Gastric dysmotility and visceral hypersensitivity – an ultrasound approach to functional GI disorders and diabetic gastroparesis

Elisabeth Kjelsvik Steinsvik

Thesis for the degree of Philosophiae Doctor (PhD)
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Scientific environment

The National Centre for Ultrasound in Gastroenterology (NCUG) was established in 2001 at Haukeland University Hospital by the Norwegian Health Authorities. The aim of the centre is to improve ultrasound methods, develop new examination techniques and to stimulate to increased use of ultrasound in gastroenterology in Norway. NCUG was accredited as a European Learning Centre for ultrasound in 2014. This dissertation is number 26 on ultrasound-related subjects from NCUG.

Bergen Research Group for Ultrasound in Gastroenterology (BRUSE) at Dept. of Clinical Medicine, University of Bergen focus on how ultrasound in clinical practice can improve management of patients with digestive diseases. A wide range of methodology has been developed and validated by BRUSE researchers, such as endosonography, three-dimensional ultrasound, hydrosonography, strain rate imaging, contrast-enhanced ultrasound, sonoelastography, advanced visualization, and several novel techniques in GI motility. BRUSE is led by Professor Odd Helge Gilja.

The National Centre of Competence in Functional Gastrointestinal Disorders at Haukeland University Hospital aims to share knowledge about clinical evaluation and treatment of patients with functional gastrointestinal disorders in Norway to health care providers and patients. Furthermore, the centre aims to improve diagnostic accuracy. The centre is led by Professor Jan Gunnar Hatlebakk.

The work in this dissertation was funded by Helse Vest, and was performed at the Department of Medicine, Section for Gastroenterology, at Haukeland University Hospital in Bergen, Norway.

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And Lars – my love. It's always been you! I'm so grateful to be yours.

Abbreviations

2D-US	Two-dimensional ultrasound
3D-US	Three-dimensional ultrasound
5-HT	Serotonin
ANOVA	Analysis of variance
CI	Confidence interval
CLE	Confocal laser endomicroscopy
DG	Diabetic gastroparesis
EKS	Elisabeth Kjelsvik Steinsvik
EPQ-N	Eysenck's Personality Questionnaire, Neuroticism scale
EPS	Epigastric pain syndrome
FD	Functional dyspepsia
FGID	Functional gastrointestinal disorder
GE	Gastric emptying
GERD	Gastroesophageal reflux disease
GES	Gastric emptying scintigraphy
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon like peptide 1
IBS	Irritable bowel syndrome
IBS-C	Irritable bowel syndrome, constipation type
IBS-D	Irritable bowel syndrome, diarrhoea type
IBS-M	Irritable bowel syndrome, mixed type
IBS-SSS	Irritable bowel syndrom symptom severity scale
ICC	Interstitial cells of Cajal
IL	Interleukin
LME	Linear Mixed Effects
MC	Mast cell
MMC	Migrating motor complex
OHG	Odd Helge Gilja

OR	Odds ratio
PDS	Postprandial distress syndrome
PI-IBS	Post-infectious irritable bowel syndrome
PPI	Proton pump inhibitor
PYY	Peptide YY
REK	Regional ethical committee
SCFA	Short chain fatty acid
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TEER	Transepithelial electrical resistance
TH	Trygve Hausken
TNF-α	Tumor necrosis factor alpha
UMAT	Ultrasound meal accommodation test
VAS	Visual analogue scale
VSI	Visceral sensitivity index

Abstract

Background

Functional dyspepsia (FD), irritable bowel syndrome (IBS) and diabetic gastroparesis (DG) are conditions with overlapping symptoms and motility characteristics. The objective of this dissertation was to investigate the link between gastric motility disturbances such as delayed gastric emptying and impaired accommodation, and symptoms from the upper gastrointestinal tract in these conditions.

Material and methods

To evaluate gastric function and upper gastrointestinal symptoms we examined patients with IBS and/or FD (n=248), diabetic patients with symptoms of gastroparesis (n=58) and healthy controls (n=30) with the ultrasound meal accommodation test (UMAT). Furthermore, patients with diabetes and symptoms of gastroparesis were examined with scintigraphy to evaluate gastric emptying.

Results

We found that patients with functional dyspepsia and diabetic gastroparesis had high levels of fasting and postprandial upper gastrointestinal symptoms and impaired gastric accommodation to a meal. All patient groups had antral distention in fasting state compared to healthy controls, and antral distention was correlated to delayed gastric emptying on scintigraphy. Furthermore, we found that the proximal gastric emptying rate in diabetic gastroparesis was reduced. There was weak or no association between ultrasound measurements and recorded symptoms. Patients with overlapping IBS and FD had severe symptom load but normal accommodation.

Conclusion

Gastric motor dysfunction is common in both functional gastrointestinal disorders and diabetic gastroparesis but cannot explain the observed symptoms. Ultrasound can be used to evaluate accommodation and emptying rate of the proximal stomach.

List of Publications

1. Steinsvik EK, Hausken T, Gilja OH. The ultrasound meal accommodation test in 509 patients with functional gastrointestinal disorders. Scandinavian Journal of Gastroenterology 2016; 51:7, 788-794, DOI: 10.3109/00365521.2016.1153138

2. Steinsvik EK, Valeur J, Hausken T, Gilja OH. Postprandial Symptoms in Patients with Functional Dyspepsia and Irritable Bowel Syndrome: Relations to Ultrasound Measurements and Psychological Factors. J Neurogastroenterol Motil 2020;26:96-105. https://doi.org/10.5056/jnm19072

3. Steinsvik EK, Sangnes DA, Søfteland E, Biermann M, Assmus J, Dimcevski G, Gilja OH and Hausken T. Gastric function in diabetic gastroparesis assessed by ultrasound and scintigraphy. *Submitted manuscript to Neurogastroenterology and Motility.*

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3: Submitted manuscript *March 22nd, 2021.*

Contents

2. Introduction

"Science and blood tests doesn't say anything 'bout how I feel"

Highasakite, lyrics by Ingrid Helene Håvik

Functional dyspepsia (FD), irritable bowel syndrome (IBS) and diabetic gastroparesis (DG) are conditions afflicting a large number of patients world-wide (1-3). A common denominator is disturbed motility of the gastrointestinal tract and altered visceral sensation. The patients also share many symptoms.

Nausea, uncomfortable fullness, pain, and discomfort in the upper abdomen after a meal are unspecific and common symptoms. There are a multitude of possible causes, and we are often unable to explain with certainty why a patient experiences these symptoms. Some pathophysiological mechanisms are however associated with these dyspeptic symptoms, such as delayed gastric emptying, visceral hypersensitivity, impaired gastric accommodation and gastrointestinal dysmotility. In this thesis, we have explored the connection between symptoms and pathophysiology, mainly by use of ultrasound of the stomach and patient-reported symptom registrations.

2.1 The normal stomach

2.1.1 Stomach anatomy and structure

The stomach has five regions: the cardia and gastroesophageal junction, the fundus, the corpus, the antrum, and the pylorus (Fig 1). It has two curvatures, the major and minor curvature. The primary electrical pacemaker of the stomach is located on the greater curvature, in the smooth muscle layer of the upper corpus. The vagus nerve is the primary source of its innervation, descending through the diaphragm along the oesophagus. (4)

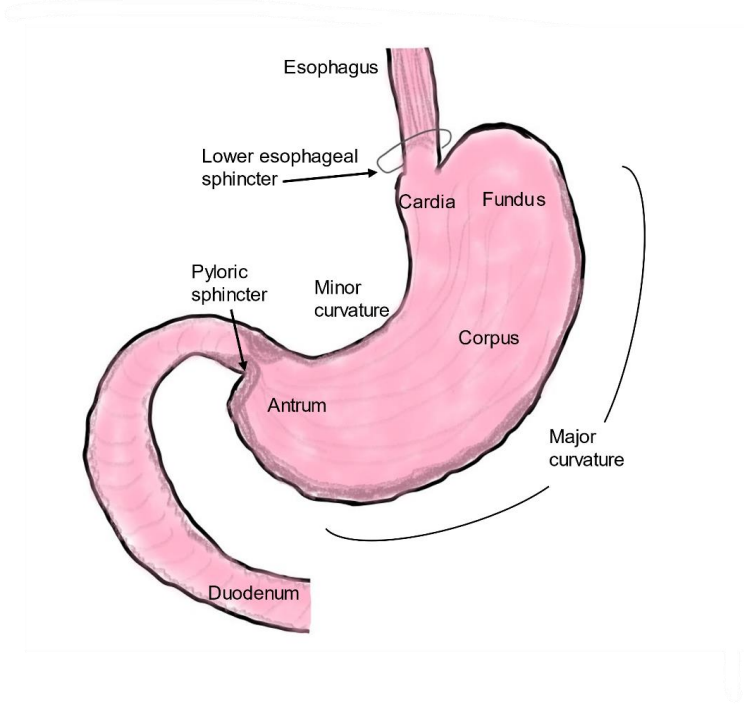

Figure 1: Normal anatomy of the stomach

The stomach has three muscle layers, the outer oblique layer, the middle longitudinal layer, and the inner circular layer. The muscular layers of the stomach enable a coordinated propulsion of the stomach contents from the corpus and the antrum, to the pylorus. The pylorus remains closed until a wave of peristalsis occurs, whereupon the pylorus opens and allows appropriate portions of food to pass over to the duodenum. (4) Interstitial cells of Cajal (ICC) serve as pacemaker cells in the stomach and communicate with the enteric nervous system. Loss of ICCs are associated with gastric dysrhythmias (5, 6).

2.1.2 The physiology and function of the stomach

The stomach is an organ with several roles. It has a secretory function, secreting hydrochloric acid and pepsinogen, and gastrointestinal hormones such as somatostatin and ghrelin. Furthermore, it has a storage function, by decreasing wall

tone and thus increasing the gastric volume (*gastric accommodation*). And of great importance, it propulses the stomach contents distally, and this muscular activity both mixes and grinds the food and transfer it to the duodenum in due time (*gastric emptying*).

Migrating motor complex

The gastrointestinal tract is never inactive in a healthy human being. Between meals, there is still contractile activity, called the migrating motor complex (MMC). The MMC is recurring waves of peristalsis moving from the stomach to the terminal ileum in different strength during a cycle. One cycle lasts for 1.5-2h. The cycle starts with phase I, where only weak and infrequent movements occurs. In phase II, stronger phasic movements can be observed, and even "rumbling" noises from the stomach. This phase is associated with the sensation of hunger and is followed by phase III (fed state): contractions of the stomach, originating in the antrum and moving distally through the small bowel. Under normal conditions, 3 antral phase III contractions occur per minute, and they are always followed by, or occurring simultaneously with, duodenal phase III contractions. The phase III contractions are important to the interdigestive flow in the stomach and small intestine (7).

The regulation of the MMC is complex, depending on several gastrointestinal hormones and neurotransmitters, and both autonomic and enteric nervous system stimuli.

Gastric contractions during and after a meal

The migrating motor complex in the stomach is interrupted when the stomach or duodenum is distended (8). When fluid or nutrients enter the small bowel, the MMC pattern is disturbed in all the small intestinal segments. After a while the MMC will restart, and the duration of the interruption of the cycles depends on the chemical

composition of the ingested meal. Lipids tend to give a longer disruption than e.g. glucose. (9)

When we eat or drink, food and liquid enter the stomach. Water does not need any "treatment" by the stomach, and can pass directly on to the duodenum (10). The fundus and proximal corpus serve as a reservoir of the food, relaxing in order to increase the gastric volume (accommodation). The distal corpus and proximal antrum serve as a mixer, churning the food to small pieces (<2-3 mm) and mixing it with hydrochloric acid and pepsin. The result is a semi-liquid substance called *chyme* (11). Finally, the terminal antrum and pyloric sphincter serve as a filter for larger chunks of food, hindering them from passing into the duodenum, and as a grinder. When a large enough portion of chyme has entered the distal antrum, the antrum will contract forcefully simultaneously with a relaxation of the pylorus, and the portion of chyme passes over to the duodenum (antegrade jet). At the same time, some of the content is usually denied entrance, returning to even more churning in the antrum as a retrograde jet. (12) This can all be observed using high-frequency ultrasound (13-15).

Gastric accommodation

The fundus has mainly a relaxive role in response to eating. The process is called *gastric accommodation* and has several mediators. Receptive and adaptive relaxations are reflexes stimulated by stretching of mechanoreceptors in the oesophageal (receptive relaxation) or gastric (adaptive relaxation) wall, generating impulses carried by the afferent sensory neuron, in turn leading to the release of nitric oxide from the efferent neuron. The result is relaxation of the circular muscle layer of the stomach. In this way, the intragastric pressure decreases and the volume of the stomach increases in response to a meal (Fig.2) (16, 17). This was documented as early as in 1898 by Cannon in a x-ray study on cat (18), and demonstrated by Jahnberg in 1977 (19). The reflex was later found to be vagally mediated through nitrogen monoxide (20-23) and by acting on 5-HT-receptors (24, 25).

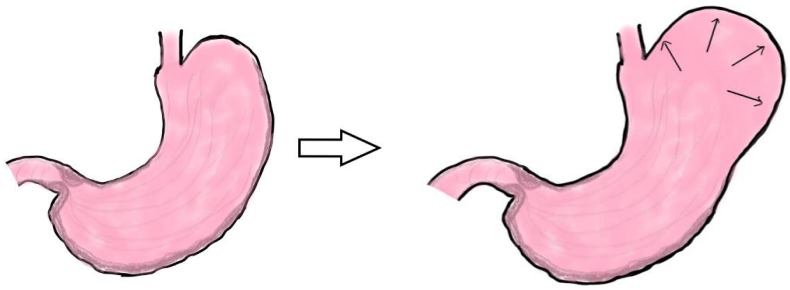

Figure 2: Gastric accommodation of the proximal stomach in response to a meal.

Mechanical stretching of the gastric wall is one important factor in triggering the accommodation reflex. However, evidence is emerging for other factors influencing the relaxation of the proximal stomach. Emotional and psychological stress may impair gastric accommodation, mainly through both activating cholinergic motor neurons. In an animal model, Miwa *et al.* showed that administrating a 5-HT_{2B} receptor antagonist could reverse the negative effect of stress on accommodation, and that administration of a 5-HT_{2B} receptor agonist could exacerbate the effect (26). In a later study, the same group demonstrated that negative effect exerted on gastric accommodation by stress could be reversed by administration of Acotiamide, a prokinetic drug facilitating acetylcholine release (27).

Some papers have reported evidence toward gastric nutrient sensing affecting gastric accommodation, but this is a field requiring more research before conclusions can be drawn. In a human study from 2009, Vanden Berghe *et al.* showed that the accommodation reflex was triggered in both the oropharyngeal, gastric, and duodenal phase of digestion. They found that by inhibiting food from passing over to the duodenum, the participants still experienced an increase in satiety, indicating a degree of chemical sensing in the stomach. They found however that food reaching the duodenum was a much stronger stimulant on gastric accommodation (28). Some have suggested that the anticipation of food in itself can trigger the accommodation reflex, but this theory was not supported by Vanden Berghe's study.

The duodenum seems to play a role in gastric relaxation as well. Lee *et al.* did a study where they infused 0.1N hydrochloric acid into the duodenum of 10 healthy subjects and observed a reaction of proximal gastric relaxation (29). This finding is supported by the results in Vanden Berghe's study from 2009 (28).

2.1.3 Regulatory hormones of the stomach

Gastrin, somatostatin, and ghrelin, as well as regulatory peptides, are all produced by cells in the stomach. In addition, hormones produced in other parts of the gastrointestinal tract affect gastric secretions and motility, such as motilin, glucagon like peptide-1, cholecystokinin, serotonin, pancreatic polypeptide, and peptide YY (PYY) (9, 16, 30). Some of these hormones are involved in decreasing the postprandial glucose level and are called *incretins*. In the following, some hormones of importance for gastric motility will be addressed.

Ghrelin is an appetite increasing protein, produced in the endocrine cells in the stomach, as well as in the myenteric plexus (31). It signals through afferent vagal nerve fibres and crosses the blood-brain-barrier to bind to cells in the hypothalamus and increases appetite. The secretion of ghrelin is stimulated by adrenergic agents. In situations of negative energy balance, such as hypoglycaemia and fasting, the secretion increases. Conditions with energy excess, such as obesity and hyperglycaemia, and during meals, are associated with lower concentrations of ghrelin (9).

Motilin is produced in the myenteric plexus (31) and by enteroendocrine cells in the duodenum and jejunum (32). Motilin can induce phase III contractions of the MMC and is associated with the sensation of hunger. The concentration of motilin fluctuates during the different phases of the migrating motor complex, with a peak concentration immediately before the phase III contractions occur (9).

Glucagon like peptide 1 (GLP-1) is an incretin is produced by L-cells in the small and large intestine, and it stimulates insulin secretion and inhibits glucagon

secretion. It decreases hunger and influences gastric motility, delaying gastric emptying of solids and thus increasing the volume of the stomach both in fasting and postprandial conditions (33).

Glucose-dependent insulinotropic polypeptide (GIP) is another incretin, secreted by endocrine cells in the small intestine. Release of GIP is stimulated by ingestion of glucose and other nutrients. Interestingly, the effect of GIP but not GLP-1 is lost in diabetes type 2. It has an important role in obesity, enhancing clearance of triglycerides and stimulates lipid deposition in adipose tissues (34).

Gastrin has its effect on acid secretion in the stomach. The hormone is produced by G cells, mainly located in the antrum region of the stomach, and is secreted in response to meal intake. It has no direct effect on gastric accommodation or gastric emptying but may have an indirect effect through acid secretion and volume increase in the stomach (30).

Pancreatic polypeptide is produced by F cells in the pancreas and is indirectly involved in the activity of the MMC by decreasing plasma levels of motilin (9).

Peptide YY (PYY) reduces appetite and food intake in humans. It has a large span of physiological effects, both gastrointestinal and others. It delays gastric emptying and slows intestinal transit when nutrients reach the small bowel (30), inhibits gall bladder emptying and pancreatic secretions (35).

Serotonin (5-HT) is a neurotransmitter present in the central nervous system, in blood platelets and in the gastrointestinal tract, where it is produced by enterochromaffin cells. Exogenous administration of serotonin increases phase III activity in all studied species. In humans, the effect on gastric and duodenal motility is mediated through 5-HT_3-receptors. This is demonstrated with administration of the 5-HT_3 receptor antagonist ondansetron, which removes the gastric component of the phase III-contractions of the MMC by inhibiting the peaks in motilin (9, 36).

2.2 Using ultrasound to assess gastric function

Ultrasound is a real-time technique. This means that the examiner can study physiological processes over time with high temporal resolution. In the field of gastroenterology, this is especially useful for assessment of the gastrointestinal tract. Ultrasound is used in assessment of the esophagus, stomach, small and large intestine (37, 38). In this thesis, the focus is on motility of the stomach. Ultrasound can be used to assess gastric volumes in both 2D and 3D, gastric emptying, and accommodation, antropyloric flow and antral contractility.

2.2.1 Gastric accommodation measured with ultrasound

As previously mentioned, the proximal stomach wall relaxes when we eat in the process called *gastric accommodation.* This dynamic process can be measured with the barostat, but ultrasound has proven to be a practical and non-invasive alternative (39, 40). The proximal stomach can be visualized with transabdominal ultrasound, using a standard curvilinear probe. 2D or 3D ultrasound can be used. If one chooses to use 2D ultrasound, a combination of sagittal and frontal sections is recommended (40).

Many studies have been performed over the years using ultrasound to assess gastric accommodation. Gilja *et al.* administered glyceryl trinitrate to study the effect of nitrogen monoxide on gastric accommodation in a double-blind placebo-controlled cross-over study to patients with functional dyspepsia. They found impaired accommodation in FD that improved after administration of glyceryl trinitrate, as well as symptom improvement, showing the usefulness of the technique (41). Several studies have been performed later using ultrasound to assess gastric accommodation on different patient groups. In addition to multiple studies on functional dyspepsia (40, 42, 43), there are reports of studies on patients with diabetes (44, 45), reflux esophagitis (46), alcoholic liver cirrhosis (47) and in children with recurrent abdominal pain (48).

2.2.2 Volume estimation of the stomach and gastric emptying

Ultrasound is a widespread method for estimating gastric emptying (GE) rates both in the clinic and in research. Although gastric emptying scintigraphy is still the golden standard for assessment of GE, ultrasound is often the method of choice because of the possibilities of real-time evaluation, its accessibility and the possibility of doing bedside examinations (49-53). Anaesthesiologists and surgeons evaluate the antrum as a Point-of-care ultrasound examination to assess gastric emptying and gastric contents both before and after surgery (54-56). Comparisons between ultrasound and gastric emptying scintigraphy have shown good agreement between the methods (50, 57, 58).

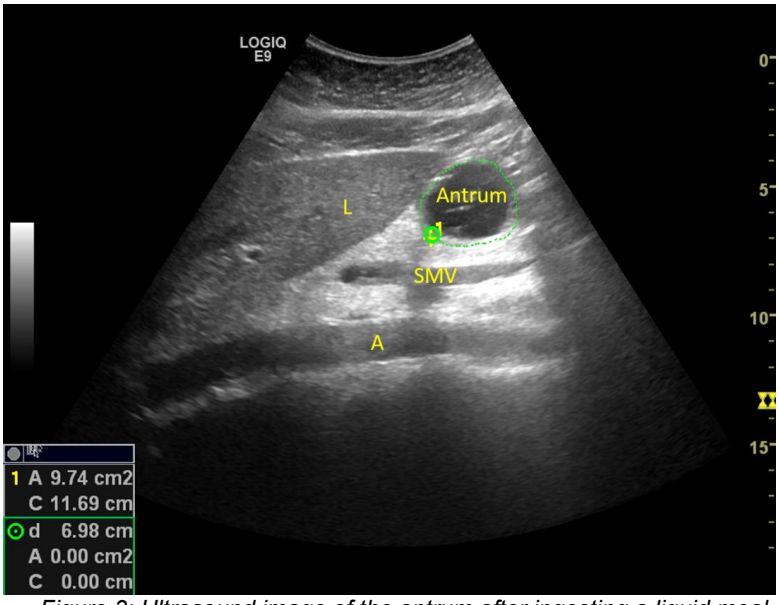

Figure 3: Ultrasound image of the antrum after ingesting a liquid meal. In this section, we find the antrum in close relation to the left liver lobe (L) and the aorta (A) and superior mesenteric vein (SMV) which are visible posterior to the antrum serving as internal landmarks.

The most common method of estimating gastric emptying by ultrasound is to measure the antral area in a sagittal section (59). The antral area (Fig.3) is a measurement that has proved to correlate well with ingested volume (60).

Total gastric volumes and intragastric distribution of meals can be estimated using three dimensional ultrasound (3D-US) (61), and 3D-US is frequently used to evaluate gastric emptying (62-65).

2.3 Functional dyspepsia

Functional dyspepsia (FD) is one of the most common conditions under the umbrella "Disorders of Brain-Gut Interactions". It is characterized by one or more of the following symptoms: 1) early satiety, 2) postprandial fullness, 3) epigastric pain or 4) epigastric burning. Other common explanations for the same symptoms, such as gastric ulcer, must be ruled out. Furthermore, the symptoms must be bothersome to the patient and impair normal activities. Patients frequently report other symptoms originating from the upper abdomen/chest, such as nausea, upper abdominal bloating, belching and heartburn. The patients are categorized by their symptoms into the following subgroups:1) Epigastric pain syndrome (EPS) and 2) Postprandial distress syndrome (PDS) or 3) overlapping EPS and PDS (Tab 2). EPS is associated with epigastric pain or burning, and not necessarily related to meals. PDS is characterized by meal-related dyspeptic symptoms. (66)

The prevalence of FD is reported to be 10% (2, 67), but may be higher. In a population study from the USA, Pleyer *et al.* found that the number of people diagnosed with gastrointestinal reflux disease (GERD) has increased dramatically over the last years, while patient-reported symptoms of reflux have been relatively unchanged. At the same time, fewer patients have been diagnosed with functional dyspepsia. The authors suggest that GERD is a more widely known diagnosis, and that the substantial marketing of proton pump inhibitors (PPIs) has influenced how upper GI symptoms have been diagnosed. The fact that many GERD patients are not responding to PPI treatment may be explained by a faulty diagnosis (68).

Patients with functional dyspepsia report reduced quality of life, and the diagnosis is associated with increased health care costs (2).

The hallmark symptoms of functional dyspepsia are early satiety, postprandial fullness and epigastric pain or discomfort. In a study from 2006, Karamanolis *et al.* found that 15 % of FD patients reported bloating as the predominant symptom, 10% reported nausea, 8% belching, 6% epigastric burning and 3% reported vomiting as their predominant symptoms. Postprandial fullness, epigastric pain and early satiety were reported as predominant symptoms in 24%, 22% and 12%, respectively (69). In addition, other co-existing conditions are common, such as anxiety, depression (70), migraine (71), fibromyalgia (72) and chronic fatigue syndrome (73, 74), or other functional gastrointestinal disorders. Both psychiatric and extraintestinal comorbidities seem to modulate FGID symptoms, and in some cases affect the quality of life to a greater degree than the FGID itself (75).

2.3.1 The Rome criteria for Functional dyspepsia

The clinical material of patients with functional dyspepsia and IBS in this thesis ranges from 1999 to 2014. During these years, there were two editions of diagnostic criteria for the functional gastrointestinal disorders; Rome II (76) and Rome III (77). The different criteria are summarized in Table 1, along with the current diagnostic criteria; Rome IV (66).

Table 1: Historic and current diagnostic criteria for Functional Dyspepsia

Rome II 1999
At least 12 weeks, which need not be consecutive, within the preceding 12 months of: 1. Persistent or recurrent dyspepsia (pain or discomfort centered in the upper abdomen); and 2. No evidence of organic disease (including at upper endoscopy) that is likely to explain the symptoms; and 3. No evidence that dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not irritable bowel).(76)
Rome III 2006
Must include 1. One or more of: a. Bothersome postprandial fullness b. Early satiation c. Epigastric pain d. Epigastric burning AND 2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms **Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis* (77)
Rome IV 2016
1. One or more of the following: a. Bothersome postprandial fullness b. Bothersome early satiation c. Bothersome epigastric pain d. Bothersome epigastric burning 2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms. Must fulfill criteria for PDS and/or EPS. Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.(66)

The greatest difference between the Rome II and III criteria, was the introduction of the two subgroups, namely Postprandial Distress Syndrome (PDS) and Epigastric Pain Syndrome (EPS) (Table 2). The rationale for introducing two subgroups was the observed heterogeneity of the patient group, leading to a theory that functional dyspepsia may be indeed two distinct conditions with different aetiologies. This was supported by population-based studies (78, 79). Furthermore, symptoms as belching and nausea were classified as separate entities. However, clinical data has shown that there is a major overlap between the EPS and PDS, and patients also report symptoms

of postprandial nausea (80, 81). The two groups are very similar regarding gastric accommodation, gastric sensitivity and gastric emptying, and may not be as different from each other as originally assumed (82). The subgroups were continued in the Rome IV criteria, with minor alterations (66).

Table 2: Epigastric Pain Syndrome and Postprandial Distress syndrome in the Rome III criteria

Diagnostic Criteria* for **Epigastric Pain Syndrome (EPS)** Must include all of the following: 1. Pain or burning localized to the epigastrium of at least moderate severity at least once per week 2. The pain is intermittent 3. Not generalized or localized to other abdominal or chest regions 4. Not relieved by defecation or passage of flatus 5. Not fulfilling criteria for gallbladder and sphincter of Oddi disorders Supportive criteria 1. The pain may be of a burning quality but without a retrosternal component 2. The pain is commonly induced or relieved by ingestion of a meal but may occur while fasting 3. Postprandial distress syndrome may coexist	Diagnostic Criteria* for **Postprandial Distress Syndrome (PDS)** Must include one or both of the following: 1. Bothersome postprandial fullness, occurring after ordinary sized meals, at least several times per week 2. Early satiation that prevents finishing a regular meal, at least several times per week Supportive criteria 1. Upper abdominal bloating or postprandial nausea or excessive belching can be present 2. 2. EPS may coexist
**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis* (77)	

In ICD-10, the diagnostic code system used by hospitals in Norway, there is no subclassification of functional dyspepsia. Thus, the patients in our material have not been classified as EPS or PDS.

2.3.2 Pathophysiological mechanisms of FD

Although some pieces of the puzzle are still missing, several abnormalities associated with functional dyspepsia are recognized. Gastric motor dysfunction is important, as

well as duodenal affection and brain-gut interactions. Based on what we know today, functional dyspepsia seems to be a multifactorial condition.

Impaired gastric accommodation

The normal accommodation reflex has been studied and documented for over 100 years (18). But what happens if the proximal stomach does not relax as a response to a meal? The result is called *impaired accommodation* and is a common finding in functional dyspepsia and gastroparesis. The role of impaired accommodation in functional dyspepsia was first documented by ultrasound and scintigraphic studies by Gilja *et al.* and Troncon *et al.* (40, 83).

When the proximal stomach fails to increase it volume sufficiently, the ingested food is forced to find its way further down to the distal part of the stomach, causing a distended antrum. This is thought to increase the symptom load. Tack *et al.* found in 1998 that patients with impaired accommodation had more symptoms of early satiety and weight loss compared to patients with normal accommodation (84). However, the correlation between dyspeptic symptoms and the finding of impaired accommodation is not consistent in all studies (82, 85).

The gold standard for evaluating gastric accommodation is the gastric barostat (86, 87). The barostat consists of a gastric balloon adhered to a double lumen tube, connected to a barostat device, enabling subsequent expansion of the balloon. Allowing control over the volume and pressure in the balloon in the stomach, changes in the gastric pressure or volume can be registered. The barostat has been thoroughly validated and shows good results, but is invasive and uncomfortable for the patient, and time consuming (88). Other options for accommodation testing include single photon emission computed tomography (89), magnetic resonance imaging (90) and ultrasound (39, 91). In this thesis, we have used ultrasound to assess gastric accommodation.

Delayed gastric emptying and antral dysmotility

Another gastric motor disturbance associated with functional dyspepsia is delayed gastric emptying. Different studies report that 15-27% of patients with FD have delayed gastric emptying (82, 92, 93). Furthermore, Wilmer *et al.* found that patients with functional dyspepsia had a prolonged cycle length of MMC, a higher percentage of phase II contractions and lower percentage of phase III contractions compared to healthy controls (94). But although it is a common finding in patients with FD, these changes are often not correlated to the patient's reported symptoms. However, a meta-analysis by Vijayvargiya and co-workers found strong correlations between several upper gastrointestinal symptoms and delayed gastric emptying in gastroparesis and functional dyspepsia (95).

In addition to delayed gastric emptying and impaired accommodation, altered antral motoric function has been reported in functional dyspepsia, and the postprandial antral area was found to correlate to dyspeptic symptoms (96, 97).

Duodenal barrier defect and low-grade inflammation

Functional dyspepsia has traditionally been considered mainly a gastric disorder, but emerging evidence points toward the duodenum as a key region for instigating both symptoms and gastric motor alterations (98). The duodenum plays an important role through reflex and hormonal control of gastric emptying and accommodation in healthy individuals, and the effect of duodenal mucosal affection on the gastric motor function as well as upper GI symptoms has been the focus of many recent studies.

Over the last decade, multiple research groups have shown that patients with functional dyspepsia have increased cell counts of eosinophils and mast cells indicating low-grade inflammation, and some have found this to correlate to dyspeptic symptoms. (99-101). Vanheel *et al.* also found low-grade inflammation, and furthermore demonstrated that patients with FD had impaired duodenal mucosal integrity, with reduced transepithelial electrical resistance (TEER), altered expression of several adhesion proteins, and increased paracellular passage (102). Nojkov *et al.*

examined 16 patients with functional dyspepsia and 18 healthy controls with upper endoscopy enhanced with duodenal confocal laser endomicroscopy (CLE), mucosal biopsies, and measured TEER. They found that patients with FD had higher epithelial gap density on CLE in the distal duodenum compared to healthy controls, and that they had impaired mucosal integrity. They also found changes in Claudin-1 and interleukin-6 expression. (103) Komori *et al.* found an altered mucosal barrier in patients with functional dyspepsia, with a lower zonula occludens-1 expression and higher interleukin-1β expression (104). Wauters *et al*. proposed in a review from 2020 that the duodenum may be not only *affected* in functional dyspepsia, but may be the *responsible* for symptom generation and that the gastric motor abnormalities may be secondary to duodenal affection (105). However, this hypothesis has not yet been proven, and many questions remain unanswered.

Visceral hypersensitivity

Another factor of great importance for many (but not all) patients with functional dyspepsia is visceral hypersensitivity (69, 106). This can be measured in several ways, for example by balloon distention in the stomach by gastric barostat, or by drink tests (107). Patients with visceral hypersensitivity have a lower threshold for pain or discomfort compared to patients with normal sensitivity. This was not associated with changes in gastric accommodation or gastric emptying, implying that visceral hypersensitivity is a separate mechanism (106). In a multicentre study from 2018, Simrén and co-workers demonstrated that visceral hypersensitivity is an important contributor to symptom generation in functional dyspepsia and irritable bowel syndrome, and that this effect remained after adjusting for psychological distress. This is important because it has been postulated that visceral hypersensitivity was merely an effect of hypervigilance due to anxiety/depression. (108).

Early life adverse events are associated with increased risk of visceral hypersensitivity in adult life, and may furthermore give rise to epigenetic changes that can be passed on to the next generation (109). Sexual and physical abuse are other factors influencing visceral sensitivity. Van Oudenhove *et al.* found in a study

that a history of sexual abuse lowered the threshold for gastric discomfort, even when controlled for comorbid depression, somatization and sociodemographic factors (110).

2.4 Irritable bowel syndrome

Irritable bowel syndrome is, along with functional dyspepsia, one of the most common functional gastrointestinal disorders with a pooled global prevalence of 11.2% (95% CI: 9.8 – 12.8%) (1). According to the current diagnostic guidelines (Rome IV), IBS is defined as a condition with recurring abdominal pain related to defecation or a change in bowel habits. Often there is a change in bowel habits (i.e. diarrhoea, constipation, or a mixed pattern) and/or symptoms of bloating or abdominal distention. Organic causes for the symptoms must be ruled out. (111)

There are four subtypes of IBS, classified by the dominant bowel habit pattern: IBS with predominant diarrhoea (IBS-D), IBS with predominant constipation (IBS-C), IBS with a mixed bowel habit pattern (IBS-M), or patients with IBS where the bowel habits cannot be classified into one of the beforementioned groups (IBS-U (unclassified)). It is estimated that approximately 1/3 of IBS patients have IBS-C and 1/3 have IBS-D (112), but many patients report that their bowel habit pattern vary over time, making prevalence studies uncertain (113).

Irritable bowel syndrome is a chronic condition, and currently there is no cure. However, many patients experience an improvement over time. Others report that the severity may fluctuate over time, typically increasing in periods of psychological stress. (114)

2.4.1 Rome criteria in IBS

Irritable bowel syndrome is acknowledged as a disorder of Gut-Brain interactions and diagnosed according to the Rome-criteria. Currently, the Rome IV criteria from 2016 are used. In the papers concerning IBS in this thesis, the Rome II and III criteria were

used (Tab.3). The main differences between the Rome II and III criteria are based on the duration and frequency of the symptoms. In a report from 2009, Dorn and co-workers showed that the two diagnostic criteria had high agreement and populations diagnosed with the two sets of criteria behaved similarly over time (115). In the Rome IV criteria *discomfort* was removed, excluding many patients and resulting in a lower prevalence (116).

Table 3: Historic and current diagnostic criteria for IBS

Rome II 1999
At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two of three features: 1. Relieved with defecation; and/or 2. Onset associated with a change in frequency of stool; and/or 3. Onset associated with a change in form (appearance) of stool.(117)
Rome III 2006
Recurrent abdominal pain or discomfort** at least 3 days per month in the last 3 months associated with 2 or more of the following: 1. Improvement with defecation 2. Onset associated with a change in frequency of stool 3. Onset associated with a change in form (appearance) of stool **Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.* ***Discomfort means an uncomfortable sensation not described as pain.* (118)
Rome IV 2016 (current)
Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria: 1. Related to defecation 2. Associated with a change in frequency of stool 3. Associated with a change in form (appearance) of stool *Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.* (111)

2.4.2 Comorbidities and risk factors

Some IBS patients report that they have had problems with abdominal pain since childhood. Others describe a gradual start, often associated with major life stress such as divorce or losing their job, and in many cases the symptoms start after a gastrointestinal infection. Because of the diverse start of symptoms, it can be challenging to design robust prospective epidemiological studies for assessing the risk factors for developing IBS. Another factor to consider, is how risk factors may

interact. It can sometimes difficult be certain what appeared first – the depression or the gastrointestinal symptoms? In a review from 2019, only including prospective population-based studies to eliminate some of these biases, Creed found that in western countries, female gender and young age were strong risk factors for developing IBS. Anxiety and depression were risk factors in all age groups. Stress, other pain conditions (such as fibromyalgia and migraine), sleep disorders and other functional gastrointestinal disorders were other risk factors. (119)

2.4.3 Pathophysiological mechanisms of IBS

Irritable bowel syndrome is a highly heterogeneous condition, perhaps consisting of different disease entities. The common denominator is abdominal pain related to bowel habits. The pathogenesis is multifactorial, and some important pathophysiological factors will be presented in the following.

Post-infectious genesis

The strongest risk factor for developing IBS is acute infectious gastroenteritis. The term *post-infectious IBS (PI-IBS)* is used about patients with symptoms of IBS that started in with an infectious gastroenteritis and has persisted for more than 6 months. The risk of developing PI-IBS is probably higher after a bacterial or protozoal gastroenteritis compared to viral ones. In a meta-analysis it was found that as many as 10% of patients with enteritis later developed PI-IBS (120). Risk factors of particular importance are young age, female gender, psychological factors such as anxiety, depression, negative health beliefs, neuroticism and somatization, and the severity of the infection (121). The first papers describing PI-IBS were published in 1950 by Stewart (122), and in 1962 by Chaudhary and Truelove (123). To date many different pathogens inducing the condition has been described. In Bergen, Norway, a large outbreak of water-borne *giardia lamblia* in 2004 resulted in 1262 subjects with laboratory-confirmed giardiasis. Many of these patients were subsequently included in the longitudinal Giardia-studies. In the 10 year follow-up study, as many as 43% (n=248) among 576 individuals who were exposed to Giardia in the 2004 outbreak still had symptoms of IBS (124).

Immune response

Irritable bowel syndrome is not associated with severe inflammation, as we find in conditions such as ulcerative colitis or Crohn's disease. However, a dysregulation of the immune system is frequently reported, as a sign of *low-grade inflammation.* Approximately 50% of IBS-patients have an increased activation of the immune system. Studies have shown increased infiltration of T-cells and mast cells (MCs) in the mucosa of the small and large intestine. In a meta-analysis, Bashashati *et al.* found that most of the included studies reported increased numbers of mast cells in biopsies from patients with IBS. In IBS-C there were only reports of increased MC counts in the descending colon, and in IBS-D there were increased cell counts in both rectosigmoid and descending colon (125). In IBS, and particularly PI-IBS and IBS-D, there have been demonstrated increased levels of MC mediators that have the ability to activate and potensate neurons, resulting in increased visceral pain perception and altered motor function (126). This can lead to pain and diarrhoea (126). Mast cells in the gut lining are situated in close proximity to GI mucosal sensory nerve fibres (127), and interactions between MCs and brain-gut neuronal networks are potentially part of the explanation of symptom perception in some IBS patients (126).

Many studies have been performed on IBS populations to investigate the role of immune activation in symptom generation, and many studies have shown signs of increased inflammatory activity in IBS. Some have found increased eosinophil counts in colonic biopsies from IBS-patients, while others have found no difference compared to healthy controls (128). In a study on patients with self-reported food sensitivity, patients with IBS had higher interleukin-10 (IL-10) secretion from dendritic cells after lipopolysaccharide stimulation compared to healthy controls (129). Other studies have shown increased IL-6 and IL-8, and lower or normal expression of IL-10. Some have found elevated levels of tumour necrosis factor alpha (TNF-α) compared to normal. But in summary, results are conflicting and not convincingly unidirectional, and although the evidence indicate that low-grade

inflammation is important in the aetiology of IBS, the role of the immune system is still not fully elucidated.

Intestinal permeability

Multiple studies have shown an increased epithelial permeability in IBS, particularly in PI-IBS and in IBS-D. The epithelial barrier defects can be mediated by chronic and acute stress in two ways: 1) Via direct modulation of the permeability of the epithelium, or 2) by an increased translocation of gut microbes or microbe associated molecules such as lipopolysaccharides as a result of altered intestinal mucosa (130).

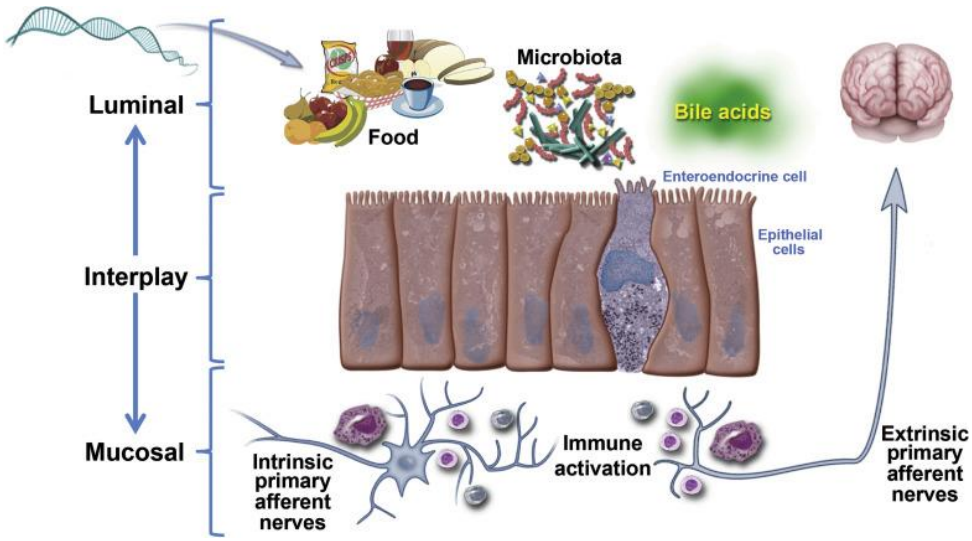

Figure 4: Representation of the interplay between luminal and mucosal factors in functional gastrointestinal disorders. Food, microbiota, and bile acids from the intestinal lumen may permeate through the leaky epithelial barrier, affecting nerves and immune system and in turn affect sensory perception and intestinal physiology.

Source: Barbara G et al. Gastroenterology 2016. Printed with permission.

Microbiota in IBS

The microbiota is emerging as a major contributor to health and disease. Changes in microbiota composition is associated with a multitude of diseases and conditions, ranging from anxiety and depression to cardiovascular disease, diabetes, and inflammatory bowel disorders. Over the last decade it has become one of the major areas of research in the field of functional gastrointestinal disorders.

The microbiota of the human gut is dominated by bacteria from the Bacteroidetes, Actinobacteria and Firmicutes phyla, and are found in greatest number in the colon (131). Many studies have been done on the IBS population, and results are somewhat conflicting. To date, it has not been possible to pinpoint one specific microbiota profile in IBS. However, some trends have been found. In a meta-analysis from 2019 Wang and co-workers found that IBS patients had lower abundance of the commensal bacteria *Lactobacilli* and *Bifidobacterium,* and an overgrowth of the potential pathogens *E. coli* and *Enterobacteriaceae (132).*

Several studies have shown that patients with comorbid IBS and anxiety/depression have a distinct microbial signature. In a meta-analysis Simpson *et al.* found that this patient group had a microbiota profile characterized by lower alpha diversity compared to patients with either disorder separately, and compared to healthy controls. Although different methods made direct comparisons difficult, a general finding was that the IBS + anxiety/depression group had a higher relative abundance of Proteobacteria and the genera *Bacteroides* and *Prevotella*, and lower abundance of the family *Lachnospiracae.(133)*

Complex carbohydrates are often not fully digested in the small intestine, and pass on to the colon, where they are fermented by bacteria. The end products of bacterial carbohydrate fermentation are short chain fatty acids (SCFA), and they are important as fuel for our intestinal cells. Furthermore, SCFAs may work as signaling molecules, and in this way the bacteria in our bowels may communicate both locally and to the brain (131). SCFAs can even affect the inflammatory response of the innate immune system via different signaling pathways (134).

The composition and function of the microbiota is a field of research in growth. New methods are opening new possibilities, and it seems we are only in the beginning of understanding this immense field yet. Although we do not know the full significance of the microbiota in IBS, there is broad agreement that the bacteria, and maybe also fungi and viruses in our intestines, are of importance in IBS.

2.5 Diabetic gastroparesis

In Norway, estimated prevalence of type 1 diabetes (T1D) was 23.000 in 2020. Type 2 diabetes (T2D), strongly associated to lifestyle and obesity, was more frequent with an estimated prevalence of 293,000 – 322,000, and approximately 60.000 of these cases were probably undiagnosed. (135)

It is common knowledge that patients with long-lasting diabetes are at risk of developing complications. Peripheral neuropathy, retinopathy and nephropathy are common examples. Diabetes can affect almost all parts of the gastrointestinal tract, giving symptoms of nausea, fullness, abdominal pain, vomiting, constipation, and diarrhoea. In this thesis, we have included patients with diabetes and a medical history suggesting gastroparesis.

Gastroparesis is a disorder of the upper GI tract defined by delayed gastric emptying (GE) without any mechanical obstruction of the gastric outlet (136). Diabetes is a common cause, and gastroparesis occurs in approximately 1-5% of diabetic patients (137, 138). In a population study from the USA, the prevalence of gastroparesis was calculated in a population of 43 million people. As type 2 diabetes is much more common than type 1 diabetes, type 2 diabetes represented 55.3% of the gastroparesis cases. But the risk of gastroparesis was markedly higher in patients with T1D (4.59%) compared to T2D (1.31%). Furthermore, women had higher risk of diabetic gastroparesis than men (62% of T1D and 63.5% of T2D were women) (138). It is estimated that approximately 5 million patients suffer from diabetic gastroparesis in the USA (139).

2.5.1 Clinical implications of gastroparesis

The classical symptoms of gastroparesis are nausea, vomiting, bloating, postprandial fullness, and early satiety (136, 140), but upper abdominal pain is also frequently reported (141). The correlation between gastric emptying scintigraphy and patient reported symptoms is however varying in different studies. Some even find that *rapid* gastric emptying present with the same symptoms as *delayed* gastric emptying (142). Delayed gastric emptying have clinically important effects not only on the gastrointestinal symptoms for patients with diabetes. It also affects blood sugar control (Fig. 4).

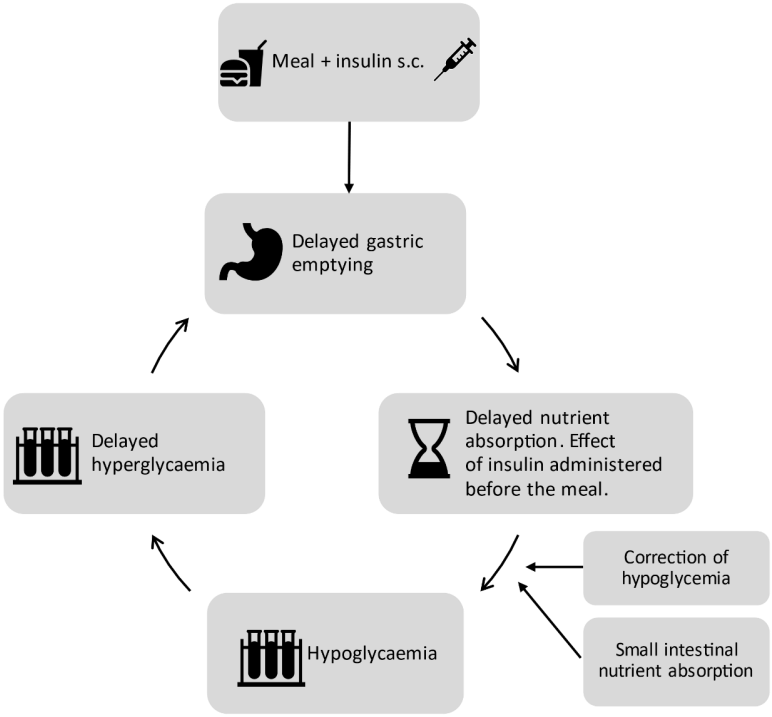

Figure 5: Diagram illustrating the complex connection between blood sugar regulation and gastric emptying in diabetic gastroparesis.

GLP-1 is an incretin hormone that in addition to increasing insulin production and suppressing glucagon, slows gastric emptying (143). GLP-1 analogue treatment is an

option in T2D but is not a good choice for all patients. Some patients with type 2 diabetes have rapid gastric emptying and may benefit from treatment with GLP-1 analogues (144). Patients with gastroparesis will however risk an exacerbation of their delayed gastric emptying and are less likely to benefit from this medication. (139)

Gastric emptying is traditionally assessed by gastric emptying scintigraphy (see methods section). Other methods are also available, including ^{13}C labelled breath test, MRI, Wireless Motility Capsule (WMC) and gastric ultrasound.

2.5.2 Pathophysiological mechanisms of diabetic gastroparesis

Gastric emptying is a complex mechanism depending on input from both the autonomic and enteric nervous system, impulses from the interstitial cells of Cajal (ICCs), hormonal control, and is influenced by blood glucose levels. Multiple parts of the stomach can be contributing to delayed emptying. Antral hypomotility and impaired pyloric relaxation are important factors. Furthermore, impaired gastric accommodation and duodenal or small bowel dysmotility are involved in symptom generation in diabetic gastroparesis.

Autonomic neuropathy

Electrophysiology studies have shown multiple effects on the autonomic nervous system in diabetes. Slow wave contraction of the stomach, prolonged pyloric contractions and dyscoordination between the antrum and duodenum have all been demonstrated (145). Changes in vagal nerve fibres, both myelinated and unmyelinated, was demonstrated in patients with diabetic gastroparesis (146).

Input from the vagus nerve is of great importance to sustain normal gastric accommodation. Patients with diabetes showed impaired accommodation (45, 140). Kumar and co-workers assessed gastric accommodation in patients with diabetic gastroparesis and found impaired accommodation in nine of 10 patients. However,

the accommodation did not correlate to the patient's postprandial symptoms in this study (147).

Enteric nervous system (ENS) and interstitial cells of Cajal (ICCs)

The ENS is located in the intestinal wall, in the myenteric and submucosal plexi. Uniquely in the body, the enteric nervous system can function on its own, independent from central nervous system, but interacts with the autonomic nervous system (148).

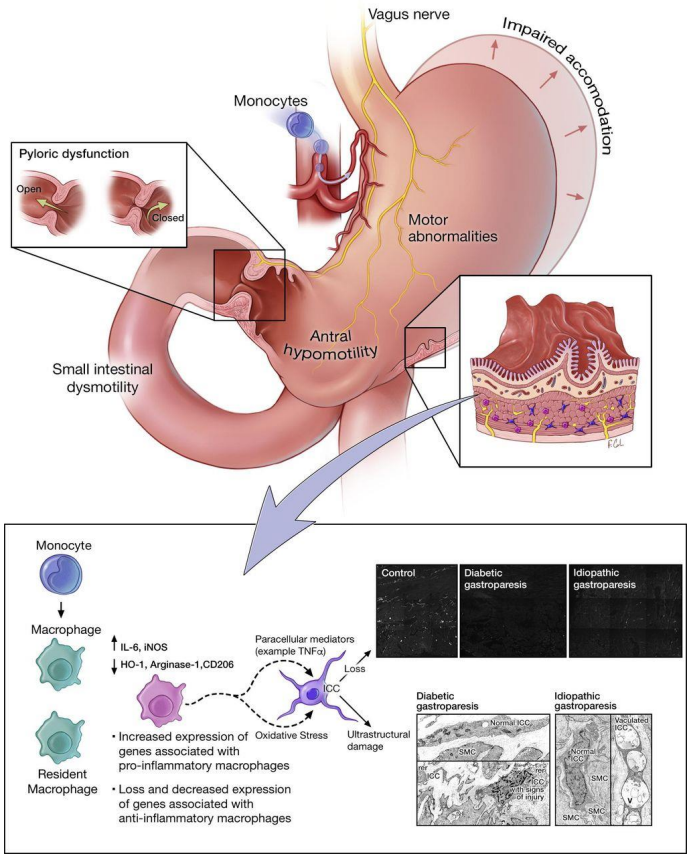

Figure 6 Pathophysiological changes in gastroparesis. Impaired accommodation of the proximal stomach, antral hypomotility and pyloric dysfunction are all physiological changes commonly seen in diabetic gastroparesis (DG). Loss or injury to Interstitial cells of Cajal (ICCs) is common in DG and is linked to macrophage activation in human and animal studies. Immune-mediated mechanisms probably play a critical role in the pathogenesis of DG. Courtesy of Grover et al, Gut 2019. Printed with permission (151)

The ENS is connected to the central nervous system, and sends signals via sensory neurons of stretch, pain, fullness, and nausea. Loss of enteric neurons, as well as loss of ICCs and smooth muscle disturbances, have all been described in human and animal studies of diabetic gastroparesis. The main mechanism of neuropathy is hypothesized to be via hyperglycemia. Enteric neurons are sensitive to glucose, and hyperglycemia can induce apoptotic pathways. Furthermore, decreased neuronal growth factors, free fatty acids in the circulation as well as oxidative stress are all contributing factors to the neuronal damage. (145, 149)

The ICCs are known as the pacemaker cells of the stomach and have important functions in the neurotransmission between smooth muscle cells in the GI wall, efferents from the CNS and enteric motor neurons (145). Depletion of ICCs in the stomach is strongly associated with gastroparesis (150, 151). Injury of ICCs is not only mediated through hyperglycemia, but probably through immune dysregulation driven by macrophages and oxidative stress (Fig. 6, courtesy of Grover et al). Furthermore, impaired insulin and insulin growth factor production (IGF-1) can cause damage to ICCs and myenteric cholinergic neurons (152).

Small bowel dysmotility

In a study using Wireless Motility Capsule (WMC), Barshop and co-workers found a negative correlation between duodenal motility and upper gastrointestinal symptoms (153). This suggests that the duodenum is involved in symptom generation in diabetic gastroparesis as well, as previously mentioned for functional dyspepsia. Cogliandro *et al.* found that enteric dysmotility was a more common finding in patients with classical gastroparesis symptoms than delayed gastric emptying, and that enteric dysmotility correlated with the degree of upper GI symptoms (154). The WMC enables investigation of the otherwise inaccessible small bowels non-invasively and is a promising tool for future studies (150).

2.6 Gut-brain interactions

According to the Rome IV criteria of 2016, functional dyspepsia and irritable bowel syndrome are defined as "Disorders of gut-brain interactions" (155). *The Gut-brain axis* is the term defining the connections between the gastrointestinal tract, the myenteric plexus, and the central nervous system. This bidirectional model explains how psychosocial factors can affect gastric and intestinal function, and how factors in the gut can modulate sensory input.

Visceral hypersensitivity

Abdominal pain is a key symptom in IBS and functional dyspepsia, although routine examinations such as endoscopies show normal results. An important explanation for the reported pain is *visceral hypersensitivity,* where mechanical or chemical stimuli such as the regular stretching of the bowel wall during peristalsis is perceived as pain. The degree of visceral hypersensitivity is correlated to the GI symptom severity in both IBS and FD (108). The mechanisms of visceral hypersensitivity are complex, probably involving neurogenic, microbial, and immunological factors. There are evidence for a crosstalk between bacteria in the gut lumen and the nervous system leading to pain sensitization, and a disruption of communication between immune cells, neurons and non-neuronal cells can result in visceral hypersensitivity (156).

Psychological factors and emotions

Emotions such as anger, anxiety and stress can affect several aspects of gastric and intestinal function, resulting in increased acid secretion, delayed gastric emptying and antral motility and impaired accommodation (27, 157, 158). Furthermore, input from the brain can delay intestinal motility, decrease colonic transit, induce defecation, and give symptoms of diarrhoea. At the same time, intestinal inflammation, altered motility and tissue damage can affect the perception of pain (159), and result in altered mental function, including depression and anxiety. The anterior cingulate cortex is a brain region involved in emotional arousal and salience network and is vulnerable for changes in the gut (155). Larsson *et al.* demonstrated that not all patients with IBS reacted strongly to rectal balloon distention. They found that the patients could be divided into two groups (normo-sensitive and hypersensitive) based

on their response to this stimuli, and found differences in brain response between the two groups (160).

Anxiety and depression are frequent conditions in the general population and are recognized comorbidities for many patients with functional gastrointestinal diseases. For this reason, functional GI diseases has by some authors been regarded as psychosomatic disorders. However, more recent knowledge has challenged this view. Results from separate prospective studies points toward a bidirectional trend; GI symptoms arose first and mood disorders later in at least half of the cases (161, 162). This illustrates the complexity of the connections between the mind and the gut; in some cases the anxiety or depression might have been the primary symptom, and should be emphasized in treatment, while other patients had gastrointestinal symptoms at first, and anxiety/depression developed subsequently. This is supported in a review by Koloski, Holtmann and Talley. They argue that some patients have primarily psychological disorders resulting in secondary FGID problems ("brain-gut"), while another subset of patients have primarily gastrointestinal problems and secondary psychological symptoms ("gut-brain") (70).

Gut-Brain interactions in diabetes

Interactions between the gastrointestinal tract and its microbes, and the brain, is possibly of importance in many conditions, not only the functional gastrointestinal disorders. There are evidence of changes of functional and structural brain patterns in diabetes, in particular in the insula region (163). Two meta-analyses demonstrated that depression was more common in patients with type 2 diabetes compared to the general population (164). Results from the Spanish ZARADEMP project suggested a bidirectionality in the association between diabetes and depression. In a 5 year prospective study, Campayo *et al.* found an 65% increased risk of type 2 diabetes in patients with clinically significant depression (165). Suffering from type 2 diabetes was associated with an increased risk of prevalent depression and incident depression (166).

Diabetes is associated with changes in the microbiome, and with affection of microbiome-gut-brain interactions (167, 168). The gut microbiota can influence glucose metabolism, and changes in the microbial composition are associated with obesity, metabolic syndrome, prediabetes and type 2 diabetes (169-171). Diabetes may exhibit low-grade inflammation, in which damaged and necrotic adipocytes release tumour necrosis factor alpha (172, 173). This is still a field of research, where much remains unknown, but there seems to be a link between the observed inflammation and the gut microbiota (172).

The role of the vagus nerve in IBS, functional dyspepsia and diabetic gastroparesis

The vagus nerve plays a pivotal role in the communication between the gastrointestinal tract and the brain, and the communication is bidirectional. The vagus nerve is composed of 80% afferent and 20% efferent nerve fibres and is involved in motility (i.e. gastric accommodation and gastric emptying), sensation, and is even involved in dampening peripheral inflammation via a cholinergic anti-inflammatory pathway. The vagus nerve is affected in both FD, IBS, and diabetic gastroparesis. Autonomic dysfunction is a well-known mechanism in diabetic gastroparesis, influencing gut transit time and gastrointestinal motility (45, 174). The functional gastrointestinal disorders are associated with autonomic disturbances of the vagus nerve (43, 97, 175, 176), with high sympathetic activation and low parasympathetic activation (177).

Afferent fibres of the vagus nerve relay sensory information from the gastrointestinal tract, and are stimulated by mechanical, osmotic, and chemical stimuli. The vagal fibres from the stomach are stimulated by stretch and tension (178), and the signals are closely connected to the sensation of fullness and satiation. In a murine model, Li and co-workers found that chronic stress increased the response to distention in tension-sensitive gastric vagal afferent fibres, resulting in a lower food intake in exposed rats (179). Their findings implied that gastric vagal afferents were of particular importance for the symptoms of early satiety and postprandial fullness as reported in functional dyspepsia. Pellisier *et al.* found that patients with IBS had a

disrupted relationship between vagal tone and cortisol levels, and further that patients with low vagal tone had high levels of norepinephrine and epinephrine in plasma. This is a sign of activation of the sympathetic nervous system and a stress response. They suggested that hypo-activation of the prefrontal cortex and hyperactivity of the amygdala can explain the vulnerability for stress commonly observed in IBS patients (180, 181). Frøkjær and co-workers investigated the role of the vagus nerve further by stimulating the auricular branch of the vagus nerve in healthy subjects by transcutaneous electrical vagal nerve stimulation and deep slow breathing. They found that vagal modulation resulted in enhanced gastric motility and reduced somatic sensitivity (182).

Diabetic gastroparesis is associated with visceral *hypo*sensitivity as well as *hyper*sensitivity (183). In a study on 20 diabetes patients with symptoms of gastroparesis Søfteland and co-workers examined rectal sensitivity and compared the results to gastric emptying. They found that diabetes was associated with reduced rectal sensitivity compared to healthy controls (184). In a meta-analysis and systematic review from 2019, Vijayvargiya and co-workers found that upper gastrointestinal symptoms correlated well to gastric emptying tests. However, the associations were weaker when only patients with diabetes were included (95).

The literature review was concluded at March 10th, 2021.

3. Aims and hypothesis

3.1 Hypotheses:

Main hypothesis: There are similarities in gastric motility and sensitivity in functional dyspepsia, irritable bowel syndrome and diabetic gastroparesis.

H1: Patients with diabetic gastroparesis and functional dyspepsia are similar regarding gastric accommodation and sensitivity.
H2: Patients with IBS have disturbed gastric motility and visceral hypersensitivity of the upper GI tract.
H3: Patients with overlapping IBS and FD differ from patients with only IBS or FD, indicating affection throughout the gastrointestinal tract.
H4: The ultrasound meal accommodation test can identify patients with delayed gastric emptying.

3.2 Aims

The objective of this dissertation was to investigate the link between gastric motility disturbances such as delayed gastric emptying and impaired accommodation, and symptoms from the upper gastrointestinal tract.

Aim of paper 1: To investigate how the ultrasound meal accommodation test for dyspepsia can been used in the clinic, and to identify patient groups in need for further investigation.

Aim of paper 2: To elucidate gastric motility in IBS, and to compare UMAT results from IBS patients with patients with functional dyspepsia or overlapping IBS/FD.

Aim of paper 3: To explore the relationship between the proximal and distal stomach in patients with diabetic gastroparesis, and to investigate the association between gastric motility parameters and upper GI symptoms.

4. Materials and Methods

4.1 Study population

4.1.1 Healthy controls

Healthy controls (HC) were recruited among colleagues using e-mail and bulletin boards at Haukeland University Hospital, and among nursing students at the University College of Western Norway. All participants received written and oral information about the study and signed consent before inclusion. All data about the participants have been stored anonymously at a secure server and in locked cabinets only available for the PhD student. Inclusion and exclusion criteria are presented in Table 4.

Table 4: Inclusion and exclusion criteria for the healthy controls study.

Inclusion criteria	Exclusion criteria
• Age 16-65 years • Healthy individuals • BMI <30 • Speak and read Norwegian language	• Use of medication known to affect gastric motility • Functional GI disorders, diabetes, or chronic GI diseases • Previous abdominal surgery, except section or appendectomy • Chronic fatigue syndrome (CFS/ME) • Allergies to ingredients in the meat soup • Confirmed pregnancy

As most patients with functional gastrointestinal disorders are women, we included more women (66%) than men.

4.1.2 Participants in Papers 1 and 2

The Ultrasound Meal Accommodation test (UMAT) has been used clinically at Haukeland University Hospital for 25 years. Patient reports from the last 15 years (1999-2014) were identified (n=509). As reported in paper 1, in 8 cases it was not possible to complete the UMAT procedure for different reasons, and 75 patients were

not able to complete the 500 mL drink test. Information was collected from questionnaires, as well as the electronic patient records, and recorded systematically in an anonymous database (FileMaker Pro). Findings from this database is described in detail in Paper 1.

Patients with irritable bowel syndrome (n=88), functional dyspepsia (n=94) or overlapping IBS and FD (n=66) were included in the data material for paper 2. Figure 7 shows an overview.

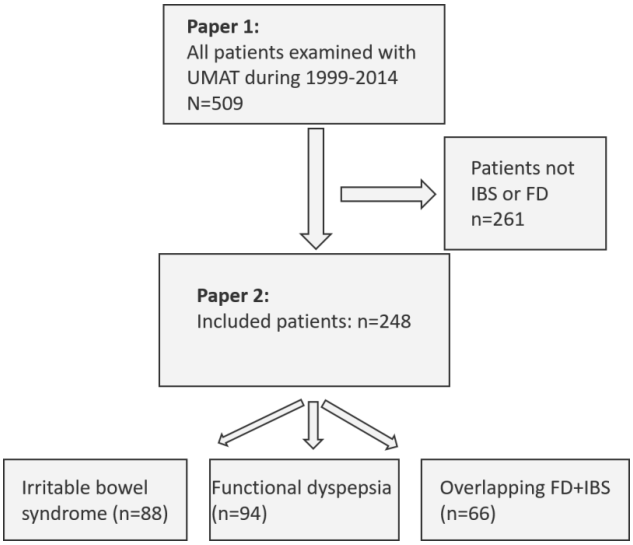

Figure 7: Overview of the included patients in paper 1 and 2, from the ultrasound meal accommodation test database.

4.1.3 DIAGAS – Diabetic gastroparesis

Patients referred to the Department of Medicine at Haukeland University Hospital with symptoms of gastroparesis were included in a prospective study (DIAGAS study). They were examined with scintigraphy, Wireless motility capsule and the ultrasound meal accommodation test, as well as clinical examination, blood samples and autonomic tests. Patients with diabetes as well as other etiologies were included.

In Paper 3, we have included all patients with diabetes who were examined with the UMAT (n=58). Due to practical challenges, not all patients were able to do this. In Figure 8 we present the DIAGAS study.

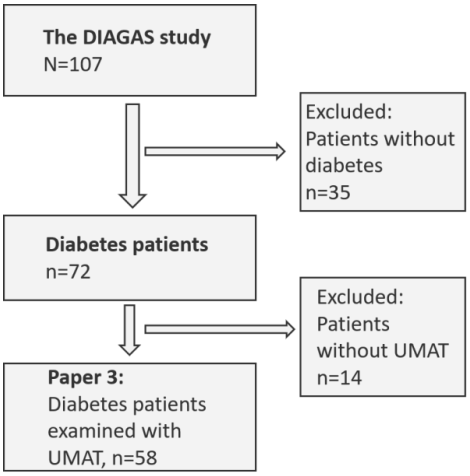

Figure 8: Overview of the patients in the DIAGAS study, and the included patients in paper 3.

4.2 The ultrasound meal accommodation test

The protocol for the ultrasound meal accommodation test (UMAT) used in this thesis has been described in Gilja *et al.* (185). Using a low-caloric commercial meat soup (Toro klar kjøttsuppe, Orkla, Norway. Contents: 84 kJ; 1.8 g protein, 1.1 g carbohydrate, 0.9 g bovine fat) as a test meal, the proximal and distal stomach can be visualized by ultrasound.

We have used different labels for the proximal measurements in paper 2 and paper 3. For clarity, “Oblique frontal diameter” in paper 2 is the same measurement as “Proximal diameter” in paper 3, and “Sagittal area” in paper 2 is the same measurement as “Proximal area” in paper 3.

For further details about the ultrasound meal accommodation test we refer to the included papers.

4.3 Gastric emptying scintigraphy

The patients included in study 3 were examined with gastric emptying scintigraphy the day after the ultrasound meal accommodation test. Thus, gastric emptying rate was not known to the examiner at the time of the ultrasound test.

The protocol for gastric emptying scintigraphy is described in paper 3 and by Sangnes *et al* (186). A gastric content retention >10% after 4h was considered pathological, and was used to define gastroparesis in our study (187).

4.4 Questionnaires

4.4.1 Diagnostic questionnaires

In paper 1, we present results from the Rome II and Rome III questionnaires, translated to Norwegian by Vandvik (188) and Lied, respectively. More details about the Rome criteria during the study period are presented in the Background section of this thesis.

4.4.2 Psychometric questionnaires

Traits of neuroticism were measured using the 12 item questionnaire from Eysenck (Eysenck's Personality Questionnaire-neuroticism (EPQ-N); Revised, Short form) (189). Gastrointestinal specific anxiety was measured with the Visceral Sensitivity Index (VSI), a questionnaire proven to be useful in populations with FGIDs (190, 191).

4.4.3 Symptom registration and symptom load

To evaluate symptom severity of IBS-related symptoms, we used the IBS Symptom severity Score (IBS-SSS). The maximum possible score is 500, and values <75 are

considered normal. Cases scoring 75-150 are considered mild, 150-300 moderate, and >300 severe (192).

Visual analogue scales (VAS) has proven valuable to record nausea and is recognized as a good method of evaluating symptoms in diagnoses such as gastroparesis (193). In all three papers of this project, we have measured nausea, epigastric pain, fullness/bloating, satiety, and upper abdominal discomfort on a VAS ranging from 0-100 mm. The measurements have been reported in a fasting state, and simultaneously with all ultrasound measurements; at 1, 10 and 20 minutes postprandially. In paper 1, we have analyzed fasting symptoms as well as the change in symptoms after drinking soup. In paper 2, we have compared fasting symptoms between groups, as well as immediate postprandial symptoms between groups, and investigated the correlations between symptoms and ultrasound measurements as well as psychometric scores. We did not have complete registrations on symptoms 10 and 20 minutes postprandially, as only one of the two physicians performing the test asked for symptom registration at these time points. In paper 3, we have included symptoms in a fasting state as well as at 1, 10 and 20 minutes and incorporated these measures to a linear mixed effects model together with ultrasound measurements and group belonging.

4.5 Methodological considerations and study limitations

4.5.1 Study design

Studies 1 and 2 were designed as retrospective cross-sectional observation studies on a clinical material. Ultrasound measurements and symptom registration, as well as some questionnaires, were systematically collected throughout the period of registration, and some information was registered systematically in the patient records of all patients. Examples are the final diagnosis after the UMAT in cases where a conclusion was drawn, or information of relevant co-morbidity such as diabetes or Parkinson's disease. Information about anxiety and depression was often reported, but this information is less certain. Unfortunately, we do not have

information about subclassification of the IBS or functional dyspepsia diagnoses (constipation/diarrhoea dominated IBS, postprandial distress syndrome or epigastric pain syndrome) on all patients. This information would certainly be useful to have in our analyses.

Study 3 was designed as a prospective, cross-sectional open observational study. The ultrasound was performed before the scintigraphy procedure, and thus the physicians were blinded for the outcome of the scintigraphy results (gastroparesis/not gastroparesis).

Causality and associations
A cross-sectional observation study does not provide evidence for *causality* or *risk*, but it allows us to investigate associations and correlations. The findings must however always be interpreted with care, as the real association may be to a third factor that may not be identified (confounding factor) (194, 195).

4.5.2 Study populations

The study population from studies 1 and 2 were patients referred to a tertiary specialist clinic because of abdominal complaints. As presented in paper 1, 51% of the patients were referred as second opinion patients from other hospitals or specialists, and 40% came from other counties than Hordaland county where Haukeland University Hospital is situated. This implicates that the patient population may not be representative for the average IBS or FD patient in society, but rather the patients we normally see at a specialist outpatient clinic at a University clinic. The retrospective design reduces however the selection bias often observed in prospective clinical studies, as almost all patients examined with this test were included in the study. Groups that may not be well represented are patients with language difficulties, who could not answer the Norwegian questionnaires, or patients with intellectual disability. We recognize that is important to study these groups as well, and it is unfortunate that they are not represented in our study. Furthermore, we have only investigated individuals aged >18 years.

In study 3, all patients referred to a clinical examination with question of diabetic gastroparesis were prospectively included. They were given the opportunity to receive the same medical care and examinations without participating in the study, but all chose to be included. This design limits selection bias. The patients are not representative for the general population of diabetes patients, but we believe they are representative for patients with suspected gastroparesis.

4.5.3 Ultrasound

Ultrasound is user-dependent, but the reproducibility of the measurements included in the ultrasound meal accommodation test has been investigated in several studies. Hveem *et al.* evaluated the intraobserver and interobserver variance of antral area measurements and found an overall coefficient of variance 6% (196). Furthermore, Gilja *et al.* studied the variance of ultrasound measurements of the proximal stomach (39) and found correlations of 0.95 and 0.94 for proximal area and proximal diameter between two examiners.

The UMAT is a well-established examination at Haukeland University Hospital, and the examinations included in Papers 1 and 2 were performed by two gastroenterologists with long experience in abdominal ultrasound (OHG and TH). Both doctors did their PhD on gastric ultrasound years before 1999, when the first patient was included in the retrospective study. In difficult or unclear cases, they consulted with each other. The ultrasound examinations in paper 3 were performed by TH and the PhD candidate (EKS). EKS had at the time 2-4 years of training in the procedure, having performed over 50 UMAT before the healthy controls study and DIAGAS study. She consulted with TH or OHG for most examinations.

Comparing ultrasound measurements to scintigraphy results

In paper 3, we have investigated the results of the ultrasound meal accommodation test to results from gastric emptying scintigraphy (GES). In GES we evaluate gastric

emptying by a solid meal and have used the gold standard measurement of gastric retention at 4h (%). As demonstrated in Figure 9, gastric emptying is markedly different for a low-calorie drink compared to a calorie-containing solid meal (12) and doing head-to-head comparisons would not be meaningful. We wanted to investigate if patients with gastroparesis differed from the ones with normal gastric emptying, and thus used the 4h scintigraphy value as a reference value.

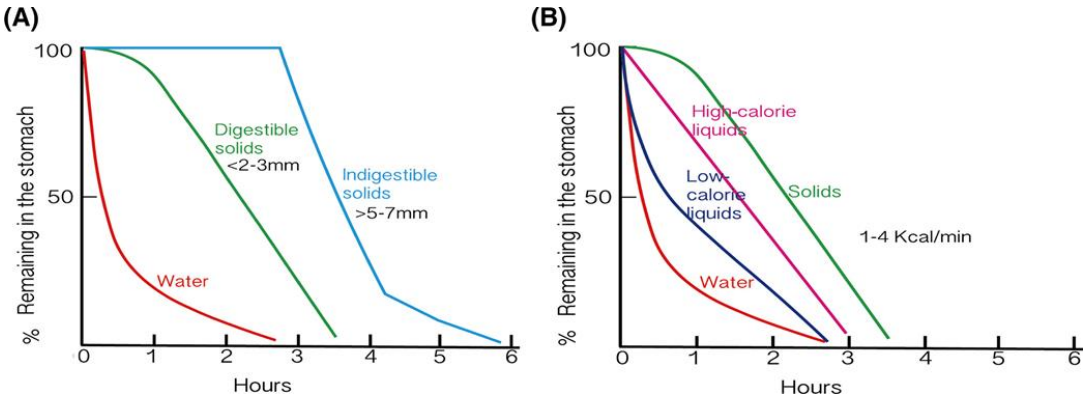

Figure 9: The physical characteristic and caloric density of food affect the gastric emptying rate. (A) Gastric emptying of food of different physical characteristics (B) The caloric density of a liquid meal is an important factor in gastric emptying. The low-calorie soup used in the UMAT protocol is estimated to empty similarly to the "Low-calorie liquids" in graph B. Printed with permission from John Wiley and Sons (12).

4.6 Statistical methods

4.6.1 Paper 1

The variables included in paper 1 were generally not normally distributed, and we used non-parametric tests to analyse differences between groups. Incidence between groups were compared using Chi-square.

4.6.2 Paper 2

This paper was written later than Paper 1, and because of new knowledge (for the candidate) after several courses in medical statistics, other considerations were done concerning the choice of tests. Due to the Central Limit Theorem, one can assume

normality of the number of observations is high enough. This was the case in study 2, and we chose to analyse the data using parametric tests. To analyse two continuous variables in independent groups, we used Student's t-test. When comparing more than two groups, we used one-way ANOVA or Welch's ANOVA depending on results from Levene's test. In the cases where the variance was different between the groups, we used Welch's ANOVA. The sample size was different between healthy controls and patients, and for this reason we used the Games-Howell *post-hoc* test.

Association were analysed using Linear regression, Pearson's correlation, and logistic regression, and we presented the results with odds ratio (OR) with 95% confidence intervals (CI).

4.6.3 Paper 3

In the work with Paper 3, we observed that the ultrasound measurements of patients with delayed gastric emptying followed a different pattern compared to patients with normal gastric emptying. To further investigate this phenomenon, we contacted a statistician at our hospital (Jürg Assmus), who suggested using a Linear Mixed Effects (LME) model to investigate how the ultrasound measurements of the stomach was influenced by time, group belonging (based on gastric emptying) and an intercept. Furthermore, we applied an LME model to study the effect on symptoms. An advantage of the LME model is that it enables us to study the effect of time on our measurements. The model adjusts for a random distribution in the population (intercept). Furthermore, the ultrasound and symptom measurements were not independent of each other. Independent observations are required in tests such as one-way ANOVA or regular regression analyses.

4.7 Ethical considerations and approvals

The retrospective study in paper 1 and 2 was defined as a quality control project and did not need approval from the Regional Ethical Committee. The study was approved by the Data Protection Official at Haukeland University Hospital (2014/20478). The healthy controls were prospectively included in a project approved by the Regional Ethical Committee of South-Eastern Norway (2014/222-20).

The prospective DIAGAS study was approved by the Western Norway Regional Ethical Committee (REK 2015/58).

All data were anonymously stored in secure servers according to guidelines. Participants in Study 3 and healthy controls signed informed consent and were able to withdraw consent at any time up to publication. Studies were performed in accordance with the Helsinki declaration.

5. Results and summary of the papers

5.1 Paper 1

This paper provides an overview of the 509 patients examined with the Ultrasound Meal Accommodation test (UMAT) during 1999-2014. We found that 49% of the referred patients were diagnosed with functional dyspepsia (FD) and/or irritable bowel syndrome (IBS). Patients with FD reported a marked increase in symptoms induced by the 500 mL meal. Patients with overlapping IBS and FD reported higher increase in upper abdominal discomfort. In FD patients, 36 % were found to have impaired accommodation, 31% had delayed gastric emptying and 20% had visceral hypersensitivity. Patients with diabetes in this material differed from FD patients with lower symptom increase after soup intake.

5.2 Paper 2

In this paper, we included the 248 patients with IBS and/or FD from the material from paper 1. We prospectively recruited 30 healthy controls to compare ultrasound measurements and symptoms. We found that patients in all groups reported higher symptoms of nausea, discomfort, epigastric pain, and fullness/bloating in both fasting and postprandial state compared to healthy controls. Functional dyspepsia patients had lower proximal stomach measurements, a sign of impaired accommodation, but patients with IBS had normal accommodation. Both IBS and FD patients had enlarged antral measurements in a fasting state.

Patients who did not complete the 500 mL meal were more likely to be female (OR 5.14 (95% CI: 1.20, 22.40)) and to be diagnosed with functional dyspepsia (OR 3.67(95% CI: 1.29, 10.41)).

Nausea was not correlated to neuroticism or gastro-specific anxiety (VSI) and was highest in patients with functional dyspepsia.

5.3 Paper 3

In this paper, we examined 58 patients with diabetes and symptoms of gastroparesis with gastric emptying scintigraphy of a solid meal, and ultrasound of the proximal and distal stomach after a liquid meal. By using a linear mixed effects model we found that gastroparesis patients (diagnosed by scintigraphy) had a slower decrease in proximal stomach size during 20 minutes after the liquid meal compared to healthy controls ($P<0.01$), and proximal stomach size at 20 minutes was correlated to scintigraphy ($r=0.510$, $P=0.001$). Furthermore, the gastroparesis patients had over twice as large antral area in a fasting state compared to healthy controls, and higher postprandial measurements of the antrum. The antral area was modestly associated with results of the scintigraphy ($r=0.329$, $P=0.013$). Patients both with and without gastroparesis had impaired accommodation after a liquid meal. The patients in both groups reported higher levels of upper GI symptoms in a fasting and postprandial state compared to healthy controls. There was no difference in symptom load between the patient groups.

6. Discussion

Our primary hypothesis was that similarities in gastric motility and sensitivity in FD, IBS, and diabetic gastroparesis exist. To investigate this hypothesis, we evaluated the results of the ultrasound meal accommodation test in 248 patients with IBS and/or FD, and in 58 patients with diabetes and symptoms of gastroparesis.

6.1.1 Gastric emptying

Delayed gastric emptying is a fundamental requirement for the gastroparesis-diagnosis, and although the gold standard is scintigraphy, the antral area as measured by ultrasound demonstrated good agreement with gastric volume and emptying (54).

In paper 3, we found that patients with gastroparesis had significantly larger antral area both fasting and postprandially, and we found a modest correlation between scintigraphy measurements 4 h after a solid meal and fasting antral area. Patients with functional dyspepsia and/or irritable bowel syndrome exhibited enlarged antral area in fasting state compared to healthy controls (Paper 2), but the antral measurements were not as large as in the gastroparesis-group. It is well-known that some patients with functional dyspepsia have delayed gastric emptying (197). Furthermore, irritable bowel syndrome is associated with delayed gastric emptying (198-200), indicating a pan-enteric motility disturbance in a subgroup of patients. To our knowledge, not many reports have been published on gastric motility in the IBS+FD group. Futagami *et al.* found delayed gastric emptying in the IBS+FD group compared to healthy controls, and found that the gastric emptying in this group was similar to findings from the other FGID groups investigated (201). This is well in accordance with our findings.

A cross-sectional area of the antrum is considered the best choice for ultrasonographic assessment of gastric emptying. In paper 3, we found a weaker association between antral area and scintigraphy than we had expected. However, surprisingly we found stronger correlation between proximal ultrasound

measurements at 20 min and scintigraphy. Furthermore, the results from the linear mixed effects model showed a slower decrease of the proximal stomach size in gastroparesis patients. Lately, other groups have studied the role of the proximal stomach in gastric emptying. Orthey *et al.* demonstrated that an enhanced gastric emptying scintigraphy protocol could be used to assess the gastric emptying rate of the proximal stomach in healthy subjects (202). Edholm *et al.* used scintigraphy to study gastric emptying, and studied the effects of incretin hormones on the proximal and distal part of the stomach during gastric emptying (203). This supports our ultrasound results indicating that the proximal stomach is of importance in the gastric emptying process in diabetic gastroparesis.

6.1.2 Accommodation of the proximal stomach

We found that patients with functional dyspepsia and diabetic gastroparesis had lower measurements on ultrasound of the proximal stomach at 1 and 10 minutes postprandially compared to healthy controls. This implies impaired accommodation, as demonstrated by Gilja *et al* on a population of functional dyspepsia patients, and Undeland *et al.* on a population of diabetes patients (39-41, 45). Thus, our findings are well in agreement with previous research. Impaired accommodation is a common finding in studies of functional dyspepsia as well as diabetic gastroparesis (183, 204).

Furthermore, we investigated the gastric accommodation in patients with irritable bowel syndrome and found that the postprandial proximal stomach in IBS patients, and in patients with overlapping IBS and FD, was not different from healthy controls. This indicates normal gastric accommodation in these groups. Gastric accommodation in patients with IBS has, to our knowledge, not been studied. In one study by Masny *et al.* on 20 patients with IBS and 20 healthy controls, the effects of an intragastric infusion of fructans vs glucose was assessed with manometry. They found no difference in the gastric accommodation between healthy and IBS (205). This is in keeping with our results from paper 2. Accordingly, our finding shows that patients with IBS are different from FD with respect to gastric accommodation.

6.1.3 Relationship between symptoms and motility, and visceral hypersensitivity

In this thesis, we found that patients with diabetic gastroparesis, functional dyspepsia and irritable bowel syndrome all reported higher postprandial upper GI symptoms compared to healthy controls. We have found some weak correlations between ultrasound measurements and symptoms, but no single mechanism or measurement can explain all findings. However, this was as expected. A common denominator for these conditions is that they are multifactorial in origin.

In paper 3, we found a negative association between epigastric pain/discomfort and the ultrasound measurements in the non-gastroparesis group. The association to the proximal stomach implies a relationship between delayed impaired accommodation and pain/discomfort. In the gastroparesis group, we found no associations between symptoms and ultrasound measurements. A possible explanation may be that some patients with gastroparesis develop hyposensitivity, causing a large variance in the reported symptoms. This is supported by studies by Søfteland and Brock who found that diabetes patients with severe gastrointestinal symptoms had lower sensitivity to painful stimuli (184, 206).

In paper 2, we found only a weak correlation between postprandial nausea and proximal diameter 20 min after the meal, in patients with IBS and/or FD. Our findings suggest that although impaired accommodation and antral distention are common findings in FD and IBS, they do not explain all the patients' symptoms. Possibly, visceral hypersensitivity is a more important factor for postprandial symptoms in these groups. This is particularly evident in the overlap group of IBS+FD. In this group, we found normal accommodation, but higher symptom scores compared to the other groups. We believe that this group is of particular interest for studying visceral hypersensitivity in later studies. This is in agreement with previous findings from several different groups. Choi *et al.* analyzed symptoms and overlapping diagnoses in a Korean out-patient Gastroenterology clinic, and found that IBS+FD patients had more severe symptoms and higher depression scores compared

to patients with only one FGID (207). In a study on FGID patients from an out-patient clinic in Australia, Von Wulffen *et al.* found that the IBS+FD patients reported higher symptom load compared to other groups (208).

The patients with IBS reported higher levels of nausea, epigastric pain and discomfort compared to healthy controls both fasting and postprandially. This observation is consistent with findings from other groups (198, 199). Slightly delayed gastric emptying and normal accommodation and marked upper GI symptom load in this patient group indicates that visceral hypersensitivity may be an important contributor to this patient group's symptoms. A strong association between GI symptoms and visceral hypersensitivity in a multicenter study on FD and IBS (108) strengthens this hypothesis.

As both gastric emptying and accommodation are depending on stimuli from efferent nerve fibers of the vagus nerve (209, 210), damage to or dysfunction of the vagus nerve is a possible explanation of both dysmotility and altered sensation in diabetic gastroparesis and functional gastrointestinal disorders.

6.1.4 Strengths and limitations

One of the main strength of this work is the large number of patients included, particularly in papers 1 and 2. Furthermore, the patients were included consecutively from the ordinary outpatient-clinic at our hospital and not specifically recruited to a clinical study, reducing recruitment bias. We believe the patients included in the studies are representative for the patients we meet on a daily basis at our University clinic.

Limitations are discussed in each paper, but worth mentioning is that the healthy controls group was not age-matched for the diabetes patients. Furthermore, we lacked consistent information about subtype of IBS and FD. Papers 1 and 2 were based on a retrospective clinical material. The use of different questionnaires and diagnostic criteria changed over the years, resulting in missing data. And finally, in paper 3, we

compared gastric emptying of a solid meal to a low-caloric liquid meal, as discussed in section 4.5.3. The results should therefore be interpreted.

7. Conclusion

We have demonstrated that functional dyspepsia, irritable bowel syndrome and diabetic gastroparesis are conditions with many overlapping symptoms. A hallmark symptom in both FD and gastroparesis is postprandial fullness and epigastric discomfort, and we have shown that nausea is very common in all three conditions. We found that gastric motor function in the three conditions have many similarities. First, we found impaired accommodation in both functional dyspepsia and diabetic gastroparesis, likely because of affection of vagal efferent fibers. Second, we found that the antrum was enlarged in diabetic gastroparesis, as well as in IBS and FD– although less pronounced. Third, we found that the proximal stomach in diabetic gastroparesis had a reduced gastric emptying rate. This illustrates the importance of assessing both proximal and distal part of the stomach when examining patients with suspected gastroparesis.

The gastric motor function was only weakly correlated to upper GI symptoms in functional dyspepsia and IBS, and visceral hypersensitivity may explain some of the symptoms these patients report.

8. Future perspectives

8.1 Clinical implications

During the work with this thesis, we have established normal values for the ultrasound meal accommodation test. This may be of value for everyday clinical work and will make it easier to implement the procedure in other clinics. We have shown that symptoms alone cannot discern between gastroparesis or no gastroparesis, but an enlarged antral area on ultrasound is a strong indication for further work-up.

8.2 Implications for further research

It is evident that impaired accommodation and delayed gastric emptying cannot explain all symptoms reported by patients with diabetic gastroparesis and functional dyspepsia. However, in recent years, several studies have found evidence for a pivotal role for the duodenum, as well as the gut microbiota. We suggest investigating this further in large studies with different modalities. Heterogeneous conditions with multifactorial genesis call for advanced computational analysis, such as machine learning models. Gastrointestinal and extraintestinal symptoms, motility parameters, psychological factors, microbiota composition and short chain fatty acids, as well as measures of brain activity should all be analyzed together in the search for answers for patients with complex functional disorders.

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