasse 100, CH-  
8091 Zurich, Switzerland;  
miriam.thumshirn@  
DIM.usz.ch

Abbreviations: IBS, irritable bowel syndrome.

has not been established. In some circumstances motor abnormalities can be demonstrated in symptom free patients, and on other occasions symptomatic patients are found to have normal motor function.

### ALTERATIONS IN VISCERAL SENSATION

Increased perception of physiological or minor noxious stimuli has been demonstrated in patients with functional dyspepsia in both the fasting and postprandial states.<sup>5,6,14,15</sup> Compared with healthy controls, as a group, patients with functional dyspepsia are hypersensitive to isobaric or isovolumetric balloon distension of the proximal stomach. In view of the normal gastric wall compliance in these studies, increased sensation during gastric distension suggests abnormal afferent function or the "irritable stomach syndrome".<sup>14</sup>

Hypersensitivity to gastric balloon distension is highly specific for functional dyspepsia, as has been shown recently by Mertz and colleagues.<sup>16</sup> Dyspeptic symptoms such as upper abdominal pain or discomfort and nausea are equally prevalent among patients with organic causes of dyspepsia and patients with functional dyspepsia. However, volume thresholds for abdominal pain in response to balloon distension of the stomach have been shown to be lower in patients with functional dyspepsia than in those with organic dyspepsia or healthy controls.<sup>16</sup> In the same study, half of the patients with functional dyspepsia but only 20% of those with organic causes of dyspepsia showed evidence of enhanced viscerosomatic referral during gastric balloon distension. Indeed, there is evidence to suggest that visceral hypersensitivity in functional dyspepsia is not confined to the stomach as heightened sensitivity was also observed by distending a balloon in the small intestine of such patients.<sup>2</sup> However, the visceral abnormalities do not extend to the somatic sensory system as perception of a somatic pain stimulus is similar to that in healthy controls.<sup>5</sup>

It is not only hypersensitivity to mechanical distension that induces dyspeptic symptoms: increased chemosensitivity of the intestinal mucosa may also play a role. Hypersensitivity to duodenal acid infusion has recently been reported in patients with functional dyspepsia.<sup>17</sup> In the fasting state, acid infusion into the duodenal bulb increased sensations of nausea in patients with functional dyspepsia but not in healthy controls. Patients with functional dyspepsia also showed decreased duodenal motor activity in the fasting state, resulting in decreased clearance of exogenous acid from the proximal duodenum.

Sensory abnormalities may be responsible for some of the apparent paradoxes identified from gastrointestinal motility studies. For example, the intimate interaction of sensory and motor function in the upper gastrointestinal tract may explain why altered motility is so frequent in functional dyspepsia yet in itself it does not fully explain the occurrence of symptoms. Whether abnormally increased perception of visceral stimuli is due to mechanoreceptor dysfunction or alterations in the transmission and processing of the sensory input at spinal or brain centres is largely unknown. However, the increased areas of viscerosomatic referred pain in patients with functional dyspepsia indicate that hypersensitivity of dorsal horn neurones or altered supraspinal processing of visceral afferent function may play a role in the process.

In analogy to the role of motility disorders in the pathophysiology of functional dyspepsia, it is uncertain whether visceral hypersensitivity is correlated to specific symptoms in functional dyspepsia. A preliminary study reported that almost half of all patients with functional dyspepsia have hypersensitivity to gastric distension, and that postprandial pain is significantly more prevalent in these patients than in patients without visceral hypersensitivity.<sup>18</sup>

Impaired gastric and intestinal reflexes have also been observed in functional dyspepsia. In these patients, duodenal balloon distension failed to induce normal reflex gastric

relaxation or normal inhibition of motility distal to the stimulus. This reflex hyporeactivity suggests that there is either abnormal afferent or abnormal efferent function. In a preliminary report, visceral hypersensitivity was shown to affect the proximal stomach as well as the antrum of patients with functional dyspepsia.<sup>19</sup> Reflex relaxation of the proximal stomach normally induced by distension of the distal stomach was also absent. These findings suggest that dyspeptic symptoms may be a consequence of antral hypersensitivity and antral overload, which is caused by impaired reflex relaxation of the proximal stomach.

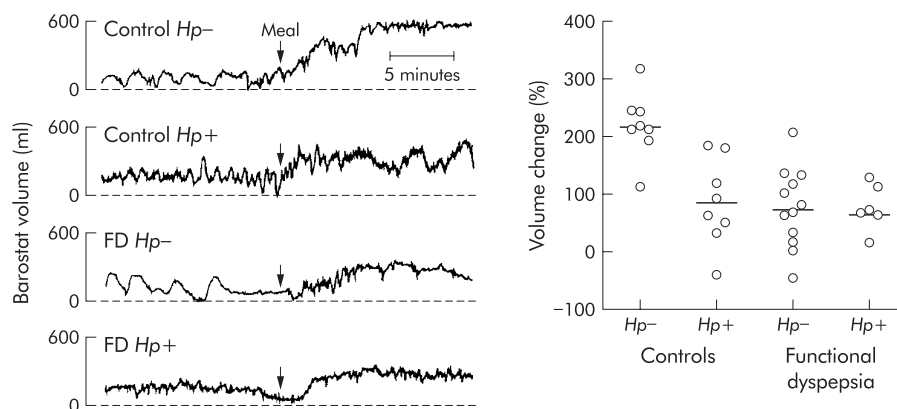
### RELATIONSHIP BETWEEN PATHOPHYSIOLOGICAL AND CLINICAL FEATURES OF FUNCTIONAL DYSPEPSIA

Although gastric sensorimotor dysfunction is the main pathophysiological finding in patients with functional dyspepsia, the relationship and relevance of these disorders to symptoms is largely unknown. There are only a few studies addressing this question in a large series of patients. Among 40 patients with functional dyspepsia who underwent measurement of gastric accommodation, Tack *et al* demonstrated that early satiety and weight loss were significantly more frequent in patients with impaired accommodation than among those with normal accommodation.<sup>6</sup> In another study in 125 patients with functional dyspepsia, the same investigators examined the relationship between sensorimotor dysfunction and symptoms according to the Rome II criteria subdivisions and individual symptom severity.<sup>20</sup> The results indicated that the prevalence of hypersensitivity and impaired accommodation did not differ significantly among the three symptom subgroups: predominant pain, predominant discomfort, and unspecified symptoms. However, impaired accommodation was again significantly associated with early satiety, and hypersensitivity was significantly associated with symptoms of pain and belching. Previously, it has been demonstrated that delayed gastric emptying of solids is a frequent finding in a subgroup of patients with functional dyspepsia and is characterised by severe and clinically relevant postprandial fullness and severe vomiting.<sup>21</sup>

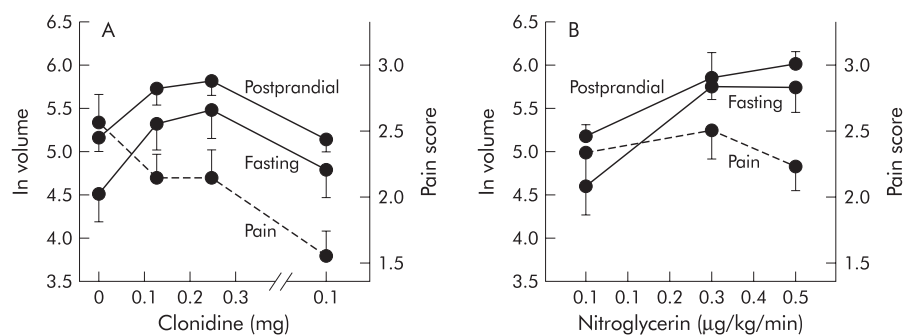
### HELICOBACTER PYLORI INFECTION

The role of *H pylori* in functional dyspepsia has long been a subject of controversy. Over the past few years, epidemiological, pathophysiological, and therapeutic studies attempting to identify a relation between *H pylori* infection and functional dyspepsia have yielded inconsistent and often confusing results. A critical review of studies investigating the possible association of *H pylori* infection and functional dyspepsia revealed that many of the studies were compromised by design weakness. Nevertheless, it appears that strictly controlled studies have failed to identify any real relationship between the two. The general consensus from the literature is that *H pylori* infection is not associated with impaired gastric emptying.<sup>4,21</sup> A comprehensive evaluation of the motor and sensory function of the stomach in *H pylori* positive and negative patients with functional dyspepsia showed that gastric accommodation to meal ingestion was reduced in patients with dyspepsia, independent of their *H pylori* status.<sup>5</sup> The impaired accommodation was associated with increased perception of distension stimuli in both subgroups (fig 1). Hypersensitivity and reduced accommodation were found to be more prevalent than delayed gastric emptying in these patients with functional dyspepsia.

A recently published meta-analysis evaluating the effect of *H pylori* eradication in patients with functional dyspepsia showed a non-significant trend towards a small benefit with *H pylori* therapy.<sup>22</sup> This meta-analysis included only randomised controlled trials that had an adequate follow up period.



**Figure 1** Gastric accommodation in healthy controls and in patients with functional dyspepsia (FD). In patients, reduced accommodation was not influenced by *Helicobacter pylori* status (Hp+ or Hp-). Reproduced with permission from Thumshirn and colleagues.<sup>5</sup>



**Figure 2** Effect of gastric relaxation and pain perception. Clonidine reduced pain perception at a 0.1 mg dose in the presence of modest gastric relaxation (A) whereas nitroglycerin did not affect pain despite significant gastric relaxation (B). Reproduced with permission from Thumshirn and colleagues.<sup>23</sup>

## APPROACHES TO RESTORE SENSORIMOTOR DYSFUNCTIONS OF THE STOMACH

In the face of impaired accommodation and hypersensitivity, there are two approaches to reducing symptoms: enhance relaxation and facilitate antinociception. In a small number of patients with functional dyspepsia, subcutaneous administration of the serotonin agonist sumatriptan, a drug which relaxes the gastric fundus, was shown to significantly increase meal induced gastric relaxation and the amount of calories inducing maximum satiety.<sup>6</sup> However, other data suggest that drug induced gastric relaxation may be insufficient to reduce dyspeptic symptoms.

Gastric relaxation and antinociception have different effects on the perception of visceral stimuli, as demonstrated in a dose-response study using nitroglycerin and the  $\alpha_2$  adrenoceptor agonist clonidine.<sup>23</sup> Both drugs produced marked relaxation of the fasting stomach without impeding normal postprandial accommodation of the proximal stomach. Perception scores during gastric balloon distension were reduced with clonidine, which is known to have antinociceptive effects, but not with nitroglycerin (fig 2). Nitroglycerin in contrast tended to increase bloating despite significant relaxation. These data suggest that relaxation alone may be insufficient to reduce sensation in response to distension in the human stomach.

## CONCLUSIONS

Delayed gastric emptying, impaired accommodation to a meal, and visceral hypersensitivity have been demonstrated in patients with functional dyspepsia. These mechanisms, rather than *H pylori* infection, are responsible for functional dyspepsia. Recent studies observed some potentially important associations between specific sensorimotor dysfunctions

of the stomach and dyspeptic symptoms. Gastric stasis is associated with postprandial fullness, nausea, and vomiting; impaired accommodation is associated with weight loss and early satiety, and hypersensitivity to balloon distension is associated with abdominal pain or belching. It is still not known whether these abnormalities are cause or effect of the disease, or whether they are generated centrally or peripherally. Further studies are needed to evaluate the role of central processing of visceral stimuli in the pathogenesis of functional dyspepsia.

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