FOOD & FGIDS WORKING TEAM

LIPIDS: FOOD INTAKE AND SYMPTOMS IN FGIDs

Short Title (Running Head): LIPIDS: FOOD INTAKE AND SYMPTOMS IN FGIDs

Christine **Feinle-Bisset** (1) and Fernando **Azpiroz** (2)

(1) University of Adelaide Discipline of Medicine and Centre of Clinical Research Excellence in Nutritional Physiology, Interventions and Outcomes, Adelaide, South Australia; (2) Digestive System Research Unit, University Hospital Vall d'Hebron; Centro de Investigaciones Biomédicas en Red de Enfermedades Hepáticas y Digestivas (Ciberhed), Barcelona, Spain; Departament de Medicina, Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain

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Address for correspondence: Prof Fernando Azpiroz

Digestive Department

Hospital General Vall d´Hebron

Barcelona 08035, Spain

Phone: +34 93 274 6222

Fax: +34 93 489 4456

E-mail: azpiroz.fernando@gmail.com

Summary

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 intervention 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.

Behavior of dietary lipids in the gastrointestinal 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 US amounts to 120-150 g/d. Dietary fat is ingested in a number of different forms, depending on the type of food eaten (e.g., intracellular versus extracellular fat) and meal temperature (solid fat versus liquid 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 with a high protein (e.g., in fatty meats or cheeses), content. Hence, the physiological and symptomatic effects of fat may vary.

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 gastrointestinal (GI) function (1-4), and hence, may also play a role in triggering digestive symptoms. Experimental studies with purposely-designed meals demonstrated that 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 layers rapidly 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 (5), so that the effects of fat increase as fat droplet size decreases. Lipid molecules 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 (6).

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 (7-16). The effects of nutrients on gut motility and energy intake also depend on the region and length of gut exposed to nutrients (17), and the load of nutrients administered is also likely to influence the degree of exposure of the small intestinal lumen (18). Once fatty acids have been released in the process of digestion, their effects depend on

their acyl chain length. Fatty acids with a chain length of ≥12 carbon atoms slow gastric emptying (19), stimulate GI hormone release (13, 20, 21) and energy intake (17, 20, 22) much more than fatty acids with ≤10 carbon atoms. Aspects of all these mechanisms may play a role for the symptomatic response to fat in functional gastrointestinal disorders (FGIDs).

Role of dietary fat in symptom induction in functional gastrointestinal disorders

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 GI disorders. However, there is currently only limited scientific evidence in the medical literature to support this common belief. This lack of reliable, evidence-based data is a real problem, since 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%) (23).

The limited currently available data, which will be reviewed below, point towards 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 functional gastrointestinal symptoms. Such large studies will then also allow analysis of specific patterns of responses in sub-groups of patients.

<u>Gastroesophageal reflux disease</u>

Transient lower esophageal sphincter relaxation (TLESR) is the most important mechanism underlying gastroesophageal reflux (24). Increased body weight, a major risk factor for the

development of gastroesophageal reflux disease (GERD) (25), adversely affects the occurrence of GERD not only by increasing abdominal pressure (26), but also by increasing TLESRs (27). Since obese individuals often have increased habitual energy and fat intakes (28) and duodenal lipid increases the number of TLESRs in patients with GERD, associated with an increased number of reflux episodes (29), it is commonly believed that dietary factors, including high-fat, energy-dense foods and large food portions, may induce reflux, thus, life-style changes, including dietary modifications, may be important in the management of GERD, not only in obese, but also normal-weight subjects (30). However, evidence is still inconclusive. For example, while an early study of 1004 patients (of whom 36% reported heartburn at least monthly) found that fried foods, spicy foods and alcohol induced heartburn (31), information was collected using a questionnaire and dietary intakes were not quantified. Fat and chocolate ingestion has been found to increase esophageal acid exposure and lower esophageal sphincter relaxation (32, 33), and recent studies, using more detailed dietary analyses found positive associations between dietary fat intake and GERD symptoms (34, 35), however, the subjects in one of the studies (34) were also overweight. In contrast, other studies were unable to demonstrate relationships between dietary fat and GERD symptoms using data from the NHANES study (36), and a large community-based study of 211 individuals evaluating risk factors for GERD concluded that only BMI, but not diet, affects symptoms (37).

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 functional dyspepsia (FD) when compared with healthy controls (38-43). Specific foods implicated in dyspeptic symptom induction include fried and fatty foods, amongst others (38, 40, 41). In one study the highest

incidence of intolerance was reported for mayonnaise (80% of patients), as well as other foods with high fat contents (42).

It appears that this association does indeed lead to some modifications in dietary behaviour in FD patients. For example, while Carvalho and colleagues (38) 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 (44), 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 (38), although both FD (n=27), IBS (n=46) as well as mixed FD/IBS (n=26) patients were included in this study (see below). Earlier work (43) 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 (45), 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 associated directly with the amount of fat ingested in FD patients (45). 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

A similar situation prevails in irritable bowel syndrome (IBS), where some studies show that a substantial proportion of patients associate symptoms with fatty foods (46-49), but no consistent dietary differences in fat intake have been observed between patients and controls. Simren and colleagues 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 (46). Likewise, a population-based study in Sweden, including 347 IBS patients and 2509 healthy controls, found that patients with IBS (constipation, diarrhea and mixture), but not healthy subjects, relate foods rich in fat with symptom development (48). This association was more prominent in women (23.5% versus 9.1% in healthy controls) than in men (14.6% versus 3.9% in healthy controls) and led patients to change their diet, which was associated with perceived symptomatic improvement (48). In a survey of 1242 IBS patients, one of the most frequent changes in lifestyle considered for symptom improvement was avoiding fatty foods (50).

Despite these subjective reports, available data on differences in dietary lipid 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 (51-53). Some reports described an increased intake of fat and saturated fatty acids in IBS patients (44, 54). 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% versus 33% reference value) (55), 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%) (56), suggesting that the effect of diets possibly depend 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; since the fatty acid composition of the body is largely determined by dietary intake, this could imply differences in diet in these groups (57).

Putative mechanisms by which fat produces functional gastrointestinal symptoms

The pathophysiology of FGIDs is not clear, but extensive research in this field has provided convincing evidence that these patients exhibit sensory and reflex dysfunctions of the gut involving hypersensitivity and abnormal reflexes, so that physiological, normally unperceived, stimuli induce symptoms (58, 59). 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 helps 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 relation between fat ingestion with functional GI symptoms.

Under normal conditions, the presence of fat in the small intestine is associated with a number of changes in gastrointestinal function, including lower esophageal sphincter relaxation, gastric motor inhibition, gastric secretion, biliopancreatic stimulation, small bowel motor inhibition and ileo-colonic motor stimulation (60) (**Table 1**). Intestinal lipids up-regulate

intestinal sensitivity and increase perception of gut stimuli, an effect mediated by sensitization of gut mechanoreceptors (61-64). Small intestinal fat also modulates the quality of perception of upper gut sensations. For example early studies have shown 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 (63, 64). 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 (65) and the fact that increasing the load of duodenal lipid increased the intensity of perception, independently of changes in gastric relaxation (66). Although the majority of these studies are relatively small, laboratory-based studies, 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 (67-70). For example, the slowing of gastric emptying by fat (68) and the stimulatory effects of intraduodenal lipid on pyloric pressures (67), have been reported to be attenuated, while both baseline plasma CCK concentrations (70), and the plasma CCK response to a standardized breakfast (69), 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 (71). Thus, 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.

A number of studies have demonstrated that FGID patients are much more sensitive to small intestinal lipid exposure (64, 72-74), 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 seems to be specific to fat, as isocaloric administration of other nutrients does not result in comparable symptomatic responses (73, 75-79). 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 FG symptoms.

Gastroesophageal reflux disease

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 (29, 78, 80-82) and symptoms, including heartburn, fullness and nausea, in GERD patients when compared with healthy controls (74, 83). Both medium- and long-chain triglycerides have these effects (81), while carbohydrate and protein infusions are ineffective (78), 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 (82).

Functional dyspepsia

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 (64, 76, 84). 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 (76). This

hypersensitivity appears to be fat-specific, since intraduodenal glucose does not increase symptoms (75). A small, laboratory-based study in both 6 healthy subjects and 6 patients with FD have also shown 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 (64), suggesting that input from the small intestine plays an important, and direct, role in the induction of symptoms, rather than indirectly via changes in gastric motor function.

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 this modulatory effect is exaggerated in IBS patients (73, 79). Lipids also modulate intestinal motor reflexes, and this modulatory effect is also exaggerated in patients. 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 up-regulated in patients with bloating (77, 85-87). 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 aborad 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 up-regulated in the IBS patients (60). 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. Hence, in contrast to the inhibitory effect on the small bowel, duodenal lipids stimulate colonic motor activity. The colonic response to lipids is up-regulated in IBS patients (88). Furthermore, lipids exacerbate rectal hypersensitivity in IBS patients (72, 73, 79). 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 (72). The magnitude of the effect was similar in IBS subtypes, but the symptom expression was specific: while IBC-C patients predominantly experienced rectal distension as pain, the predominant symptom in IBS-D was rectal urgency (72). 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.

A recent pilot study showed that among 49 IBS-D 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%) of patients (49). 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 IBS-D patients, 26 IBS-C patients or 26 healthy contols showed that on a high-fat diet patients with IBS-D synthesize and excrete higher levels of bile acids than IBS-C 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 IBS-D 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).

Potential mediators of lipid-induced FGI symptoms

Since 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 (101), it is possible that these mediate, at least in part, the effects of fat on FGI symptoms. CCK mediates, at least in part, the effects of fat on gastric emptying and biliopancreatic secretion, gut motility, gut perception and energy intake (8, 13, 82, 102-104).

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 (80-82). In addition, the study by van Boxel and colleagues demonstrated increased release of apo-AIV and CCK in GERD patients compared with healthy subjects (74), which may, thus, mediate these effects.

The associations between fat ingestion (or duodenal lipid infusion) and symptoms (76, 84) have implicated CCK in the pathophysiology of FD. For example, a small study of 8 FD patients and 8 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 (105). Administration of the CCK-1 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 (64). Interestingly, dexloxiglumide improved dyspeptic symptoms despite reducing gastric relaxation.

CCK potently enhances colonic motility and has been implicated in the gastrocolonic reflex (104), 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 (106). Hence, these data suggest that CCK antagonism increases intestinal capacitance and reverts lipid-induced hypersensitivity. Chronic studies are required to evaluate the role of CCK-1 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 (101). While both GLP-1 and PYY reduce appetite, ghrelin increases it. These peptides may potentially also play a role in FGIDs. PYY can induce gastrointestinal symptoms when given to healthy subjects in supraphysiological doses (107), although basal and postprandial PYY release seems to be reduced in FD patients (108), while the ghrelin response varies (108, 109), 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 (110).

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 A-IV, with subsequent release of CCK, which transmits information about the presence of fat in the small intestine to the CNS by activating CCK_1 receptors located on vagal afferent neurons, associated with the induction of c-fos-like immunoreactivity in the NTS, and subsequent induction of reflex pathways to induce slowing of gastric emptying and food intake inhibition (reviewed in detail in (101, 111)). From the NTS, the information is also transmitted to higher brain centres; 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 the CCK_1-receptor antagonist, dexloxiglumide (112). Thus, CCK secretion, mediated by apo-AIV, and the subsequent activation of CCK_1 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 (113-115). 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.

Dietary lipids and gastroparesis

As described above, the effects of lipids on symptoms in patients with true functional gut disorders (e.g., GERD, FD and IBS) 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 (116-118). 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 (119, 120). 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 (62), suppression of antral and duodenal contractions and stimulation of isolated pyloric pressure waves and basal pyloric pressure (121). These physiological effects result in slowing of gastric emptying (121); fundic relaxation and pyloric closure oppose liquid emptying, while reduced antral peristalsis impairs solid grinding, and hence, pyloric

passage of particulate solids (122). Diet therapy recommendations empirically involve reduction of fat intake, but systematic studies are lacking (123-125).

Challenge tests

While, as discussed above, a number of studies have evaluated foods and food components that FGID patients associated 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 necessarily, 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 (74, 83), in addition to the effects on gastroesophageal function and acid reflux (29). Moreover, intraduodenal lipid infusion hastens the onset, and increases the severity, of heartburn in response to esophageal acid infusion (83). However, while, as discussed earlier, a number of studies have implicated high-fat foods in the induction of GERD symptoms (31, 34, 35), a study in the laboratory was unable to induce symptoms in the laboratory in response to high-fat versus 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 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 relatively low fat content can provoke symptoms in FD patients. It is important to note, however, that the patients were recruited in a tertiary referral centre 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 (41, 135). Although 75-100% (41, 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 (84), 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 (84, 136) the effect of fat cannot be dissociated from the potential effect of increased energy content. However, a small, recent study of 8 FD patients and 8 healthy controls, using equicaloric (500 kcal, 400 g) yoghurt-based meals either high in fat (56%) or carbohydrate (74%), and a low-calorie (180 kcal) 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 (108).

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 (77, 85, 86). 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 (49).

Conclusions

Dietary fat triggers a large range of physiological functions related to the control of gut motility and sensitivity, and these effects may, under certain circumstances, induce gastrointestinal 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 of 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 warranted in this area of food and FGIDs.

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Figure legends

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

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 (74) 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 (step-wise increases in pressure at 1 mmHg/min) with a flaccid bag in FD patients (n=6, closed symbols) when compared with healthy controls (n=6, open symbols). * significantly different from healthy controls ($P<0.05$). Adapted from (64). (C) Intraduodenal lipid (at 0.5 kcal/min for 10 min) significantly increased perception of rectal distension, applied by a tensostat, in IBS patients (n=16 (8 with IBS-C, 8 with IBS-D, closed triangles) when compared with healthy controls (n=6, closed squares). * significantly different from healthy controls ($P<0.05$). Reproduced in adapted form from (72) with permission from the publisher.

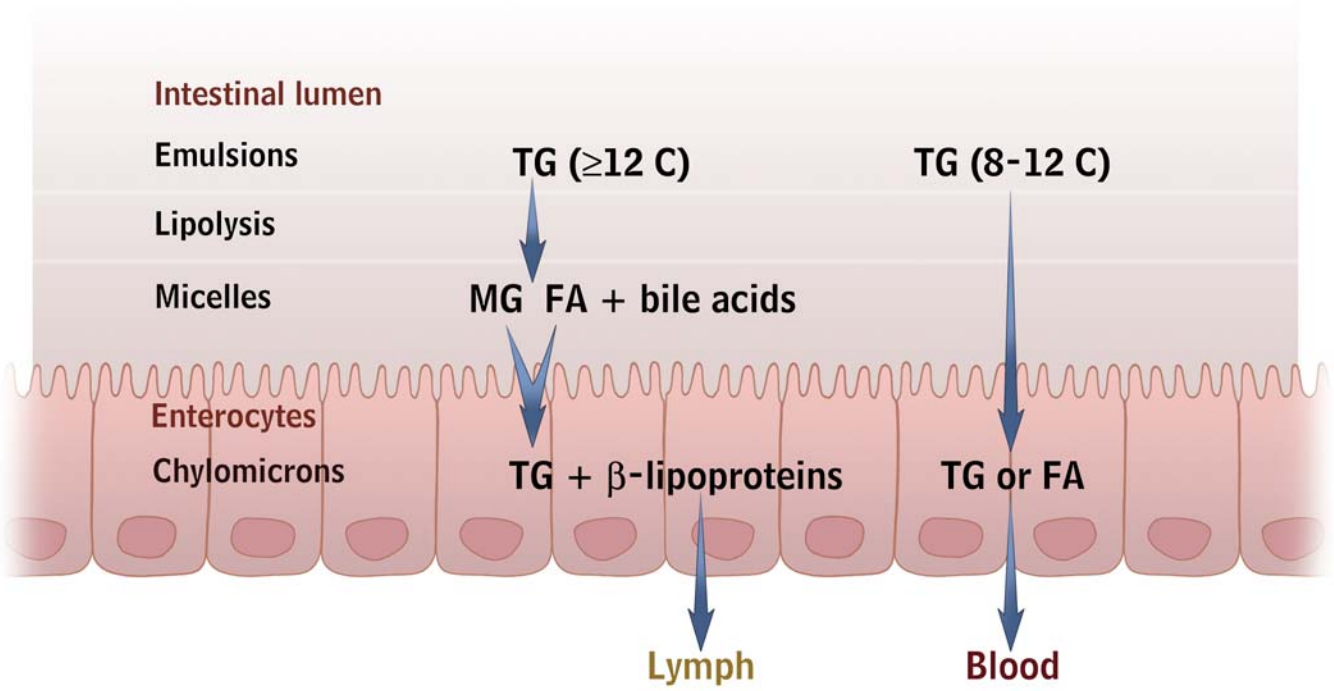
Figure 3: Lipids normally trigger a range of physiological effects on gut motility and sensitivity. Patients with FGIDs exhibit a series of basal gut dysfunctions, somewhat similar to the effects of lipìds in healthy subjects, and these dysfunctions are further exacerbated by

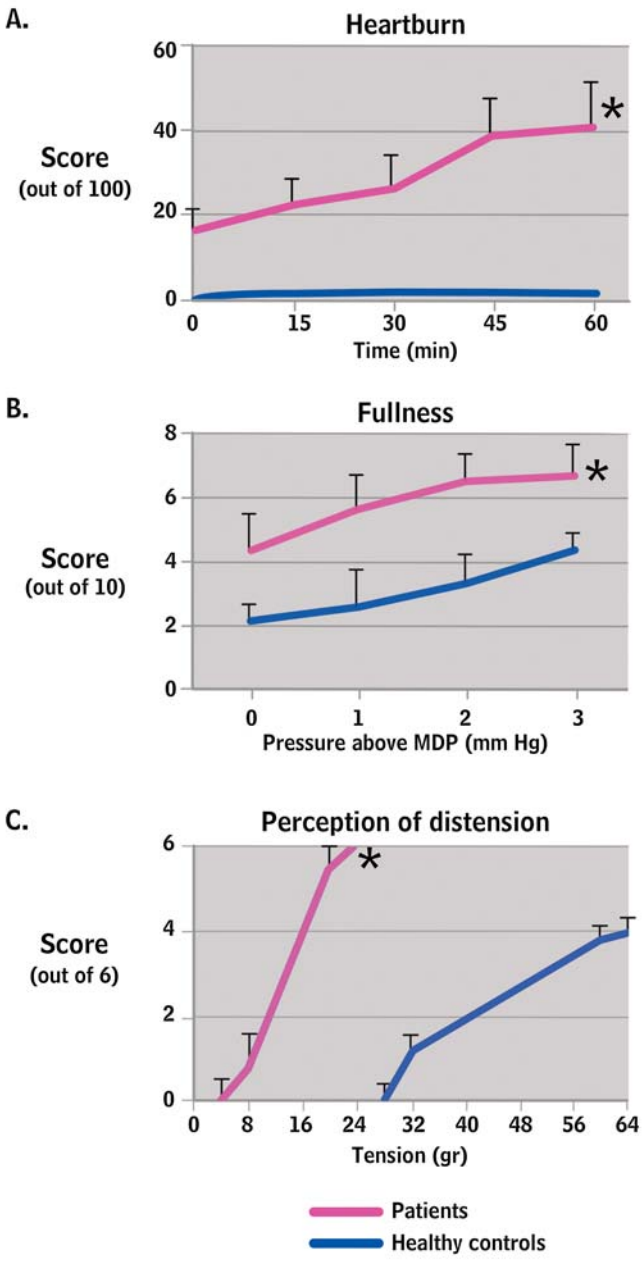
fat due to hypersensitivity and hyperreactivity to luminal lipids, which may explain the development of symptoms.

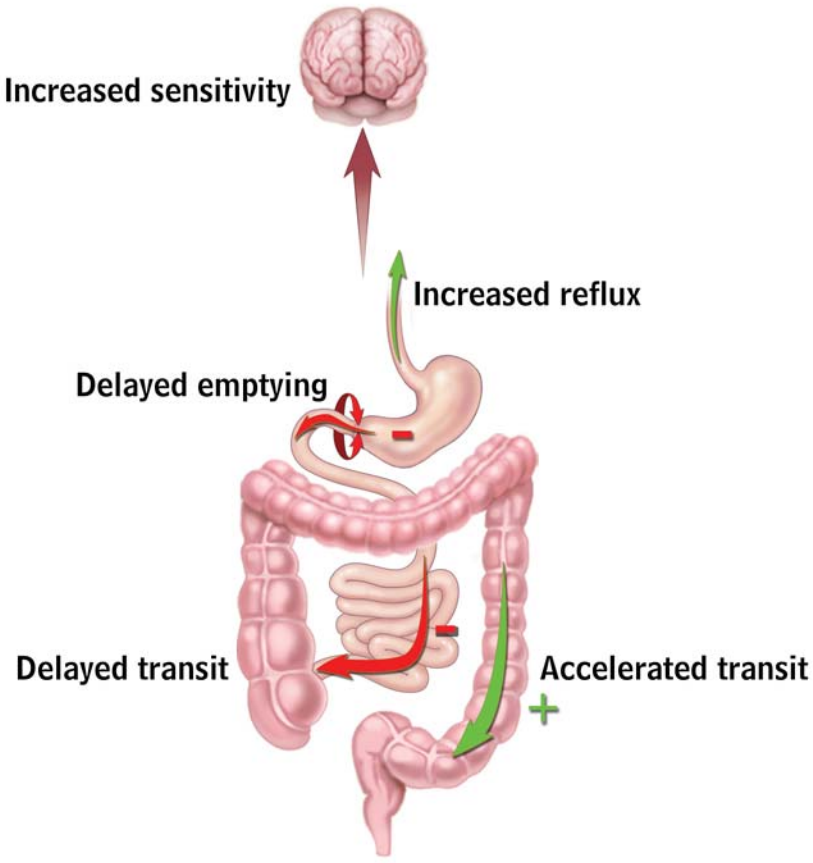
Table 1: Summary of effects of luminal lipids on upper GI motility and sensitivity in healthy subjects and in patients with functional gastroinestinal disorders.

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

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


Intestinal lumen
Emulsions
Lipolysis
Micelles
TG (≥12 C)
TG (8-12 C)
MG FA + bile acids
Enterocytes
Chylomicrons
TG + β-lipoproteins
TG or FA
Lymph
Blood


A.
Heartburn
Score
(out of 100)
60
40
20
0
0
15
30
45
60
Time (min)
*
B.
Fullness
Score
(out of 10)
8
6
4
2
0
0
1
2
3
Pressure above MDP (mm Hg)
*
C.
Perception of distension
Score
(out of 6)
6
4
2
0
0
8
16
24
32
40
48
56
64
Tension (gr)
*
Patients
Healthy controls


Increased sensitivity
Increased reflux
Delayed emptying
Delayed transit
Accelerated transit