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ARTICLE

Functional dyspepsia

SUMMARY

Functional dyspepsia is characterised by troublesome early satiety, fullness, or epigastric pain or burning. It can easily be overlooked as the symptoms overlap with gastro-oesophageal reflux disease and irritable bowel syndrome.

Diagnosis is clinical, however it requires exclusion of structural gastrointestinal disease. The presence of red flags, such as weight loss or anaemia, should prompt investigation including gastroscopy.

The pathophysiology of functional dyspepsia is not completely understood. It is thought to be associated with upper gastrointestinal inflammation and motility disturbances, which may be triggered by an infectious or allergenic agent, or a change in the intestinal microbiome. Slow gastric emptying occurs in 20% of cases.

While functional dyspepsia is distressing and affects quality of life, it has no long-term impacts on mortality.

There are many treatment options available, with varying levels of evidence of efficacy. These include reassurance, dietary modification, acid suppression, prokinetic drugs including fundic relaxors, tricyclic antidepressants, rifaximin and psychological therapy.

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Introduction

Functional dyspepsia is a common problem in Australia and often impacts on quality of life and work productivity.[1,2] It affects 10% of the population and is more prevalent in women.[3-5]

Functional dyspepsia refers to troublesome upper gastrointestinal symptoms including inability to finish a meal (early satiety), postprandial fullness, and epigastric pain or burning.[6] Some patients also complain of nausea, heartburn (although this is not the predominant complaint) and even weight loss (few patients with functional dyspepsia are obese). Peptic ulceration, reflux oesophagitis and gastric cancer may present with identical complaints but the vast majority of patients with these symptoms have functional dyspepsia.

There are two subtypes of functional dyspepsia, although these often overlap in practice (see Box).[6] The largest group (70%) have early satiety or postprandial fullness, termed postprandial distress syndrome. The other group experience ulcer-like pain or burning, termed epigastric pain syndrome.

Early satiety is a prevalent symptom in population-based surveys (5–11%).[3,4] Unless specifically asked about, it may often be missed or misinterpreted as bloating, discomfort or fullness after eating. These are also very common complaints even if meal size is not affected.[3,4] Most patients with these symptoms have no serious pathology on routine testing including gastroscopy, and are labelled as having functional or non-ulcer dyspepsia.[4,6]

Correctly diagnosing functional dyspepsia is important to guide appropriate therapy and reduce unnecessary procedures or treatments.

Differential diagnosis

Distinguishing functional dyspepsia from gastro-oesophageal reflux disease (GORD) without oesophagitis has been an area of clinical confusion, as early satiety can occur in both conditions.[4,6]

Box Rome IV diagnostic criteria for functional dyspepsia subtypes

Postprandial distress syndrome

Bothersome postprandial fullness or early satiety severe enough to impact on regular activities or finishing a regular-size meal for 3 or more days per week in the past 3 months, with at least a 6-month history.

Epigastric pain syndrome

Bothersome epigastric pain or epigastric burning 1 or more days per week in the past 3 months, with at least a 6-month history.

Note: both require the absence of evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy).
Source: Reference 6

Recent evidence suggests GORD is often the diagnostic label applied to patients even if they have typical symptoms of functional dyspepsia with little or no heartburn.[7] In patients with functional dyspepsia and no reflux symptoms, there is a substantially increased risk of GORD developing over the next 10 years.[4,8] Some patients with GORD who fail to respond to acid suppression with proton pump inhibitors may have functional dyspepsia so they should be asked about their symptoms.[4] Emerging data suggest GORD and functional dyspepsia are part of the same disease spectrum.

Symptoms of irritable bowel syndrome often overlap with those of functional dyspepsia, with epigastric pain and postprandial fullness often occurring with lower abdominal pain and bloating (diagnostic criteria in irritable bowel syndrome). However, unlike in irritable bowel syndrome, the symptoms of functional dyspepsia alone are not associated with a change in bowel habit. Both can arise after acute infectious gastroenteritis.[4]

Gastroparesis is often confused with functional dyspepsia but is rare.[4,6] This should be considered in patients with persistent vomiting or weight loss associated with dyspepsia.[4,6] A nuclear medicine gastric-emptying test can be helpful in this setting.

Pathophysiology

Functional dyspepsia has been considered an idiopathic disorder but this view is changing. In some cases, functional dyspepsia develops after acute infectious gastroenteritis, suggesting acute intestinal inflammation may play a role.[4,6]

Helicobacter pylori is a recognised cause of functional dyspepsia.[9] Most patients with *H. pylori* do not develop functional dyspepsia so in many of these cases it is an incidental finding. However in a minority, eradicating the infection cures dyspepsia long term, especially in those with epigastric pain as the main problem.[4,9]

Gastric and duodenal motility disturbances have been observed in functional dyspepsia. Gastric emptying is often normal but may be slow in 25% of patients or occasionally fast.[10] However, symptoms have generally not correlated with slow gastric emptying in functional dyspepsia.[4] Other abnormalities include failure of the gastric fundus to relax normally after eating. This occurs in up to 40% of patients and is linked to early satiety.[4,10] Hypersensitivity to distension of the stomach or duodenum (visceral hypersensitivity) occurs in about one-third of cases.[4,11]

People with postprandial distress have unique duodenal pathology, namely increased duodenal eosinophils that may degranulate.[11-15] Duodenal eosinophils have been linked to increased mucosal permeability, submucosal neuronal structural and functional changes, and symptoms.[12,13] They may reflect an infectious or allergenic trigger. In functional dyspepsia, the duodenal microbiome is also abnormal with increased oral streptococci.[16]

Psychological distress is common in patients with functional dyspepsia but may begin after the gut symptoms manifest.[3,8,17] Anxiety is prevalent but depression can occur and should not be missed.

Proposed disease model

Recently a unifying disease model has been proposed for functional dyspepsia.[4] Either an infection, microbiome alteration or a food allergen, such as wheat, induces increased duodenal permeability and duodenal eosinophilia with or without increased mast cells. This activates a mucosal immune response. Local duodeno-gastric reflex responses to low-grade inflammation alter gastroduodenal function, including impaired fundic relaxation in a subset of patients. Circulating cytokines such as tumour necrosis factor alpha may lead to systemic and central nervous system symptoms such as anxiety.[18]

These concepts are all supported by experimental evidence and, if correct, the model represents a paradigm shift with profound treatment implications.

Diagnosis

A typical history of long-standing troublesome early satiety and postprandial fullness is sufficient to make a clinical diagnosis and commence treatment, but often gastroscopy is required.[4,6] Any of the following red flag symptoms should prompt endoscopy:

- new onset in older age
- unintended weight loss
- vomiting
- bleeding
- iron deficiency anaemia
- family history of upper gastrointestinal cancer
- progressive dysphagia or odynophagia.

It is otherwise reasonable to screen for *H. pylori* infection by breath or stool antigen test and treat positive cases. Non-steroidal anti-inflammatory drugs should be stopped before either investigation or an empiric trial of therapy, usually a proton pump inhibitor for 2–4 weeks, in those who are still symptomatic.[4,6]

If gastroscopy is required, biopsies can be obtained from the duodenum as well as stomach to look for coexistent pathology even if the mucosa looks normal.

Treatment

There are many treatment options available for functional dyspepsia, with some being more effective than others (see Table). Many patients will respond to non-pharmacological management and drug therapy should be reserved for refractory cases.

Reassurance and explanation

Making a firm diagnosis even in the absence of endoscopy is sound medical practice and probably therapeutic. Functional dyspepsia is common and impacts on quality of life, but the good news is there is no associated increased mortality.[19] Reassurance, explanation and advice to reduce stress should be routine. Depression should be excluded by asking simple screening questions.[20]

Diet

Traditionally eating smaller regular low-fat meals is the advice offered, as the stomach and duodenum can process these more easily (a high fat intake slows gastric emptying)[21] and gastric distension is minimised. Wheat may induce typical dyspepsia symptoms. Eliminating it may provide relief in some patients although strong empirical evidence is lacking.[22] Theoretically a low FODMAP diet, an established therapy for irritable bowel syndrome, may help by reducing upper intestinal distension but there is no empirical evidence in functional dyspepsia.[22] Other triggers have been identified, including fatty, fried or spicy foods, and carbonated drinks, and avoiding these may be of benefit.[23]

Table **Usefulness of therapies for functional dyspepsia**

Therapy	Functional dyspepsia subtypes	
	Epigastric pain syndrome	Postprandial distress syndrome
Reassurance	+	+
Diet	+	+
Acid suppression	++	+
Prokinetics	+	++
Fundic relaxors	-	+
Tricyclic antidepressants	++	+
Rifaximin	+	+
Psychological therapy	+	+

- not useful
+ limited evidence of efficacy
++ efficacious

Acid suppression

Reducing the amount of acid bathing the duodenum may be helpful.[4] Proton pump inhibitors are superior to placebo in functional dyspepsia. However, they have risks with long-term use. The majority of patients do not respond to this therapy, and it is most useful in those with epigastric pain.[24] An alternative is H_2 receptor antagonist therapy, which is also superior to placebo. Some patients find this helpful even if proton pump inhibitors have failed.[24] Antacids and sucralfate are not efficacious.[24]

Prokinetics

In Australia, domperidone is sometimes prescribed but the evidence for efficacy in functional dyspepsia is very limited.[24] Cisapride has a better evidence base and is available from compounding chemists.[24] Both of these drugs prolong the QT interval and must be used with caution. ECG monitoring is recommended. Prokinetics help postprandial distress more than pain. Metoclopramide should be avoided unless nausea is a serious issue as irreversible tardive dyskinesia is a concern. For nausea in such cases a $5HT_3$ antagonist (ondansetron) is preferred.[24]

Fundic relaxors

Fundic relaxors can be considered for people unresponsive to prokinetics. Cisapride relaxes the gastric fundus, but alternative options include the anti-anxiety drug buspirone[25] or the over-the-counter product Iberogast.[26]

Antidepressants

Low-dose tricyclic antidepressants are superior to placebo for functional dyspepsia, but they are probably most helpful for those with epigastric pain.[27,28] Consider amitriptyline 10–25 mg at night increasing to 50 mg if tolerated after 2–4 weeks. Some people may need doses up to 100 mg. These doses may be associated with adverse effects, especially in older patients.

Selective serotonin reuptake inhibitors and selective noradrenaline reuptake inhibitors are reported to be no better than placebo.[27] Mirtazepine may have some efficacy particularly if nausea is associated.[29]

Non-absorbable antibiotic rifaximin

The microbiome is disturbed in functional dyspepsia. One randomised controlled trial from Hong Kong has reported rifaximin was superior to placebo, although this is currently an expensive off-label therapy and data

on relapse and retreatment are not available.[30] While rifaximin's predominant effect in functional dyspepsia is believed to be antibiotic, its anti-inflammatory properties may contribute to symptom relief.[30]

Psychological therapy

Evidence for psychological therapy in functional dyspepsia is limited. However, for patients with a strong psychological component, offering cognitive behavioural therapy is reasonable.[4,6]

The future

Low-grade duodenal inflammation may be amenable to anti-inflammatory therapy and possible cure. An eosinophil-stabilising drug montelukast appeared to have efficacy in children with functional dyspepsia.[31]

Conclusion

Functional dyspepsia is common, and the diagnosis can be made clinically in the absence of red flags. Concerning features on history or physical examination should prompt referral to a gastroenterologist for consideration of gastroscopy. Although symptoms can be significantly troublesome or disabling, there is no long-term effect on mortality. Multiple pharmacological and non-pharmacological therapies are available for patients with functional dyspepsia, giving clinicians several options for managing patients with this condition. <

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