

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/236138892>

Dietary Lipids and Functional Gastrointestinal Disorders

Article in *The American Journal of Gastroenterology* · April 2013

DOI: 10.1038/ajg.2013.76 · Source: PubMed

CITATIONS

61

READS

391

2 authors:



Christine Feinle-Bisset
University of Adelaide

215 PUBLICATIONS 8,376 CITATIONS

[SEE PROFILE](#)



Fernando Azpiroz
University Hospital Vall d'Hebron

482 PUBLICATIONS 10,992 CITATIONS

[SEE PROFILE](#)

Some of the authors of this publication are also working on these related projects:



Effects of an oral mixed-nutrient meal on gastrointestinal hormone release, gastric emptying and appetite perceptions over a 2-week refeeding period in adolescent anorexia nervosa [View project](#)



Abdomino-Thoracic Mechanisms of Functional Abdominal Distension And Correction by Biofeedback. [View project](#)

Dietary Lipids and Functional Gastrointestinal Disorders

Christine Feinle-Bisset, PhD¹ and Fernando Azpiroz, MD, PhD²⁻⁴

There is convincing evidence that patients with functional gastrointestinal disorders (FGIDs) exhibit dysfunctions of the gut involving hypersensitivity and abnormal reflexes, so that physiological, normally unperceived, stimuli induce symptoms. The type of symptoms depends on the specific sensory–reflex pathways and region(s) affected. Fat modulates the responses of the gut to various stimuli, and some of these modulatory mechanisms are abnormal in patients with FGIDs. Indeed, laboratory-based studies have shown that the symptoms experienced by these patients can be induced, or exacerbated, by administration of lipids in amounts that are well tolerated by healthy controls, and, thus, demonstrate a hypersensitivity to lipid. Very few studies have evaluated dietary patterns and eating behavior in these patients, with often-conflicting outcomes, and no studies have been performed to evaluate the role of targeted dietary interventions for the relief of symptoms. Given the evidence from laboratory studies, as well as patient experience, such studies, in large cohorts of patients, are needed with the view to develop personalized, cost-effective treatment approaches.

Am J Gastroenterol 2013; 108:737–747; doi:10.1038/ajg.2013.76; published online 9 April 2013

INTRODUCTION

There is a substantial amount of anecdotal information in the public domain, and in internet and other media, discussing the effects of fatty foods on digestive symptoms, as well as dietary “advice” supposed to aid in the prevention, or improvement, of gastrointestinal (GI) disorders. However, there is currently only limited scientific evidence in the scientific literature to support this common belief. This lack of reliable, evidence-based data is a real problem, as the most requested information by patients relates to “foods to avoid” and the most desired source of information is “my own doctor” (68%), followed by the internet (62%) (1).

The aim of this work is to review the existing scientific information in relation to dietary lipid, food intake and symptoms in patients with functional gastrointestinal disorders (FGIDs). While only functional dyspepsia (FD) and irritable bowel syndrome (IBS) are “true” FGIDs, we will also include a discussion of gastroesophageal reflux disease (GERD) and gastroparesis, as patients with GERD frequently experience hypersensitivity to lipid, and gastroparesis is a severe motor disorder that can be exacerbated by lipid. Specifically the following aspects will be addressed: (i) behavior and effects of dietary lipid in the GI lumen, (ii) role and putative mechanisms of dietary lipid in the induction of symptoms in FD and IBS, as well as GERD and gastroparesis, (iii) potential mediators involved in the symptomatic responses to lipids, and (iv) effects of experimental induction of symptoms in laboratory challenge tests.

METHODS

A comprehensive literature search (using the full PubMed database until 10 December 2012) was performed using terms including “functional gastrointestinal disorders,” “gastroesophageal reflux disease,” “functional dyspepsia,” “postprandial distress syndrome,” “irritable bowel syndrome” OR “gastroparesis,” AND “fat,” “lipids,” “diet,” “dietary factors,” “energy intake,” “food intake,” “eating patterns” OR “nutrients.” Only full-text, English articles were included. In addition, the reference lists of papers identified in the above search were screened for further relevant publications.

BEHAVIOR OF DIETARY LIPIDS IN THE GI LUMEN

Lipids are a group of chemical compounds that include triglycerides, the most abundant lipids in the body, mono- and diglycerides, and their constituent fatty acids, as well as cholesterol, phospholipids, and sterols. Average intake of dietary fat in the United States amounts to 120–150 g/day. Dietary fat is ingested in a number of different forms, depending on the type of food eaten (e.g., intracellular vs. extracellular fat) and meal temperature (solid fat vs. oil), and in varying proportions with other macronutrients. Thus, the fat content of certain foods may not be appreciated, also because a high-fat content is frequently associated with a high-carbohydrate (e.g., in rich, sweet foods), or high-protein (e.g., in fatty meats or cheeses), content. Hence, the physiological and symptomatic effects of fat may vary.

¹Centre of Research Excellence in Translating Nutritional Science to Good Health, University of Adelaide Discipline of Medicine, Adelaide, South Australia;

²Digestive System Research Unit, Digestive Department, University Hospital Vall d’Hebron, Barcelona, Spain; ³Centro de Investigaciones Biomédicas en Red de Enfermedades Hepáticas y Digestivas (Ciberehd), Barcelona, Spain; ⁴Departament de Medicina, Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Barcelona, Spain. **Correspondence:** Fernando Azpiroz, MD, PhD, Digestive System Research Unit, Digestive Department, University Hospital Vall d’Hebron, Barcelona 08035, Spain. E-mail azpiroz.fernando@gmail.com

Received 17 December 2012; accepted 26 February 2013

The initial step of lipid digestion is the formation of emulsions of finely dispersed lipids, which takes place before entering the small bowel. The physiological mechanisms that control this process are not known, but the size of the fat droplets and the stability of the emulsion are important factors that determine the effects of fat on GI function (2–5), and hence, may also have a role in triggering digestive symptoms. For example, in studies using purposely designed meals, acid-stable emulsions result in an initially rapid phase of gastric emptying that increases the exposure of the small intestine to fat and its digestion products, associated with increased plasma cholecystokinin (CCK) secretion and fullness, and reduced hunger, compared with acid-unstable emulsions, in which the oil forms a layer above the aqueous components and, therefore, empties into the small intestine much more slowly.

Lipolysis of triglycerides commences in the stomach (about 30% by gastric lipase) and is completed in the duodenum by pancreatic lipase, releasing fatty acids and monoglycerides. Of note, normal lipolysis can be accomplished in the presence of only 5% of maximal pancreatic secretion. Fat digestion is controlled primarily by the ability of lipase to bind to the surface of emulsion droplets, which increases exponentially as droplet size decreases. Using experimental lipid emulsions with a range of droplet sizes, it has been shown that fat droplet size also affects gut function and symptoms (6), so that the effects of fat increase as fat droplet size decreases. Once digested, the lipid components (fatty acids and monoglycerides) need to form water-soluble micelles with conjugated bile acids to be absorbed. Following transport across the enterocyte membrane, triglycerides are reassembled, incorporated into chylomicrons and then transported in the lymphatic system. In contrast to long-chain triglycerides (consisting of fatty acids with a chain length of >12 carbon atoms), medium-chain triglycerides (8–12 carbon atoms) do not require luminal lipolysis and micelle formation, but can be absorbed intact directly into the bloodstream (Figure 1). Fat is digested and completely absorbed in the small bowel; thus, normally no dietary fat enters the colon. Short-chain fatty acids (<8 carbon atoms) are generated by colonic bacteria in the process of fermentation of unabsorbed carbohydrates. These are an important source of energy for colonocytes, as well as for the colonic microbiota, and also have other important physiological functions (7).

The use of lipase inhibitors in physiological studies has revealed that the digestion of fat, and consequently the release of fatty acids in the small intestinal lumen, is essential for the effects of fat on gastric emptying, antropyloroduodenal motility, GI hormone secretion (including CCK, peptide YY (PYY), glucagon-like peptide-1 (GLP-1), and ghrelin), gut perceptions, and energy intake (8–17). The effects of nutrients on gut motility and energy intake also depend on the region and length of gut exposed to nutrients (18), and the load of nutrients administered is also likely to influence the degree of exposure of the small intestinal lumen (19). Once fatty acids have been released in the process of digestion, their presence in the small intestine is associated with a number of changes in GI function, including lower esophageal sphincter relaxation, gastric motor inhibition, gastric secretion, biliopancreatic stimulation, small bowel motor inhibition, and ileo-colonic

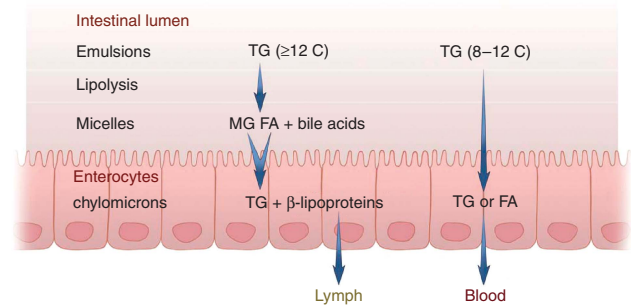


Figure 1. Schematic summary of digestion and absorption of dietary fats in the gastrointestinal lumen. C, carbon atoms; FA, fatty acid; MG, monoglyceride; TG, triglycerides.

motor stimulation (20) (Table 1). These effects depend on the acyl chain length; fatty acids with a chain length of ≥12 carbon atoms slow gastric emptying (21), stimulate GI hormone release (22–24), and reduce energy intake (14,18,22) much more than fatty acids with ≤10 carbon atoms. Intestinal lipids increase intestinal sensitivity and perception of gut stimuli, an effect mediated, at least in part, by sensitization of gut mechanoreceptors (25–28). Small intestinal fat also modulates the quality of perception of upper gut sensations. For example, early studies showed that the pressure sensation elicited by gastric distension was experienced as a more “meal-like” sensation of fullness during simultaneous small intestinal administration of lipid (27). That this experience is regulated through activation of small intestinal receptors is supported by the finding that small intestinal administration of the local anesthetic, benzocaine, reduced the intensity of perception (29) and the fact that increasing the load of duodenal lipid increased the intensity of perception, independently of changes in gastric relaxation (30). Although the majority of these laboratory-based studies are relatively small, their findings have been remarkably consistent.

There is evidence that changes in habitual fat intake modulate GI function in healthy humans, such that the sensitivity to the effects of fat on GI function and energy intake may be reduced by a high-fat diet (31–34). For example, the slowing of gastric emptying by fat (32) and the stimulatory effects of intraduodenal lipid on pyloric pressures (31) have been reported to be attenuated, while both baseline plasma CCK concentrations (34), and the plasma CCK response to a standardized breakfast (33), are increased, following consumption of a high-fat diet. On the other hand, even a short-term reduction in energy intake can substantially enhance the sensitivity to duodenal lipid, resulting in enhanced stimulation of pyloric pressures, reduction in hunger and energy intake (35).

All these mechanisms may have a role for the symptomatic response to fat in FGIDs.

ROLE AND PUTATIVE MECHANISMS OF FAT IN SYMPTOM INDUCTION IN FGIDS

The pathophysiology of FGIDs is not clear, but extensive research in this field has provided convincing evidence that FGID patients exhibit sensory and reflex dysfunctions of the gut involving

Table 1. Summary of effects of luminal lipids on upper GI motility and sensitivity in healthy subjects and in patients with functional GI disorders

	Health	FGIDs	
	Effects of lipids	Basal function	Effect of lipids
<i>Motility</i>			
TLESRs/GER	↑	↑	↑↑
Gastric accommodation	↑	↓	±
Gastric emptying	↓	±	↓↓
Small bowel gas transit	↓	↓	↓↓
Colonic motility/transit (gastrocolonic reflex)	↑	↑	↑↑
<i>Sensitivity</i>			
Gut distension (gastric, small bowel, colon)	↑	↑	↑↑
Luminal lipids	↔	–	↑

FGIDs, functional gastrointestinal disorders; GER, gastroesophageal reflux; GI, gastrointestinal; TLESRs, transient lower esophageal sphincter relaxations.

hypersensitivity and abnormal reflexes, so that physiological, normally unperceived, stimuli induce symptoms (36,37). The type of symptoms depends on the specific sensory–reflex pathways and region(s) affected. This working hypothesis that proposes a common pathophysiology for various FGIDs may help to explain the heterogeneity and the frequent overlap of syndromes. Fat modulates the responses of the gut to various stimuli; interestingly, some of these modulatory mechanisms are abnormal in patients with FGIDs (Figure 2) and may explain the relationship between fat ingestion with functional GI symptoms.

A number of studies have demonstrated that FGID patients are much more sensitive to small intestinal lipid exposure (28,38–40), which induces symptoms of fullness, bloating, and nausea at lower nutrient loads than in healthy controls and also enhances gut sensitivity to mechanical distension. These effects seem to be specific for fat, as isocaloric administration of other nutrients does not result in comparable symptomatic responses (39,41–45). Furthermore, several studies have shown that lipid-dependent modulatory mechanisms are exacerbated in FGIDs (Figure 3). Hence, patients with FGIDs have increased sensitivity to lipids and also abnormal lipid-dependent modulation of the responses to other gut stimuli, and this dual mechanism may explain the relation between lipids and FGI symptoms. Furthermore, it is conceivable that not only the luminal responses to dietary lipids, but also the adaptive mechanisms to foods or diets with varying fat content could be abnormal in FGIDs leading to symptoms.

The limited currently available data, which will be reviewed below, point toward an important role of dietary fat, as well as

energy content of meals, in the induction of postprandial symptoms in FGID patients, but no studies have evaluated the symptomatic response to every-day meals. Moreover, prospective, long-term dietary intervention studies in large patient cohorts are needed to evaluate the hypothesis that specific reductions in the fat content of meals alleviate FGI symptoms. Such large studies will then also allow analysis of specific patterns of responses in subgroups of patients.

Gastroesophageal reflux disease

Transient lower esophageal sphincter relaxation (TLESR) is the most important mechanism underlying gastroesophageal reflux (46). Both oral and duodenal nutrients, particularly lipid, have been demonstrated to relax the lower esophageal sphincter, specifically, to increase TLESRs, acid reflux into the esophagus and symptoms, including heartburn, fullness, and nausea, in GERD patients when compared with healthy controls (40,44,47–51). Both medium- and long-chain triglycerides have these effects (49), while carbohydrate and protein infusions appear ineffective (44), implicating a specific role for lipid. Furthermore the slowing of gastric emptying produced by lipids, as a result of fundic relaxation, further contributes to reflux (51).

Increased body weight, a major risk factor for the development of GERD (52), adversely affects the occurrence of GERD not only by increasing abdominal pressure (53), but also by increasing TLESRs (54). As obese individuals often have increased habitual energy and fat intakes (55) and duodenal lipid increases the number of TLESRs in patients with GERD, associated with an increased number of reflux episodes (48), it is commonly believed that dietary factors, including high-fat, energy-dense foods and large food portions, may induce reflux, thus, lifestyle changes, including dietary modifications, may be important in the management of GERD, not only in obese, but also normal-weight subjects (56). However, evidence is still inconclusive. For example, while an early study of 1,004 patients (of whom 36% reported heartburn at least monthly) found that fried foods, spicy foods, and alcohol induced heartburn (57), information was collected using a questionnaire and dietary intakes were not quantified. Fat and chocolate have been found to increase esophageal acid exposure and lower esophageal sphincter relaxation (58,59), and recent studies, using more detailed dietary analyses found positive associations between dietary fat intake and GERD symptoms (60,61), however, the subjects in one of the studies (60) were also overweight. In contrast, other studies were unable to demonstrate relationships between dietary fat and GERD symptoms using data from the National Health and Nutrition Examination Survey (NHANES) study (62), and a large community-based study of 211 individuals evaluating risk factors for GERD concluded that only body mass index, but not diet, affects symptoms (63).

Functional dyspepsia

A wide range of foods have been linked to dyspepsia anecdotally, and studies indicate that “food intolerances” are more frequent in patients with FD when compared with healthy controls (64–69). Specific foods implicated in dyspeptic symptom induction include fried and fatty foods, among others (64,66,67). In one

study, the highest incidence of intolerance was reported for mayonnaise (80% of patients), as well as other foods with high-fat contents (68).

Studies involving the infusion of nutrient solutions into the stomach or duodenum suggest that about 60–70% of patients with FD are hypersensitive to nutrients (28,42,70). Intraduodenal infusion of a long-chain triglyceride emulsion (Intralipid®) induces markedly greater symptoms, including fullness, nausea, and bloating, in patients with FD than healthy subjects, and also exacerbates symptoms induced by gastric distension in these patients (42). This hypersensitivity appears to be fat-specific, as intraduodenal glucose does not increase symptoms (41). A small, laboratory-based study in both six healthy subjects and six patients with FD also showed that, while gastric relaxation in response to duodenal lipid infusion is compromised in FD, increasing the caloric rate of lipid administration increases the severity of symptoms, without further changes in gastric relaxation (28), suggesting that input from the small intestine has an important, and direct, role in the induction of symptoms, rather than indirectly via changes in gastric motor function.

It appears that these effects may indeed lead to some modifications in dietary behavior in FD patients. For example, while Carvalho *et al.* (64) reported no difference in total caloric intake between 41 FD patients and 30 healthy controls, they found differences in macronutrient intakes, with a reduction in fat intake (both in absolute amounts (g) and proportions (%)) and an increase in % carbohydrate intake. Total energy intake also did not differ between 99 patients and 119 controls in another study (71), however, fat intake (particularly of saturated and monounsaturated fat) was reported to be higher, and carbohydrate intake to be less, in patients compared with controls, contrasting the findings by Carvalho *et al.* (64), although both FD ($n=27$), IBS ($n=46$), as well as mixed FD/IBS ($n=26$) patients were included in this study. Earlier work (69) showed that FD patients had lower intakes of energy, fat and carbohydrate, moreover, modification of diet appeared to be gender-specific; females with FD had significantly lower

intakes of fat and carbohydrate than controls, while such differences were not observed between male patients and controls. The latter findings are supported by a relatively recent study (72), in which 20 FD patients and 21 healthy subjects completed detailed 7-day food diaries, recording times and quantities of all foods and beverages that they consumed, as well as the occurrence, timing, and severity of dyspeptic symptoms. The study found a trend for reductions in both fat and energy intakes and established that fullness was related directly to both the amount of fat ingested and overall energy intake (and inversely to the amount of carbohydrate ingested), while bloating was related directly to the amount of fat

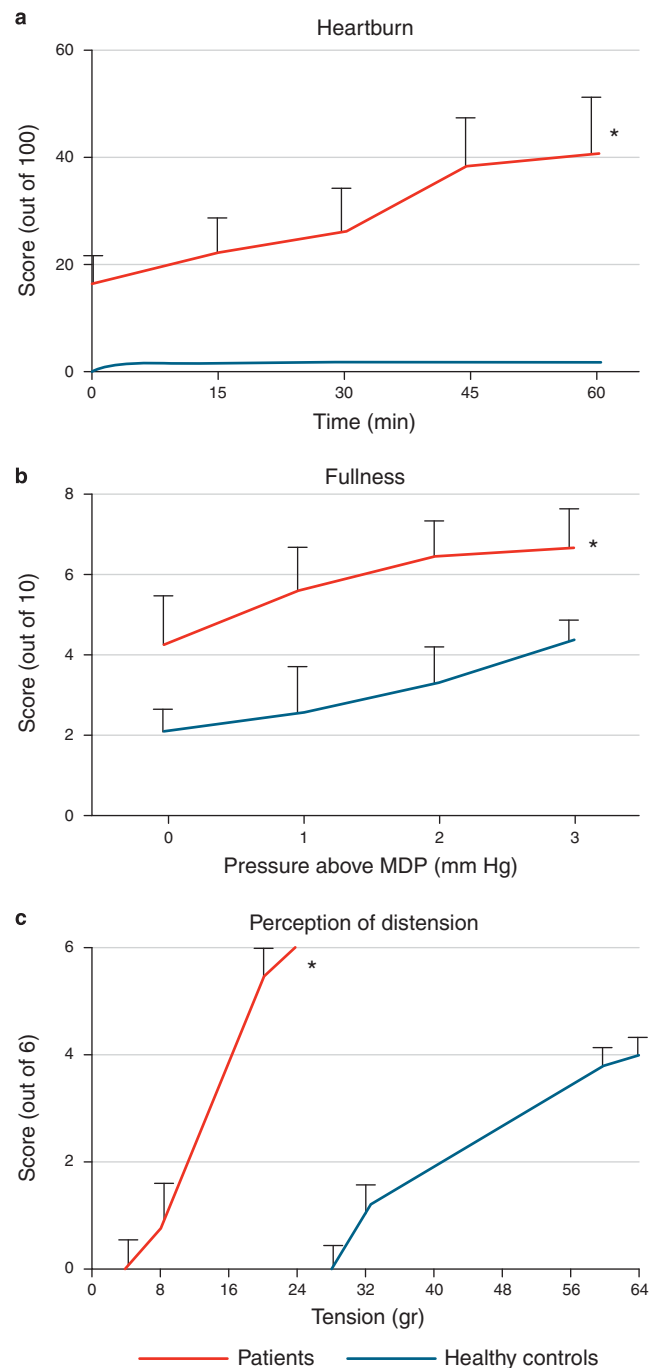


Figure 2. Symptomatic responses to small intestinal lipid administration in (a) gastroesophageal reflux disease (GERD), (b) functional dyspepsia (FD), and (c) irritable bowel syndrome (IBS). (a) Intraduodenal lipid (at 2 kcal/min for 60 min) significantly increased scores for heartburn, as well as other symptoms (not shown), in GERD patients ($n=10$; open symbols), but not healthy controls ($n=10$, closed symbols). *Significantly different from healthy controls ($P < 0.05$). Reproduced from van Boxtel and colleagues (40) with permission from the publisher. (b) Intraduodenal lipid (at 2 kcal/min for 30 min) was associated with significantly greater scores for fullness, as well as other symptoms (not shown), during gastric distension (stepwise increases in pressure at 1 mm Hg/min) with a flaccid bag in FD patients ($n=6$, closed squares) when compared with healthy controls ($n=6$, open symbols). *Significantly different from healthy controls ($P < 0.05$). Adapted from Feinle *et al.* (28). (c) Intraduodenal lipid (at 0.5 kcal/min for 10 min) significantly increased perception of rectal distension, applied by a tensostat, in IBS patients (8 with IBS-C and 8 with IBS-D, $n=16$, closed triangles) when compared with healthy controls ($n=6$, closed squares). *Significantly different from healthy controls ($P < 0.05$). MDP, minimal distending pressure. Reproduced in adapted form from Caldarella *et al.* (38) with permission from the publisher.

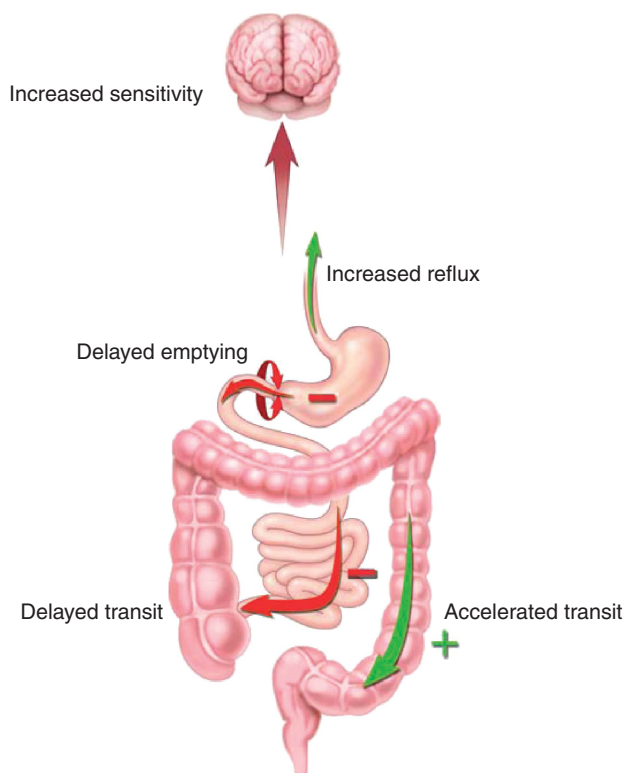


Figure 3. Lipids normally trigger a range of physiological effects on gut motility and sensitivity. Patients with functional gastrointestinal disorders exhibit a series of basal gut dysfunctions, somewhat similar to the effects of lipids in healthy subjects, and these dysfunctions are further exacerbated by fat due to hypersensitivity and hyperreactivity to luminal lipids, which may explain the development of symptoms.

ingested in FD patients (72). Thus, it appears that FD patients may indeed reduce their fat intake, either as a result of an overall reduction in energy intake or specifically by avoiding offending high-fat foods, and that the therapeutic role of dietary modification of fat intake to control symptoms clearly warrants detailed evaluation.

Irritable bowel syndrome

In analogy to FD, patients with IBS and related disorders have increased sensitivity of the bowel to various stimuli. Normally, intraluminal lipids increase perception of concurrent intestinal stimuli and modulate intestinal motor reflexes, and these effects are exaggerated in IBS patients (39,45). It has been shown that patients with FGIDs whose predominant complaint is abdominal bloating exhibit slow transit of intestinal gas, due to an inhibition of small bowel motor activity. Duodenal lipids inhibit small bowel motility and delay intestinal gas transit, and this effect is upregulated in patients with bloating (43,73–75). Hence, lipid loads that are ineffective in healthy subjects worsen the slow transit of gas, inducing gas retention and bloating.

Meal ingestion normally induces a reflex stimulation of colonic motor activity (increase in tone, phasic contractions, and aboral movement of contents), known as the gastrocolonic reflex. This reflex also involves the ileum, and a study of 122 IBS-D patients

and 41 healthy volunteers showed it to be upregulated in the IBS patients (20). The reflex has two phases triggered initially by gastric filling and subsequently by the entry of nutrients into the duodenum. Among nutrients, lipids exhibit the most potent effect. Thus, in contrast to the inhibitory effect on the small bowel, duodenal lipids stimulate colonic motor activity. The colonic response to lipids is enhanced in IBS patients (76). Furthermore, lipids exacerbate rectal hypersensitivity in IBS patients (38,39,45). For example, a duodenal lipid load that exerted no effects on rectal sensation in healthy subjects increased the sensitivity of the rectum and increased perception of rectal distension in IBS patients (38). The magnitude of the effect was similar in IBS subtypes, but the symptom expression was specific: while constipation-predominant IBS patients predominantly experienced rectal distension as pain, the predominant symptom in diarrhea-predominant IBS was rectal urgency (38). Hence, differences in central processing may explain the specific effects of fat on different categories of symptoms. Furthermore, ileal and colonic overstimulation by lipids in patients may explain postprandial diarrhea.

Some studies show that a substantial proportion of patients with IBS associate symptoms with fatty foods (77–80), but no consistent dietary differences in fat intake have been observed between patients and controls. Simren and colleagues (77) showed in a study of 330 IBS patients and 80 healthy controls that a large proportion of IBS patients (63%) consider their symptoms related to meals, and fatty foods were some of the most frequently reported. Likewise, a population-based study in Sweden, including 347 IBS patients and 2,509 healthy controls, found that patients with IBS (constipation, diarrhea, and mixture), but not healthy subjects, relate foods rich in fat to symptom development (79). This association was more prominent in women (23.5% vs. 9.1% in healthy controls) than in men (14.6% vs. 3.9% in healthy controls) and led patients to change their diet, which was associated with perceived symptomatic improvement (79). In a survey of 1,242 IBS patients, one of the most frequent changes in lifestyle considered for symptom improvement was avoiding fatty foods (81).

Despite these subjective reports, available data on differences in dietary fat intake between patients and controls are inconsistent. A series of studies failed to detect differences in the profile of fat intake between IBS patients and controls (82–84). Some reports described an increased intake of fat and saturated fatty acids in IBS patients (71,85). On the other hand, using a validated food frequency questionnaire, a recent study in 104 IBS patients found that despite a higher total energy intake than the UK Dietary Reference Values, % energy from fat was significantly lower (29.8% vs. 33% reference value) (86), which may be interpreted as compensatory correction to prevent symptoms. In contrast, a very small study of 13 patients with diarrhea-predominant IBS reported adequate symptom relief with a very low carbohydrate (4%), but a high fat (51%), content when compared with a normal diet with lower fat content (30%) (87), suggesting that the effect of diet possibly depends on the overall composition, rather than on a single component. Increased plasma levels of omega-3 polyunsaturated fatty acids and their metabolites have been found in women with IBS compared with matched healthy controls; as the fatty acid

composition of the body is largely determined by dietary intake, this could imply differences in diet in these groups (88).

A recent pilot study showed that among 49 diarrhea-predominant IBS patients who recognized a triggering food as the cause of postprandial symptoms, pancreolipase administration before meals relieved postprandial symptoms, particularly urgency, stool consistency, cramping, pain and bloating, in 30 (61%) patients (80). Pancreolipase has been shown to reduce the symptomatic response of 18 healthy subjects to a high-fat meal (89) and IBS symptoms in patients with pancreatic insufficiency (90,91). Incomplete digestion/absorption of lipids in the small bowel would result in diarrhea due to the local effect of lipids on active colonic ion secretion. However, diarrhea *per se* may produce some flushing of lipids into the colon. Pancreolipase also reduced bile acid malabsorption in patients with cystic fibrosis (92,93) or alcoholic pancreatitis (94). Interestingly, a recent study in three groups of 26 diarrhea-predominant IBS patients, 26 constipation-predominant IBS patients or 26 healthy controls showed that on high-fat diet patients with diarrhea-predominant IBS synthesize and excrete higher levels of bile acids than constipation-predominant IBS patients and healthy controls, leading to bile acid malabsorption (95). This is a potential cause of diarrhea, due to the cathartic effects of bile acids in the colon (by stimulating active Cl secretion), however, these preliminary observations need further investigation.

Not all reports in relation to dietary fat and FGI symptoms describe adverse effects. Polyunsaturated fatty acids (with linoleic acid as the major representative in the human diet) and their metabolites can influence gene expression and have beneficial effects on intestinal inflammation (96). It is conceivable that, in the long-term, this effect could alleviate diarrhea-predominant IBS symptoms, because these symptoms have been related to mucosal inflammatory changes (97,98).

Various oils are popular remedies for constipation, but in the absence of pancreatic insufficiency, ingested oil is absorbed in the small bowel. Lipase inhibitors produce some degree of steatorrhea, which may help constipation (99). Nonabsorbable paraffin oil, a noncaloric oil substitute, may improve functional outlet obstruction due to fecal lubrication, but this remains to be proven (100).

DIETARY LIPIDS AND GASTROPARESIS

As described above, the effects of lipids on symptoms in patients with true functional gut disorders (FD and IBS), and to an extent also in GERD, are related to a specific susceptibility to fat with abnormal responses to intraluminal lipids. A different case is gastroparesis, a motor disorder with an organic substrate affecting the stomach (101–103). Gastroparesis is characterized by a severe delay of gastric emptying, due to gastric hypomotility. Patients exhibit both reduced tonic contraction of the corpus-fundus and reduced antral contractions (104,105). Fat exacerbates gastric hypomotility, and this explains its deleterious effect on gastroparesis. Indeed, fat produces an overall inhibitory effect on the stomach, including tonic relaxation of the corpus-fundus (26), suppression of antral and duodenal contractions, and stimulation of isolated pyloric pressure waves and basal pyloric pressure (106).

These physiological effects result in slowing of gastric emptying (106); fundic relaxation and pyloric closure oppose liquid emptying, while reduced antral peristalsis impairs solid grinding, and hence, pyloric passage of particulate solids (107). Diet therapy recommendations empirically involve reduction of fat intake, but systematic, prospective studies are lacking (108–110).

POTENTIAL MEDIATORS OF LIPID-INDUCED FGI SYMPTOMS

As lipid potently releases gut hormones, including CCK from the proximal, and GLP-1 and PYY from the distal, small intestine, and suppresses ghrelin secretion from the stomach (111), it is possible that these hormones have a role in the effects of fat on FGI symptoms. Indeed, studies have shown that CCK mediates, at least in part, the effects of fat on gastric emptying and biliopancreatic secretion, gut motility, gut perception, and energy intake (9,14,51,112–114).

A role for CCK, mediated by activation of CCK₁ receptors, in inducing lower esophageal sphincter relaxation, reflux episodes with increased times of esophageal, pH < 4, is well established (47,49,51). In addition, the study by van Boxel and colleagues (40) demonstrated increased release of apo-AIV and CCK in GERD patients compared with healthy subjects, which may, thus, mediate these effects.

The associations between fat ingestion (or duodenal lipid infusion) and symptoms (42,70) have implicated CCK also in the pathophysiology of FD. For example, a small study of eight FD patients and eight healthy volunteers found that in response to a high-fat test meal plasma CCK concentrations are higher in FD patients. In addition, FD patients appear to have an exaggerated symptomatic response to exogenous CCK administration (115). Administration of the CCK₁ receptor antagonist, dexloxiglumide, in 12 patients with “dysmotility-like” FD, alleviated fullness, bloating, and nausea during gastric distension and duodenal lipid infusion when compared with placebo (28). Interestingly, dexloxiglumide improved dyspeptic symptoms despite reducing gastric relaxation.

CCK potently enhances colonic motility and has been implicated in the gastrocolonic reflex (114), and this may mediate the effects of lipids on postprandial cramping, pain, urgency, and diarrhea. Using an experimental model of intestinal gas infusion in humans, it was shown that in the presence of intestinal lipids patients with FD and IBS have delayed transit and increased perception of intraluminal gas; dexloxiglumide further reduced transit, but despite the larger volume of gas retention, significantly reduced perception, and particularly bloating sensation (116). Hence, these data suggest that CCK antagonism increases intestinal capacitance and reverts lipid-induced hypersensitivity. Chronic studies are required to evaluate the role of CCK₁ receptor antagonists in the treatment of FGIDs.

A number of other gut peptides are involved in the regulation of gut motor function, appetite and food intake, including GLP-1, PYY, and ghrelin (111), and may potentially also have a role in FGIDs. While both GLP-1 and PYY reduce appetite, ghrelin increases it. PYY can induce GI symptoms when given to healthy

subjects in supraphysiological doses (117), although basal and postprandial PYY release seems to be reduced in FD patients (118), while the ghrelin response varies (118,119), thus, their contribution to symptoms is not clear. One study found that IBS patients ($n = 18$) appear to exhibit abnormal responses to a fatty meal, with blunted motilin and exaggerated CCK secretion (120).

The interaction of fatty acids with specific fatty acid-sensing receptors located on enteroendocrine cells triggers the production of a number of mediators, including oleoylethanolamine and apo-AIV, with subsequent release of CCK, which transmits information about the presence of fat in the small intestine to the central nervous system by activating CCK₁ receptors located on vagal afferent neurons, associated with the induction of c-fos-like immunoreactivity in the nucleus tractus solitarius, and subsequent induction of reflex pathways to induce slowing of gastric emptying and food intake inhibition (reviewed in detail in Little and Feinle-Bisset (111,121)). From the nucleus tractus solitarius, the information is also transmitted to higher brain centers; e.g., the fatty acid, lauric acid, has been shown in a functional magnetic resonance imaging study of 19 healthy subjects to increase activity in the brainstem and hypothalamus, an effect abolished by dexloxiglumide (122). Thus, CCK secretion, mediated by apo-AIV, and the subsequent activation of CCK₁ receptors on vagal afferents may be critical for the gut-to-brain signaling response to ingested fat.

At the level of the central nervous system, it has been shown that central processing of peripheral (esophageal, gastric, and rectal) stimuli is altered in FGIDs (123–125). Although conceivable, it is not known whether lipid further exacerbates these dysfunctions.

It is currently unknown at which level(s) the abnormal responses to lipids originate in FGIDs, including whether the function of fatty acid receptors in the intestinal wall, or the sensitivity of the gut-brain axis is altered, e.g., through changes in the sensitivity of receptors located on vagal afferents, including CCK receptors and those of other hormones, or whether the changes occur centrally. Much research is still required to identify the location(s) of lipid-related dysfunctions.

CHALLENGE TESTS

While, as discussed above, a number of studies have evaluated foods and food components that FGID patients associate with the induction, or exacerbation, of their postprandial symptoms, a critical step to establish definitive links involves the ability to induce these symptoms reliably in provocation studies. Patients recognize that the triggering effect of fatty foods on symptoms is quite inconsistent, and this variability reduces the sensitivity of challenge tests. Research in this area is clearly lacking.

As described earlier, studies have demonstrated that duodenal lipids exacerbate symptoms in patients with GERD (40,50), in addition to the effects on gastroesophageal function and acid reflux (48). Moreover, intraduodenal lipid infusion hastens the onset, and increases the severity, of heartburn in response to esophageal acid infusion (50). However, while, as discussed earlier, a number of studies have implicated high-fat foods in the induction of GERD symptoms (57,60,61), a study in the laboratory was unable to

induce symptoms in response to a high-fat vs. a low-fat test meal (126), although this study only included healthy subjects. Thus, the advice in clinical practice to patients to avoid such foods (127) is currently not unequivocally justified.

A number of groups have used so-called “drink tests” (128–133), which were developed primarily to study the pathophysiology underlying FD, rather than the direct association of drink ingestion with symptoms, and involve ingestion of either water, low-nutrient soup or a mixed-nutrient liquid at standardized rates (15–100 ml/min) to maximum tolerance. The rationale behind these tests is that if impaired accommodation and/or hypersensitivity were associated with early satiety in FD patients, the drinking test might provide a non-invasive means for the detection of these dysfunctions (132). These tests use only liquids, thus are not representative of most of the foods that patients ingest in every-day life, which are solid or semi-solid, have a higher fat content and energy density, and are much more palatable.

A small number of studies have evaluated the direct relationship between ingestion of a meal and the time course of symptom induction. A large study of 218 FD patients showed that FD symptoms increased within 15 min of ingestion of a small, mixed solid-liquid test meal, consisting of white bread, egg, and water, and reached a moderate-to-severe intensity in 94% of patients (134). Interestingly, the meal only contained 250 kcal and 10 g fat, indicating that even a small meal with a low-fat content can provoke symptoms in FD patients. It is important to note, however, that the patients were recruited in a tertiary referral center and had a high prevalence of weight loss > 5% (51% of patients), thus, the symptomatic response to such a meal may be much less pronounced in patients that suffer from milder symptoms. A few studies evaluated specifically the role of the fat content of a meal on symptom induction. In early studies, attempts to provoke symptoms by offering the putative offending food(s), particularly fatty foods, in the laboratory setting were made with disappointing outcomes (67,135). Although 75–100% (67,135) of patients reported that fried or fatty foods caused symptoms in their daily lives, these symptoms could not be reproduced during studies. However, these studies were not well controlled, and patients also included those with reflux and hiatus hernia. In 31 FD patients, addition of 30 g margarine to a soup resulted in greater symptoms (including epigastric pain, bloating, fullness, and nausea), when compared with a soup without fat (70), although the margarine-containing soup was most likely less palatable than the control soup. Ingestion of 300 g of a palatable yoghurt containing 24 g fat (330 kcal) increased bloating, fullness, and nausea in 15 patients with FD (none of whom were lactose-intolerant), when compared with a control yoghurt containing 1 g fat (143 kcal) by 30–40% (136). It is important to note that in both studies (70,136) the effect of fat cannot be dissociated from the potential effect of increased energy content. However, a small, recent study of eight FD patients and eight healthy controls, using equicaloric (500 kcal, 400 g) yoghurt-based meals either high in fat (56%) or carbohydrate (74%), or a low-calorie (180 kcal) control meal of the same volume, showed that symptoms occurred in response to all meals, but nausea, pain, and fullness were significantly greater after the high-fat meal (118).

In contrast to FD, very few data are available in IBS. In a small number of studies involving $n = 6-30$ patients whose predominant complaint was abdominal bloating, by-and-large IBS and functional bloating, jejunal gas infusion combined with simultaneous duodenal lipid infusion, used as a challenge test, induced gas retention and reproduced their customary symptoms in a large proportion of patients as compared with healthy controls (43,73,74). Other studies have used the trigger foods previously identified by the patients themselves (fried food in 59% of a group of IBS-D) as a challenge meal to test potential treatments (80).

CONCLUSIONS

Dietary fat modulates a large range of physiological functions related to the control of gut motility and sensitivity, and these effects may, under certain circumstances, induce GI symptoms, even in healthy subjects. Symptoms in patients with FGIDs appear to be related to specific sensory-reflex dysfunctions, which are exacerbated by fat, because these patients are hypersensitive and hyperreactive to intraluminal lipids. Despite a body of evidence from mainly laboratory-based studies, the evidence relating dietary fat intake to FGIDs is limited. This applies both to epidemiological data on dietary habits, as well as to the potential for fat to trigger symptoms by controlled challenge tests. Hence, to reconcile this apparent discrepancy between theory (physiological effects of lipid) and facts (epidemiological and experimental evidence), more research is clearly warranted in this area of food and FGIDs.

CONFLICT OF INTEREST

Guarantor of the article: Fernando Azpiroz, MD, PhD.

Specific author contributions: Christine Feinle-Bisset and Fernando Azpiroz equally contributed to the review and interpretation of the literature, and the writing of the manuscript, and both approved the final draft submitted.

Financial support: Christine Feinle-Bisset is supported by a Senior Research Fellowship (grant no. 627002, 2010–2014) from the National Health and Medical Research Council of Australia. Fernando Azpiroz acknowledges support from the Dirección General de Investigación (SAF 2009-07416) and Centro para el Desarrollo Tecnológico Industrial (CEN-20101016), Spain. Ciberehd is funded by the Instituto de Salud Carlos III.

Potential competing interests: None.

REFERENCES

- Halpert A, Dalton CB, Palsson O *et al*. Patient educational media preferences for information about irritable bowel syndrome (IBS). *Dig Dis Sci* 2008;53:3184–90.
- Marciani L, Faulks R, Wickham MS *et al*. Effect of intragastric acid stability of fat emulsions on gastric emptying, plasma lipid profile and postprandial satiety. *Br J Nutr* 2009;101:919–28.
- Marciani L, Wickham M, Singh G *et al*. Enhancement of intragastric acid stability of a fat emulsion meal delays gastric emptying and increases cholecystokinin release and gallbladder contraction. *Am J Physiol Gastrointest Liver Physiol* 2007;292:G1607–13.
- Meyer JH, Elashoff JD, Lake R. Gastric emptying of indigestible versus digestible oils and solid fats in normal humans. *Dig Dis Sci* 1999;44:1076–82.
- Meyer JH, Hlinka M, Kao D *et al*. Gastric emptying of oil from solid and liquid meals. Effect of human pancreatic insufficiency. *Dig Dis Sci* 1996;41:1691–9.
- Seimon RV, Wooster T, Otto B *et al*. The droplet size of intraduodenal fat emulsions influences antropyloroduodenal motility, hormone release, and appetite in healthy males. *Am J Clin Nutr* 2009;89:1729–36.
- Hamer HM, Jonkers D, Venema K *et al*. Review article: the role of butyrate on colonic function. *Aliment Pharmacol Ther* 2008;27:104–19.
- Borovicka J, Schwizer W, Guttman G *et al*. Role of lipase in the regulation of postprandial gastric acid secretion and emptying of fat in humans: a study with orlistat, a highly specific lipase inhibitor. *Gut* 2000;46:774–81.
- Degen L, Drewe J, Piccoli F *et al*. Effect of CCK-1 receptor blockade on ghrelin and PYY secretion in men. *Am J Physiol Regul Integr Comp Physiol* 2007;292:R1391–9.
- Degen L, Matzinger D, Drewe J *et al*. Role of free fatty acids in regulating gastric emptying and gallbladder contraction. *Digestion* 2006;74:131–9.
- Feinle C, O'Donovan D, Doran S *et al*. Effects of fat digestion on appetite, APD motility, and gut hormones in response to duodenal fat infusion in humans. *Am J Physiol Gastrointest Liver Physiol* 2003;284:G798–807.
- Feinle C, Rades T, Otto B *et al*. Fat digestion modulates gastrointestinal sensations induced by gastric distention and duodenal lipid in humans. *Gastroenterology* 2001;120:1100–7.
- Feinle-Bisset C, Patterson M, Ghatei MA *et al*. Fat digestion is required for suppression of ghrelin and stimulation of peptide YY and pancreatic polypeptide secretion by intraduodenal lipid. *Am J Physiol Endocrinol Metab* 2005;289:E948–53.
- Matzinger D, Degen L, Drewe J *et al*. The role of long chain fatty acids in regulating food intake and cholecystokinin release in humans. *Gut* 2000;46:688–93.
- O'Donovan D, Feinle-Bisset C, Wishart J *et al*. Lipase inhibition attenuates the acute inhibitory effects of oral fat on food intake in healthy subjects. *Br J Nutr* 2003;90:849–52.
- Pilichiewicz A, O'Donovan D, Feinle C *et al*. Effect of lipase inhibition on gastric emptying of, and the glycemic and incretin responses to, an oil/aqueous drink in type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2003;88:3829–34.
- Schwizer W, Asal K, Kreiss C *et al*. Role of lipase in the regulation of upper gastrointestinal function in humans. *Am J Physiol* 1997;273:G612–20.
- Meyer JH, Hlinka M, Tabrizi Y *et al*. Chemical specificities and intestinal distributions of nutrient-driven satiety. *Am J Physiol* 1998;275:R1293–307.
- Pilichiewicz AN, Papadopoulos P, Brennan IM *et al*. Load-dependent effects of duodenal lipid on antropyloroduodenal motility, plasma CCK and PYY, and energy intake in healthy men. *Am J Physiol Regul Integr Comp Physiol* 2007;293:R2170–8.
- Deiteren A, Camilleri M, Burton D *et al*. Effect of meal ingestion on ileocolonic and colonic transit in health and irritable bowel syndrome. *Dig Dis Sci* 2010;55:384–91.
- Hunt JN, Knox MT. A relation between the chain length of fatty acids and the slowing of gastric emptying. *J Physiol* 1968;194:327–36.
- Feltrin KL, Little TJ, Meyer JH *et al*. Effects of intraduodenal fatty acids on appetite, antropyloroduodenal motility, and plasma CCK and GLP-1 in humans vary with their chain length. *Am J Physiol Regul Integr Comp Physiol* 2004;287:R524–33.
- Feltrin KL, Patterson M, Ghatei MA *et al*. Effect of fatty acid chain length on suppression of ghrelin and stimulation of PYY, GLP-2 and PP secretion in healthy men. *Peptides* 2006;27:1638–43.
- McLaughlin J, Grazia Luca M, Jones MN *et al*. Fatty acid chain length determines cholecystokinin secretion and effect on human gastric motility. *Gastroenterology* 1999;116:46–53.
- Accarino AM, Azpiroz F, Malagelada JR. Modification of small bowel mechanosensitivity by intestinal fat. *Gut* 2001;48:690–5.
- Caldarella MP, Azpiroz F, Malagelada JR. Selective effects of nutrients on gut sensitivity and reflexes. *Gut* 2007;56:37–42.
- Feinle C, Grundy D, Read NW. Effects of duodenal nutrients on sensory and motor responses of the human stomach to distension. *Am J Physiol* 1997;273:G721–6.
- Feinle C, Meier O, Otto B *et al*. Role of duodenal lipid and cholecystokinin A receptors in the pathophysiology of functional dyspepsia. *Gut* 2001;48:347–55.
- Feinle C, Grundy D, Fried M. Modulation of gastric distension-induced sensations by small intestinal receptors. *Am J Physiol Gastrointest Liver Physiol* 2001;280:G51–7.

30. Feinle C, Grundy D, Otto B *et al.* Relationship between increasing duodenal lipid doses, gastric perception, and plasma hormone levels in humans. *Am J Physiol Regul Integr Comp Physiol* 2000;278:R1217–23.
31. Boyd KA, O'Donovan DG, Doran S *et al.* High-fat diet effects on gut motility, hormone, and appetite responses to duodenal lipid in healthy men. *Am J Physiol Gastrointest Liver Physiol* 2003;284:G188–96.
32. Cunningham KM, Daly J, Horowitz M *et al.* Gastrointestinal adaptation to diets of differing fat composition in human volunteers. *Gut* 1991;32:483–6.
33. French SJ, Murray B, Rumsey RD *et al.* Adaptation to high-fat diets: effects on eating behaviour and plasma cholecystokinin. *Br J Nutr* 1995;73:179–89.
34. Little TJ, Feltrin KL, Horowitz M *et al.* A high-fat diet raises fasting plasma CCK but does not affect upper gut motility, PYY, and ghrelin, or energy intake during CCK-8 infusion in lean men. *Am J Physiol Regul Integr Comp Physiol* 2008;294:R45–51.
35. Brennan IM, Seimon RV, Luscombe-Marsh ND *et al.* Effects of acute dietary restriction on gut motor, hormone and energy intake responses to duodenal fat in obese men. *Int J Obes (Lond)* 2011;35:448–56.
36. Azpiroz F, Bouin M, Camilleri M *et al.* Mechanisms of hypersensitivity in IBS and functional disorders. *Neurogastroenterol Motil* 2007;19:62–88.
37. Kellow JE, Azpiroz F, Delvaux M *et al.* Applied principles of neurogastroenterology: physiology/motility sensation. *Gastroenterology* 2006;130:1412–20.
38. Caldarella MP, Milano A, Laterza F *et al.* Visceral sensitivity and symptoms in patients with constipation- or diarrhea-predominant irritable bowel syndrome (IBS): effect of a low-fat intraduodenal infusion. *Am J Gastroenterol* 2005;100:383–9.
39. Simren M, Abrahamsson H, Bjornsson ES. Lipid-induced colonic hypersensitivity in the irritable bowel syndrome: the role of bowel habit, sex, and psychologic factors. *Clin Gastroenterol Hepatol* 2007;5:201–8.
40. van Boxel OS, ter Linde JJ, Oors J *et al.* Duodenal lipid-induced symptom generation in gastroesophageal reflux disease: role of apolipoprotein A-IV and cholecystokinin. *Neurogastroenterol Motil* 2012;24:350–e168.
41. Barbera R, Feinle C, Read NW. Nutrient-specific modulation of gastric mechanosensitivity in patients with functional dyspepsia. *Dig Dis Sci* 1995;40:1636–41.
42. Barbera R, Feinle C, Read NW. Abnormal sensitivity to duodenal lipid infusion in patients with functional dyspepsia. *Eur J Gastroenterol Hepatol* 1995;7:1051–7.
43. Serra J, Salvioli B, Azpiroz F *et al.* Lipid-induced intestinal gas retention in irritable bowel syndrome. *Gastroenterology* 2002;123:700–6.
44. Lacy BE, Carter J, Weiss JE *et al.* The effects of intraduodenal nutrient infusion on serum CCK, LES pressure, and gastroesophageal reflux. *Neurogastroenterol Motil* 2011;23:631–e256.
45. Simren M, Agerforz P, Bjornsson ES *et al.* Nutrient-dependent enhancement of rectal sensitivity in irritable bowel syndrome (IBS). *Neurogastroenterol Motil* 2007;19:20–9.
46. El-Serag H. Role of obesity in GORD-related disorders. *Gut* 2008;57:281–4.
47. Clavé P, Gonzalez A, Moreno A *et al.* Endogenous cholecystokinin enhances postprandial gastroesophageal reflux in humans through extrapancreatic receptors. *Gastroenterology* 1998;115:597–604.
48. Holloway RH, Lyrenas E, Ireland A *et al.* Effect of intraduodenal fat on lower esophageal sphincter function and gastro-oesophageal reflux. *Gut* 1997;40:449–53.
49. Ledebner M, Masclee AA, Biemond I *et al.* Effect of medium- and long-chain triglycerides on lower esophageal sphincter pressure: role of CCK. *Am J Physiol* 1998;274:G1160–5.
50. Meyer JH, Lembo A, Elashoff JD *et al.* Duodenal fat intensifies the perception of heartburn. *Gut* 2001;49:624–8.
51. Zerbib F, Bruley Des Varannes S, Scarpignato C *et al.* Endogenous cholecystokinin in postprandial lower esophageal sphincter function and fundic tone in humans. *Am J Physiol* 1998;275:G1266–73.
52. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. *Ann Intern Med* 2005;143:199–211.
53. Pandolfino JE, El-Serag HB, Zhang Q *et al.* Obesity: a challenge to esophagogastric junction integrity. *Gastroenterology* 2006;130:639–49.
54. Wu JC, Mui LM, Cheung CM *et al.* Obesity is associated with increased transient lower esophageal sphincter relaxation. *Gastroenterology* 2007;132:883–9.
55. Stewart JE, Seimon RV, Otto B *et al.* Marked differences in gustatory and gastrointestinal sensitivity to oleic acid between lean and obese men. *Am J Clin Nutr* 2011;93:703–11.
56. Richter JE, Friedenberg FK. Gastroesophageal reflux disease. In: Feldman M, Friedman LS, Brandt LJ (eds). *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management*. Saunders Elsevier: Philadelphia, PA, 2010, pp. 705–26.
57. Nebel OT, Fornes MF, Castell DO. Symptomatic gastroesophageal reflux: incidence and precipitating factors. *Am J Dig Dis* 1976;21:953–6.
58. Becker DJ, Sinclair J, Castell DO *et al.* A comparison of high and low fat meals on postprandial esophageal acid exposure. *Am J Gastroenterol* 1989;84:782–6.
59. Murphy DW, Castell DO. Chocolate and heartburn: evidence of increased esophageal acid exposure after chocolate ingestion. *Am J Gastroenterol* 1988;83:633–6.
60. El-Serag HB, Satia JA, Rabeneck L. Dietary intake and the risk of gastro-oesophageal reflux disease: a cross sectional study in volunteers. *Gut* 2005;54:11–7.
61. Shapiro M, Green C, Bautista JM *et al.* Assessment of dietary nutrients that influence perception of intra-oesophageal acid reflux events in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2007;25:93–101.
62. Ruhl CE, Everhart JE. Overweight, but not high dietary fat intake, increases risk of gastroesophageal reflux disease hospitalization: the NHANES I Epidemiologic Followup Study. *First National Health and Nutrition Examination Survey*. *Ann Epidemiol* 1999;9:424–35.
63. Nandurkar S, Locke GR III, Fett S *et al.* Relationship between body mass index, diet, exercise and gastro-oesophageal reflux symptoms in a community. *Aliment Pharmacol Ther* 2004;20:497–505.
64. Carvalho RV, Lorena SL, Almeida JR *et al.* Food intolerance, diet composition, and eating patterns in functional dyspepsia patients. *Dig Dis Sci* 2010;55:60–5.
65. Cuperus P, Keeling PW, Gibney MJ. Eating patterns in functional dyspepsia: a case control study. *Eur J Clin Nutr* 1996;50:520–3.
66. Filipovic BF, Randjelovic T, Kovacevic N *et al.* Laboratory parameters and nutritional status in patients with functional dyspepsia. *Eur J Intern Med* 2011;22:300–4.
67. Friedlander PH. Food and indigestion. An investigation of possible relationships. *Br Med J* 1959;2:1454–8.
68. Kaess H, Kellermann M, Castro A. Food intolerance in duodenal ulcer patients, non ulcer dyspeptic patients and healthy subjects. A prospective study. *Klin Wochenschr* 1988;66:208–11.
69. Mullan A, Kavanagh P, O'Mahony P *et al.* Food and nutrient intakes and eating patterns in functional and organic dyspepsia. *Eur J Clin Nutr* 1994;48:97–105.
70. Houghton LA, Mangall YF, Dwivedi A *et al.* Sensitivity to nutrients in patients with non-ulcer dyspepsia. *Eur J Gastroenterol Hepatol* 1993;5:109–14.
71. Saito YA, Locke GR III, Weaver AL *et al.* Diet and functional gastrointestinal disorders: a population-based case-control study. *Am J Gastroenterol* 2005;100:2743–8.
72. Pilchiewicz AN, Horowitz M, Holtmann GJ *et al.* Relationship between symptoms and dietary patterns in patients with functional dyspepsia. *Clin Gastroenterol Hepatol* 2009;7:317–22.
73. Passos MC, Serra J, Azpiroz F *et al.* Impaired reflex control of intestinal gas transit in patients with abdominal bloating. *Gut* 2005;54:344–8.
74. Salvioli B, Serra J, Azpiroz F *et al.* Impaired small bowel gas propulsion in patients with bloating during intestinal lipid infusion. *Am J Gastroenterol* 2006;101:1853–7.
75. Serra J. Intestinal gas: has diet anything to do in the absence of a demonstrable malabsorption state? *Curr Opin Clin Nutr Metab Care* 2012;15:489–93.
76. Simren M, Abrahamsson H, Bjornsson ES. An exaggerated sensory component of the gastrocolonic response in patients with irritable bowel syndrome. *Gut* 2001;48:20–7.
77. Simren M, Mansson A, Langkilde AM *et al.* Food-related gastrointestinal symptoms in the irritable bowel syndrome. *Digestion* 2001;63:108–15.
78. Bhat K, Harper A, Gorard DA. Perceived food and drug allergies in functional and organic gastrointestinal disorders. *Aliment Pharmacol Ther* 2002;16:969–73.
79. Faresjo A, Johansson S, Faresjo T *et al.* Sex differences in dietary coping with gastrointestinal symptoms. *Eur J Gastroenterol Hepatol* 2010;22:327–33.
80. Money ME, Walkowiak J, Virgilio C *et al.* Pilot study: a randomised, double blind, placebo controlled trial of pancrealipase for the treatment of postprandial irritable bowel syndrome-diarrhoea. *Frontline Gastroenterol* 2011;2:48–56.

81. Halpert A, Dalton CB, Palsson O *et al.* What patients know about irritable bowel syndrome (IBS) and what they would like to know. National Survey on Patient Educational Needs in IBS and development and validation of the Patient Educational Needs Questionnaire (PEQ). *Am J Gastroenterol* 2007;102:1972–82.
82. Jarrett M, Heitkemper MM, Bond EF *et al.* Comparison of diet composition in women with and without functional bowel disorder. *Gastroenterol Nurs* 1994;16:253–8.
83. Ostgaard H, Hausken T, Gundersen D *et al.* Diet and effects of diet management on quality of life and symptoms in patients with irritable bowel syndrome. *Mol Med Report* 2012;5:1382–90.
84. Sicherer SH, Sampson HA. Food allergy: recent advances in pathophysiology and treatment. *Annu Rev Med* 2009;60:261–77.
85. Prescha A, Pieczynska J, Ilow R *et al.* Assessment of dietary intake of patients with irritable bowel syndrome. *Rocz Panstw Zakl Hig* 2009;60:185–9.
86. Williams EA, Nai X, Corfe BM. Dietary intakes in people with irritable bowel syndrome. *BMC Gastroenterol* 2011;11:9.
87. Austin GL, Dalton CB, Hu Y *et al.* A very low-carbohydrate diet improves symptoms and quality of life in diarrhea-predominant irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2009;7:706–8 e1.
88. Clarke G, Fitzgerald P, Hennessy AA *et al.* Marked elevations in pro-inflammatory polyunsaturated fatty acid metabolites in females with irritable bowel syndrome. *J Lipid Res* 2010;51:1186–92.
89. Suarez F, Levitt MD, Adsheed J *et al.* Pancreatic supplements reduce symptomatic response of healthy subjects to a high fat meal. *Dig Dis Sci* 1999;44:1317–21.
90. Leeds JS, Hopper AD, Sidhu R *et al.* Some patients with irritable bowel syndrome may have exocrine pancreatic insufficiency. *Clin Gastroenterol Hepatol* 2010;8:433–8.
91. Money ME, Hofmann AF, Hagey LR *et al.* Treatment of irritable bowel syndrome-diarrhea with pancrealipase or colesvelam and association with steatorrhea. *Pancreas* 2009;38:232–3.
92. Boyle BJ, Long WB, Balistreri WF *et al.* Effect of cimetidine and pancreatic enzymes on serum and fecal bile acids and fat absorption in cystic fibrosis. *Gastroenterology* 1980;78:950–3.
93. Stern RC, Eisenberg JD, Wagener JS *et al.* A comparison of the efficacy and tolerance of pancrelipase and placebo in the treatment of steatorrhea in cystic fibrosis patients with clinical exocrine pancreatic insufficiency. *Am J Gastroenterol* 2000;95:1932–8.
94. Dutta SK, Anand K, Gadacz TR. Bile salt malabsorption in pancreatic insufficiency secondary to alcoholic pancreatitis. *Gastroenterology* 1986;91:1243–9.
95. Wong BS, Camilleri M, Carlson P *et al.* Increased bile acid biosynthesis is associated with irritable bowel syndrome with diarrhea. *Clin Gastroenterol Hepatol* 2012;10:1009–15 e3.
96. Marion-Letellier R, Dechelotte P, Iacucci M *et al.* Dietary modulation of peroxisome proliferator-activated receptor gamma. *Gut* 2009;58:586–93.
97. Martinez C, Lobo B, Pigrau M *et al.* Diarrhoea-predominant irritable bowel syndrome: an organic disorder with structural abnormalities in the jejunal epithelial barrier. *Gut* 2013; e-pub ahead of print.
98. Martinez C, Vicario M, Ramos L *et al.* The jejunum of diarrhea-predominant irritable bowel syndrome shows molecular alterations in the tight junction signaling pathway that are associated with mucosal pathology and clinical manifestations. *Am J Gastroenterol* 2012;107:736–46.
99. Guarino AH. Treatment of intractable constipation with orlistat: a report of three cases. *Pain Med* 2005;6:327–8.
100. Mueller-Lissner SA, Wald A. Constipation in adults. *Clin Evid (Online)*; advance online publication, 5 July 2010;pii 0413.
101. Faussone-Pellegrini MS, Grover M, Pasricha PJ *et al.* Ultrastructural differences between diabetic and idiopathic gastroparesis. *J Cell Mol Med* 2012;16:1573–81.
102. Grover M, Bernard CE, Pasricha PJ *et al.* Clinical-histological associations in gastroparesis: results from the Gastroparesis Clinical Research Consortium. *Neurogastroenterol Motil* 2012;24:531–9, e249.
103. Grover M, Farrugia G, Lurken MS *et al.* Cellular changes in diabetic and idiopathic gastroparesis. *Gastroenterology* 2011;140:1575–85, e8.
104. Azpiroz F, Malagelada JR. Gastric tone measured by an electronic barostat in health and postsurgical gastroparesis. *Gastroenterology* 1987;92:934–43.
105. Thumshirn M, Bruninga K, Camilleri M. Simplifying the evaluation of postprandial antral motor function in patients with suspected gastroparesis. *Am J Gastroenterol* 1997;92:1496–500.
106. Hedde R, Collins PJ, Dent J *et al.* Motor mechanisms associated with slowing of the gastric emptying of a solid meal by an intraduodenal lipid infusion. *J Gastroenterol Hepatol* 1989;4:437–47.
107. Azpiroz F, Tack J. Gastric disorders. In: Spiller R, Grundy D (eds). *Pathophysiology of the Enteric Nervous System: A Basis for Understanding Functional Diseases*. Wiley-Blackwell: Oxford, 2004, pp. 126–33.
108. Abell TL, Bernstein RK, Cutts T *et al.* Treatment of gastroparesis: a multidisciplinary clinical review. *Neurogastroenterol Motil* 2006;18:263–83.
109. Parkman HP, Camilleri M, Farrugia G *et al.* Gastroparesis and functional dyspepsia: excerpts from the AGA/ANMS meeting. *Neurogastroenterol Motil* 2010;22:113–33.
110. Parrish CR. Nutrition concerns for the patient with gastroparesis. *Curr Gastroenterol Rep* 2007;9:295–302.
111. Little TJ, Feinle-Bisset C. Effects of dietary fat on appetite and energy intake in health and obesity—oral and gastrointestinal sensory contributions. *Physiol Behav* 2011;104:613–20.
112. Feinle C, D'Amato M, Read NW. Cholecystokinin-A receptors modulate gastric sensory and motor responses to gastric distension and duodenal lipid. *Gastroenterology* 1996;110:1379–85.
113. Fried M, Erlacher U, Schwizer W *et al.* Role of cholecystokinin in the regulation of gastric emptying and pancreatic enzyme secretion in humans. Studies with the cholecystokinin-receptor antagonist loxiglumide. *Gastroenterology* 1991;101:503–11.
114. Karas M, Niederau C. Effects of CCK-receptor antagonist on colonic motor activity in dogs. *Neurogastroenterol Motil* 1995;7:63–71.
115. Chua AS, Dinan TG, Rovati LC *et al.* Cholecystokinin hyperresponsiveness in dysmotility-type nonulcer dyspepsia. *Ann N Y Acad Sci* 1994;713:298–9.
116. Lobo B, Serra J, Azpiroz F *et al.* Dexloxiglumide, a CCK1-antagonist, improves gas-related symptoms in healthy subjects. *Gastroenterology* 2006;130:A597.
117. Degen L, Oesch S, Casanova M *et al.* Effect of peptide YY3-36 on food intake in humans. *Gastroenterology* 2005;129:1430–6.
118. Pilichiewicz AN, Feltrin KL, Horowitz M *et al.* Functional dyspepsia is associated with a greater symptomatic response to fat but not carbohydrate, increased fasting and postprandial CCK, and diminished PYY. *Am J Gastroenterol* 2008;103:2613–23.
119. Lanzini A, Magni P, Petroni ML *et al.* Circulating ghrelin level is increased in coeliac disease as in functional dyspepsia and reverts to normal during gluten-free diet. *Aliment Pharmacol Ther* 2006;23:907–13.
120. Sjolund K, Ekman R, Lindgren S *et al.* Disturbed motilin and cholecystokinin release in the irritable bowel syndrome. *Scand J Gastroenterol* 1996;31:1110–4.
121. Little TJ, Feinle-Bisset C. Oral and gastrointestinal sensing of dietary fat and appetite regulation in humans: modification by diet and obesity. *Front Neurosci* 2010;4:178.
122. Lassman DJ, McKie S, Gregory LJ *et al.* Defining the role of cholecystokinin in the lipid-induced human brain activation matrix. *Gastroenterology* 2010;138:1514–24.
123. Lawal A, Kern M, Sanjeevi A *et al.* Neurocognitive processing of esophageal central sensitization in the insula and cingulate gyrus. *Am J Physiol Gastrointest Liver Physiol* 2008;294:G787–94.
124. Tillisch K, Mayer EA, Labus JS. Quantitative meta-analysis identifies brain regions activated during rectal distension in irritable bowel syndrome. *Gastroenterology* 2011;140:91–100.
125. Van Oudenhove L, Vandenberghe J, Dupont P *et al.* Regional brain activity in functional dyspepsia: a H(2)(15)O-PET study on the role of gastric sensitivity and abuse history. *Gastroenterology* 2010;139:36–47.
126. Pehl C, Waizenhoefer A, Wendl B *et al.* Effect of low and high fat meals on lower esophageal sphincter motility and gastroesophageal reflux in healthy subjects. *Am J Gastroenterol* 1999;94:1192–6.
127. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol* 2005;100:190–200.
128. Boeckxstaens GE, Hirsch DP, van den Elzen BD *et al.* Impaired drinking capacity in patients with functional dyspepsia: relationship with proximal stomach function. *Gastroenterology* 2001;121:1054–63.
129. Delgado-Aros S, Camilleri M, Cremonini F *et al.* Contributions of gastric volumes and gastric emptying to meal size and postmeal symptoms in functional dyspepsia. *Gastroenterology* 2004;127:1685–94.
130. Hjelland IE, Ofstad AP, Narvestad JK *et al.* Drink tests in functional dyspepsia: which drink is best? *Scand J Gastroenterol* 2004;39:933–7.

131. Kindt S, Coulie B, Wajs E *et al*. Reproducibility and symptomatic predictors of a slow nutrient drinking test in health and in functional dyspepsia. *Neurogastroenterol Motil* 2008;20:320–9.
132. Tack J, Caenepeel P, Piessevaux H *et al*. Assessment of meal induced gastric accommodation by a satiety drinking test in health and in severe functional dyspepsia. *Gut* 2003;52:1271–7.
133. van den Elzen BD, Bennink RJ, Holman R *et al*. Impaired drinking capacity in patients with functional dyspepsia: intragastric distribution and distal stomach volume. *Neurogastroenterol Motil* 2007;19:968–76.
134. Bisschops R, Karamanolis G, Arts J *et al*. Relationship between symptoms and ingestion of a meal in functional dyspepsia. *Gut* 2008;57:1495–503.
135. Taggart D, Billington BP. Fatty foods and dyspepsia. *Lancet* 1966;2:465–6.
136. Feinle-Bisset C, Meier B, Fried M *et al*. Role of cognitive factors in symptom induction following high and low fat meals in patients with functional dyspepsia. *Gut* 2003;52:1414–8.