# Diabetic gastroenteropathy examined with wireless motility capsule

Dag A. Sangnes

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2022

UNIVERSITY OF BERGEN

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Date of defense: 11.03.2022

Year: 2022

Title: Diabetic gastroenteropathy examined with wireless motility capsule

Name: Dag A. Sangnes

Print: Skipnes Kommunikasjon / University of Bergen

## Scientific environment

The completion of the doctoral degree and publication of the dissertation and the three papers was supported by the University of Bergen.


The study was performed at the Department of Medicine and Centre for Nuclear Medicine and PET, Department of Radiology, Haukeland University Hospital, Bergen, Norway.


The study has been performed with support and collaboration from the National Centre for Functional Gastrointestinal Disorders, and the National Centre for Ultrasound in Gastroenterology, Haukeland University Hospital.


The study was supported by a PhD Scholarship grant from the Western Norway Regional Health Authority.

# Acknowledgements

How you end up buried deep inside an obscure research field, is often coincidental. As a young doctor, I was fortunate to get a position at the Section of gastroenterology and invited into the pancreas research group. One of the members was Eirik Søfteland, an endocrinologist and soon-to-be PhD with a peculiar interest in the association between diabetes and gastrointestinal dysfunction. Another was his main supervisor, Georg Dimcevski, a gastroenterologist with a background from Denmark, where the collaboration between gastroenterology and endocrinology had a much longer tradition than in Norway. The gastroenterologist also happened to be my boss – and that is how the study began.

When I now sit on the opposite end of the study, there are several good friends and colleagues I would like to thank. First, I want to thank my supervisors, Eirik, Georg, and Odd Helge Gilja. Over the years, you have trusted me with great responsibility, but also given me support whenever I have needed it. Even when you were busy commuting around Vestland County, performing endoscopic examinations down by the canal, or being on a flight to Africa, you have always provided quick and constructive feedback. You have taught me about the many facets of research, about the clinical complexity of diabetic gastroenteropathy, and not least the one thing I naively thought I mastered – how to write papers. I have always been fond of writing, at one time even pursuing a career as a journalist. When I proudly presented my first manuscript to you in the fall of 2014, I was therefore both surprised and a little insulted when I received the judgement: more than half of the text was superfluous. After swallowing my pride, I presented a revised version, and another, and yet another. Eventually, the manuscripts became shorter and more concise, the red markings became fewer – and I became a better writer. I thank you for our good friendship and all the help you have given me, and I look forward to our many future collaborations.

Georg, you have always had an open-door policy, where everyone were free to sit down in the leather couch, drink a cup of coffee and have a professional discussion –

or just a friendly chat. When Trond Engjom took over as head of the gastro section, he continued this policy, even though he was aware that there were three PhD students and aspiring gastroenterologists close by. Trond, you have provided me with much valuable tutorage for which I am very grateful. I am also grateful for being part of the Bergen Pancreatic Club, an inspiring, productive and very inclusive research group – where the regular Friday lunch meetings at Trond's office are one of the weekly highlights. All group members are highly appreciated friends and colleagues, but Ingrid Nordaas, a fellow PhD student, deserves special mention. Although being engaged in different projects, we have collaborated closely, and given each other much constructive criticism, which has improved both of our studies. I would also thank my other fellow PhD students at the Department of Medicine, Elisabeth Steinsvik and Eivind Rath, for providing me with much support and many pleasant conversations.

During the study period, I have had the great pleasure of collaborating with both the National Centre for Functional Gastrointestinal Disorders, and the National Centre for Ultrasound in Gastroenterology. Jan Gunnar Hatlebakk and Trygve Hausken have taught me a lot, and it is always a joy to cooperate with Birgitte Berentsen. I have also had the privilege to work with Mattis Bekkelund, Katarina Lundervold, and Hilde von Volkmann, who – amongst many things – have assisted me in analysing wireless motility capsule examinations. I would also like to thank Jakub Frey, who is both a study collaborator and my main supervisor in the clinic. Many other colleagues deserve mention, but I would like to highlight Renée Fjellanger who has always taken her time to answer all my clinical questions ever since we shared an office in 2014. This has been of invaluable help.

After conducting a clinical study, admitting patients weekly at a hospital ward, and performing multiple tests involving different hospital departments – and most things eventually worked out as intended – I have good reason to be grateful. Without the help from all my colleagues at the Department of Medicine and Centre for Nuclear Medicine and PET, completing this study would have been impossible. I would like to thank everyone involved in the study for your dedication, especially the nurses

responsible for initiating the wireless motility capsule examinations: Merete Favang, Inger-Lise Moe, Maj Cecilie Bachmann Eriksen, and Jorid Tufteland Rekdal. I would also like to thank Jostein Frid and Martin Biermann at the Centre for Nuclear Medicine and PET, Dag Olav Langeland at the gastroenterological ward, and Roy Cato Solheim at the endoscopy unit for good collaboration.

Finally, I would like to thank my family. To my parents, you have always supported me, even when I moved 450 km westwards to study – and decided to stay. I am also immensely grateful for my two beloved children, Sivert and Solveig. You are, by far, my greatest achievement. However, my deepest gratitude goes to Ida, my girlfriend for the last twenty years and wife for the last eleven. Thank you for being so kind, caring, funny, and knowledgeable – and thank you for being patient with me every time I had to work late in the scholarship period because I went cross-country skiing during the day.

# Abstract

## *Background*

Diabetic gastroenteropathy may affect all parts of the gastrointestinal tract. Despite being prevalent, knowledge is limited and treatment often generalised and unsatisfactory. To deliver personalised treatment, there is a need for improved diagnostics. In this study, we have investigated the role of the wireless motility capsule in the evaluation of gastroparesis, diarrhoea, and constipation, the three main manifestations of diabetic gastroenteropathy.

## *Methods*

We included 72 diabetes patients (49 women; 59 type 1 diabetes) with gastrointestinal symptoms. They were investigated with blood, urinary and faecal samples, questionnaires, autonomic function tests, and gastrointestinal motility and function tests, including wireless motility capsule and gastric emptying scintigraphy. During fasting and examinations, patients were kept on intravenous glucose-insulin infusion. We also investigated 26 healthy participants using wireless motility capsule.

## *Results*

In paper 1, we found that the wireless motility capsule had high diagnostic accuracy compared to scintigraphy for determining gastric emptying. In paper 2, we found that patients with diarrhoea had increased gastric emptying time, reduced colonic transit time, and altered gastrointestinal pH levels. In paper 3, we found no difference in transit times when comparing diabetes patients with and without constipation, but both diabetes groups had slower whole gut transit than healthy controls.

## *Conclusions*

The wireless motility capsule may have a role in the investigation of patients with suspected diabetic gastroenteropathy. It has high diagnostic accuracy for measuring gastric emptying and may identify clinically relevant alterations in gastrointestinal transit and pH levels. We recommend further validation of the capsule's pH and contractility measurements before they are used in routine examinations.

# Contents

# Abbreviations

ANOVA: one-way independent analysis of variance

ANS: autonomic nervous system

ECG: electrocardiogram

ENS: enteric nervous system

EPQ: Eysenck Personality Questionnaire

FDA: United States Food and Drug Administration

GLP-1: glucagon-like peptide-1

GCSI: Gastroparesis Cardinal Symptom Index

GSRS: Gastrointestinal Symptom Rating Scale

HADS: Hospital Anxiety and Depression Scale

HbA1c: glycosylated haemoglobin

ICC: interstitial cells of Cajal

LHBT: lactulose hydrogen breath test

MMC: migrating motor complex

MRI: magnetic resonance imaging

PAGI-SYM: Patient Assessment of Upper Gastrointestinal Symptom Severity Index

ROC: receiver operating characteristics

SIBO: small intestinal bacterial overgrowth

# List of papers

1. Sangnes, Dag A., Eirik Søfteland, Mattis Bekkelund, Jakub Frey, Martin Biermann, Odd Helge Gilja, and Georg Dimcevski. Wireless motility capsule compared with scintigraphy in the assessment of diabetic gastroparesis. *Neurogastroenterology and Motility*. 2020; 32(4): e13771. https://doi.org/10.1111/nmo.13771

2. Sangnes, Dag A., Georg Dimcevski, Jakub Frey, and Eirik Søfteland. Diabetic diarrhoea: a study on gastrointestinal motility, pH Levels and autonomic function. *Journal of Internal Medicine*. 2021; 290: 1206-1218. https://doi.org/10.1111/joim.13340

3. Sangnes, Dag A., Katarina Lundervold, Mattis Bekkelund, Hilde L. von Volkmann, Birgitte Berentsen, Odd Helge Gilja, Georg Dimcevski, and Eirik Søfteland. Gastrointestinal transit and contractility in diabetic constipation: a wireless motility capsule study on diabetes patients and healthy controls. *United European Gastroenterology Journal*. 2021; 1-10. https://doi.org/10.1002/ueg2.12169

# Preface

This study was originally intended to evaluate new diagnostic methods in the diagnosis of diabetic gastroparesis, the most well-known gastrointestinal diabetes complication. However, soon after getting to know some of the diabetes patients I have been so fortunate to meet during the last eight years, I discovered that most did not just present typical gastroparesis-symptoms like nausea and vomiting, bloating and post-prandial discomfort. In addition, they also had diarrhoea and constipation, both having a major negative impact on their quality of life. As a relatively inexperienced doctor, never-mind researcher, inside the field of gastrointestinal diabetes complications, this was a surprising revelation, since almost all recent research were concentrated on gastroparesis. Our group therefore decided to broaden the focus of the study: instead of just investigating suspected diabetic gastroparesis, we also attempted to delve into the seemingly long-forgotten intestinal manifestations of diabetic gastroenteropathy.

# 1. Introduction

Diabetic gastroenteropathy is a multiregional diabetes complication, potentially affecting all segments of the gastrointestinal tract. Although affecting a large percentage of diabetes patients, knowledge surrounding this condition is still limited, especially regarding its intestinal manifestations. Suffering from the lack of pathophysiological knowledge, treatment is often insufficient and largely follows the same stereotypical approach for all patients. In line with advancements inside other medical disciplines, there is a need for more personalised medicine. To reach this goal, however, there is a need for improved diagnostics.

The aim of this study is to evaluate the role of the wireless motility capsule (Figure 1) in the diagnostic investigation of diabetic gastroenteropathy. The wireless motility capsule measures pH, pressure and temperature throughout the whole gastrointestinal tract. In this study, we have focused on the three major manifestations of diabetic gastroenteropathy: gastroparesis, diarrhoea, and constipation.


***Figure 1:*** *Wireless motility capsule. Photo by Dag A. Sangnes. SmartPill® (Medtronic, Minneapolis, USA).*

## 1.1 Normal gastrointestinal anatomy and physiology

The gastrointestinal tract is a continuous hollow organ, where its separate compartments are responsible for different parts of the digestive process. In this brief review of normal gastrointestinal anatomy and physiology, I will concentrate on the stomach, small bowel and colon. Although being distinct compartments, they all share important features, including a common anatomical structure (Figure 2) [1–3]. In line with the theme of the dissertation, I will mainly focus on the different aspects of motility but will also add an introduction to gastrointestinal pH balance.

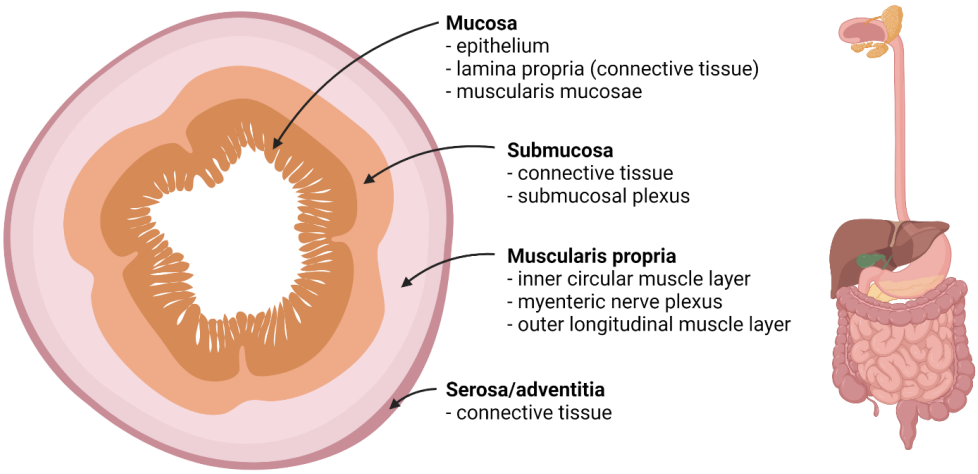



***Figure 2:*** *The gut wall is built up by four main layers: 1) Mucosa: surrounds the lumen and is composed by an epithelium, a connective tissue layer (lamina propria), and a thin layer of smooth muscle (muscularis mucosae). 2) Submucosa: mainly connective tissue, but also includes the submucosal nerve plexus. 3) Muscularis propria: an inner circular muscle layer and an outer longitudinal muscle layer. In-between lies the myenteric nerve plexus. The stomach has an additional oblique muscle layer, while the longitudinal layer in the colon is band-shaped (taenia coli). 4) An outer layer of connective tissue called serosa when covering the intraperitoneal compartments or adventitia when covering the retroperitoneal compartments [1–3].* *Created by Dag A. Sangnes using BioRender.com.*

### 1.1.1 Myoelectrical activity

#### *Slow wave activity*

Throughout the gastrointestinal tract, smooth muscle cells continuously display rhythmical electrical oscillations called slow waves. These are initiated by interstitial cells of Cajal (ICC) inside the nerve plexuses of the gut wall. ICCs are often called gastrointestinal pacemaker cells [4]. Another cell-type, platelet-derived growth factor receptor-α-positive cells, also transmit electrical signals [5]. Slow waves are variations in smooth muscle membrane potentials and are dependent on excitatory external stimuli like gut wall distention or neurohormonal impulses to elicit contractions [1,6].

### *Types of contractions*

Although their frequency varies depending on the location, types of contractions are similar in both the stomach and intestines: peristaltic contractions move the intraluminal content aborally, while mixing contractions segment and distribute the content along the intestinal mucosa. There is an overlap between the two, exemplified by the peristaltic contractions of the stomach's essential role in mixing the meal. Contractions may also be categorised as tonic or phasic. While both peristaltic and mixing contractions are phasic – rhythmical and of short duration – tonic contractions are continuous and long-lasting, like the contractions of the gastroesophageal or pyloric sphincters. Tonic contractions do not depend on slow-wave activity [7,8].

### *Migrating motor complexes*

During fasting state, the myoelectrical activity follows a cyclic pattern called the migrating motor complex (MMC). The MMC consists of three different phases, where phase I has no contractile activity, phase II has irregular contractions, and phase III is dominated by high-amplitude contractions. These appear at regular intervals of 90-120 minutes and migrate from the stomach towards the proximal ileum. They may also be initiated in the duodenum. Phase III MMCs transport undigested food from the stomach and small bowel towards the colon [9]. The MMC activity is interrupted by meals [10–13]. In the colon, high amplitude propagating contractions are believed to hold a similar role as the phase III MMCs. High amplitude propagating contractions correspond with colonic mass movements [6,14].

## 1.1.2 Neurohormonal regulation

Gut motility is regulated by neurohormonal mechanisms. The regulatory systems are closely integrated, for instance communicating through different reflexes. Some are transmitted locally in the gut, while others are mediated via the sympathetic and parasympathetic nervous system or involving the central nervous system.

### *Enteric nervous system*

The enteric nervous system (ENS) is the intrinsic nervous system of the gastrointestinal tract, where it is dispersed in a meshwork inside the submucosal and

myenteric plexus. ENS neurons are tightly linked to ICCs and modulate smooth muscle activity through the release of excitatory and inhibitory neurotransmitters. The ENS can control most gastrointestinal functions on its own but correspond closely with neurons from the autonomic nervous system (ANS). Some writers consider ENS as the third division of the ANS. In this dissertation I have chosen to refer to the ANS as a common term for the parasympathetic and sympathetic nervous system [6,8].

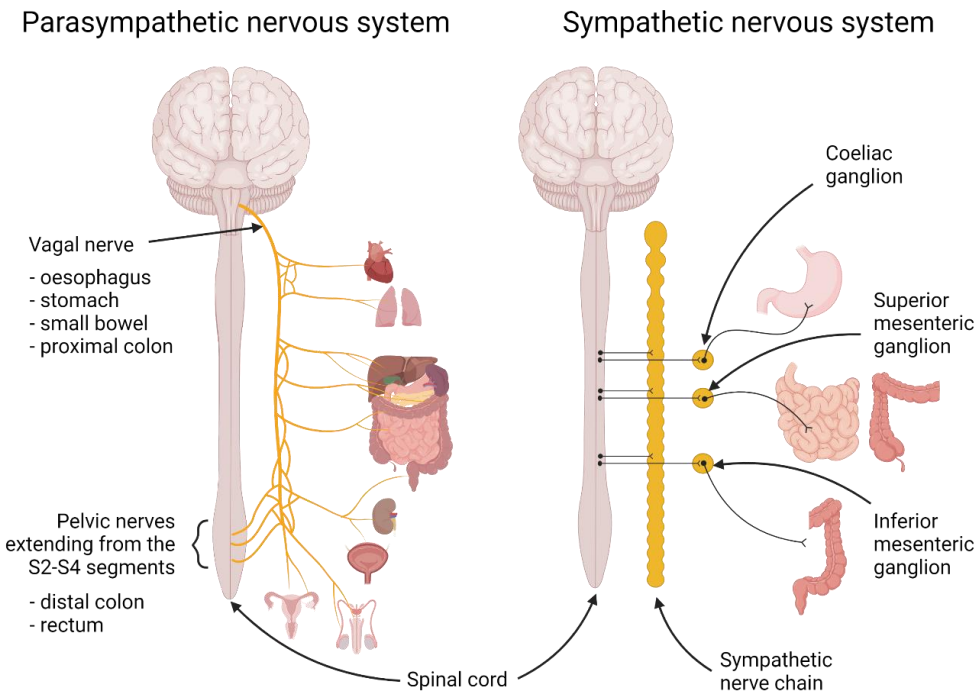



***Figure 3:*** *The autonomic nervous system. A description of the figure is given in the main text.* *Created by Dag A. Sangnes using BioRender.com.*

## *Autonomic nervous system*

ANS is also central in the regulation of gastrointestinal motility, mostly exhibiting its effects indirectly through ENS neurons. Cranial nerve X (the vagal nerve) has 75% of all parasympathetic nervous fibers, innervating the oesophagus, stomach, small bowel, and proximal half of the colon. The rest of the colon and the rectum are

innervated by pelvic nerves, extending from the S2-S4 spinal segments. The parasympathetic innervation is most dense in the upper and lower parts of the gastrointestinal tract. In contrast, the sympathetic nervous system neurons are evenly distributed throughout all gastrointestinal compartments, receiving nerve supply from the spinal cord via sympathetic nerve chains and ganglia. The parasympathetic and sympathetic nervous systems are illustrated in Figure 3. The two ANS branches generally exhibit opposite effects on motility: the parasympathetic nervous system acts excitatory through the release of acetylcholine, while the sympathetic nervous system is inhibitory through the secretion of norepinephrine [1,3,15].

### 1.1.3 Gastric motility

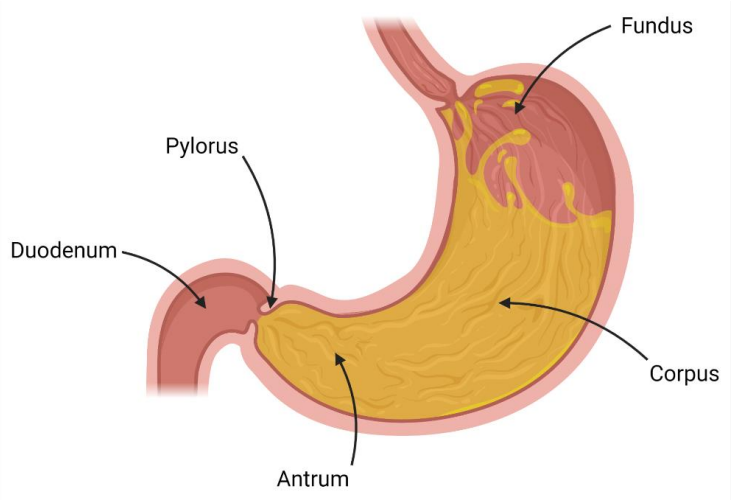



***Figure 4:*** *Anatomical regions of the stomach and the proximal duodenum.* *Created by Dag A. Sangnes using Biorender.com.*

The stomach has the largest lumen of the gastrointestinal tract, normally containing 200 ml but being able to increase its size tenfold postprandially. The stomach has three main parts: the fundus, corpus and antrum (Figure 4). Its main function is to store ingested food and grind it into small particles before gradually expelling it into the duodenum [1,7,16]. As food enters the oesophagus, the fundus relaxes in preparation for accommodating the meal, a process called receptive relaxation [13,17]. In contrast to smooth muscle in the corpus and antrum, smooth muscle in the fundic wall is tonically contracted in the fasting state. After the meal has entered the fundus, the stomach wall relaxes further without increasing intragastric pressure [18].

When the meal has been accommodated, fundic contractions start moving contents towards the proximal corpus, where waves of peristaltic activity commences at a rate of 3-per-minute, like the frequency of the gastric myoelectrical slow-waves. These are initiated by ICCs located in the “pacemaker region” on the stomach’s major curvature. Ring-formed contractions propel the meal through the corpus and antrum with increasing strength towards the closed pylorus. As a result, the meal is triturated into tiny particles blended with gastric juice, a solution called chyme. When particles are 1-2 mm in diameter, they are pushed through the pylorus by strong peristaltic contractions [7,13]. The emptying is facilitated by pyloric relaxation by enteric neurons [19].

The period from the start of the meal until the first nutrients enter the duodenum, is called the lag phase. Depending on its size, composition, and caloric content, the lag phase of a solid meal normally lasts 45-60 minutes. In healthy individuals, more than 90% of the meal is emptied within 4 hours [13,20]. In contrast to solid meals, water leaves the stomach almost immediately. The emptying of caloric liquids is also more rapid than solids [13,18]. To facilitate nutrient absorption and avoid duodenal overload, neurohormonal feedback mechanisms modify the gastric emptying rate [7,13,21].

### 1.1.4 Small bowel motility

The 3 to 7 meter long, tubular and small-calibre small bowel, consists of three parts: the duodenum, jejunum and ileum (Figure 5). Its main function is nutrient absorption, in addition to dispelling indigestible residuals and keeping its environment free of bacterial overgrowth. Recently, its role as an endocrine organ has been increasingly appreciated, particularly when it comes to secretion of the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). They are central in the regulation of energy and glucose homeostasis [22]. When chyme enters the duodenum, small bowel motor activity increases, the opposite of what happens in the stomach. The duodenal mucosa rapidly senses the nutrient

composition, osmolarity and pH level of the chyme, while increased stretch is likely recognised by receptors on smooth muscle cells [7,8].

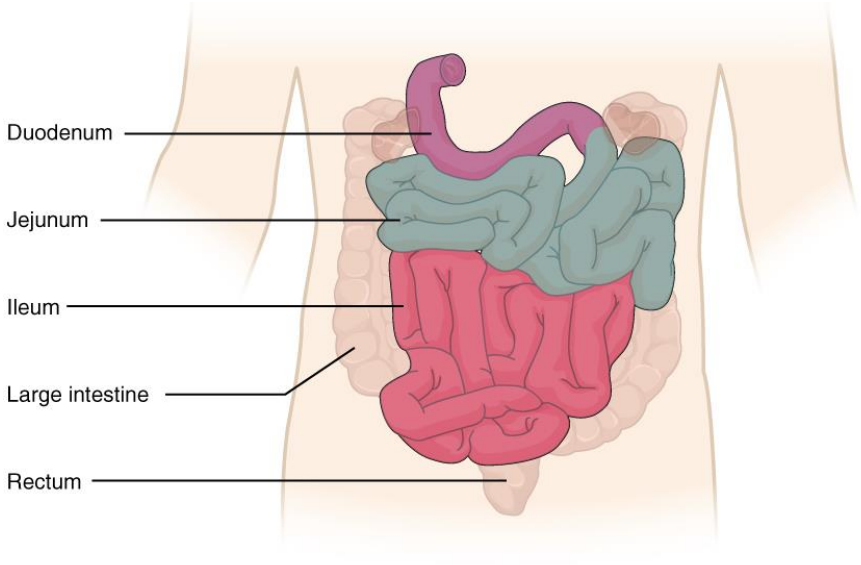



***Figure 5:*** *Anatomical regions of the small bowel.* *Image: "Small Intestine" by Phil Schatz (http://philschatz.com/anatomy-book/resources/2417_Small_IntestineN.jpg) License: CC BY 4.0*

In the duodenum, the number of contractions can reach 12 per minute, while the frequency is 7-9 per minute in the ileum. Peristaltic contractions slowly propel the chyme aborally at a slow velocity (1 cm per min). Mixing contractions split and spread the chyme to facilitate its exposure to digestive enzymes and enterocytes. Although most peristaltic activity is antegrade, movements can also be retrograde. Like the stomach, small bowel motility is tightly regulated by neurohormonal mechanisms [7,8].

### 1.1.5 Colonic motility

The colon is approximately 1 m long, larger in diameter than the small bowel, and can be divided into the caecum, ascending colon, transverse colon, descending colon, sigmoid colon, and the rectum (Figure 6). The colon is connected to the small bowel at the ileocaecal junction, where the ileocaecal valve and surrounding muscular sphincter provide a physiological barrier preventing reflux of faecal contents. The

main function of the colon is storage and expulsion of faeces, but it also absorbs water, electrolytes and short-chain fatty acids [1,6].

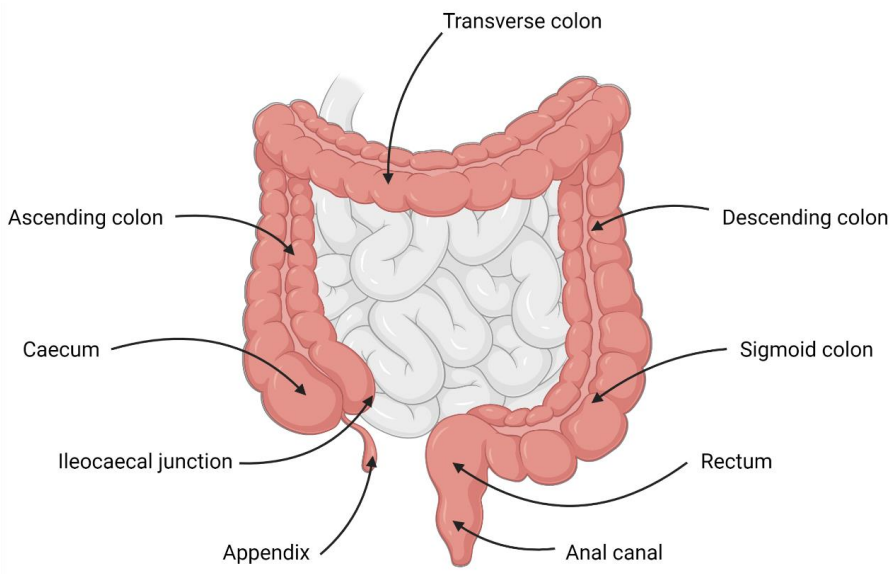



***Figure 6:*** *Anatomical regions of the colon. Created by Dag A. Sangnes using Biorender.com.*

Colonic movements are slower and less frequent than in the small intestine [23]. Transfer from the ileum to the caecum occurs in a pulsatile fashion, when propagating ileal contractions are synchronised with reduced ileocaecal junction pressure. In the colon, mixing contractions called haustrations appear at a rate of 2-4 per minute. Haustrations propagate over short distances in both directions. Mass movements are strong propagating contractions appearing only 1-3 times a day, most often in the morning and after meals. They move faeces over long distances and often precede defecation [24,25].

Retrograde flow is frequent in the colon, especially in the distal part, and may have a braking role limiting the inflow of faeces to the rectum. Neural reflexes are central in the regulation of colonic movement, like the gastrocolic reflex leading to a postprandial increase in colonic myoelectrical activity [6,25]. Intact neural responses are also essential in the complex process of defecation, as described in detail by Palit et al. (2012) [25].

### 1.1.6 Gastrointestinal pH balance

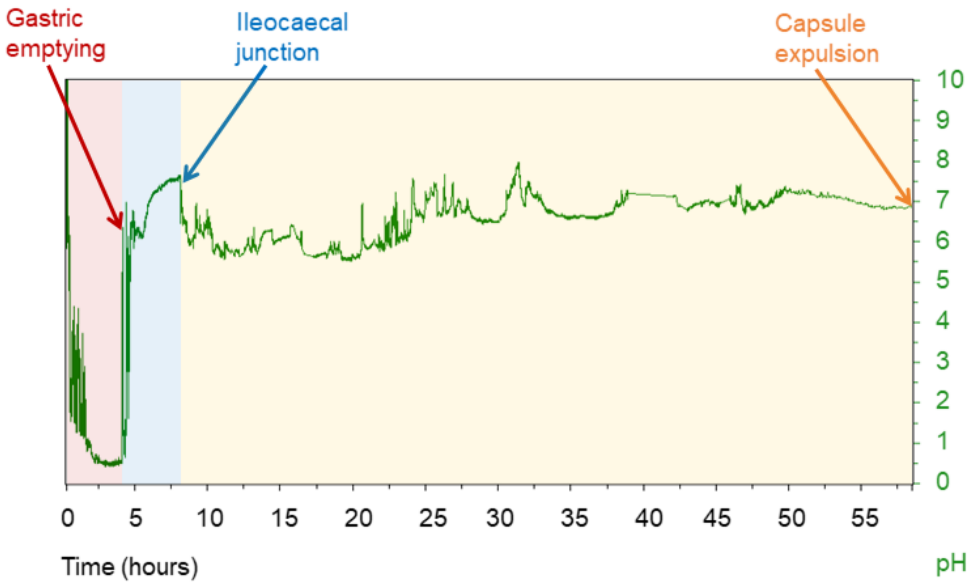



***Figure 7:*** *Wireless motility capsule recording showing the gastrointestinal pH levels (green curve) in a healthy participant. The capsule is ingested together with a solid meal, and the gradual decrease of pH mirrors the dissolution of the meal into a highly acidic blend of tiny food particles and gastric acid. When the meal has been emptyied from the stomach, the indigestible capsule is expelled through the pylorus by the the phase III MMC (marked by the red arrow). In the duodenum, pH levels are alkaline and gradually increases throughout the small bowel until an abrupt fall at the ileocaecal junction (blue arrow). The pH levels in the colon show a fluctuating pattern, with a slight overall increase in the middle part, before another small dip before capsule expulsion from the rectum (orange arrow). Red background colour indicate that the capsule is in the stomach, blue in the small bowel, and yellow in the colon.* Figure by Dag A. Sangnes.

In normal conditions, the stomach has an acidic pH level (below 3) caused by the secretion of hydrochloric acid from parietal cells in the gastric body. Hydrochloric acid secretion is stimulated through a cascade involving preganglionic vagal neurons and ENS neurons, as well as the release of gastrin and histamine [23,26,27]. In contrast, the small bowel has an alkaline pH level due to the secretion of pancreatic bicarbonate upon stimulation from secretin when duodenal pH levels fall below 4.5. Like gastrointestinal motility and secretion, secretion of enzymes and bicarbonate-rich fluid from the pancreas is strongly dependent on neurohormonal regulation [21,28]. The pH levels increase gradually throughout the small bowel, from

approximately 6.5 in the duodenum to 7.5 in the ileum. The pH level dips about 1 pH unit when entering the colon, and thereafter displays a slightly increasing, irregular pattern [23,27]. The more acidic colonic pH levels are mainly caused by bacterial fermentation of carbohydrates and the production of short chain fatty acids [23]. Figure 7 illustrates the gastrointestinal pH profile in a healthy individual. Multiple external factors influence the gastrointestinal pH balance, including antireflux medications, *Helicobacter pylori* infections, pancreatic exocrine insufficiency, small intestinal bacterial overgrowth, and dietary components [23,29–31].

## 1.2 Diabetes and its complications

Diabetes mellitus is a chronic metabolic disorder defined by elevated blood glucose levels (resulting in glycosylated haemoglobin, HbA1c, >48 mmol/mol), and various levels of insulin deficiency and peripheral insulin resistancy. Diabetes is a heterogenous disease classified into different subgroups, where type 1 diabetes (10-15%) and type 2 diabetes (>80%) are the most common. Other diabetes types are monogenic diabetes, gestational diabetes, and diabetes secondary to structural pancreatic disorders [32]. The incidence of diabetes has increased rapidly during the last decades. In 2019, the estimated global prevalence was 463 million people, equivalent to 9.3% of the total population. In 2045, these numbers are expected to rise to 700 million (10.9%) [33].

*Type 1 diabetes* is characterised by a progressive loss of beta cells in the pancreatic islets of Langerhans. When 40-80% of beta cells are destroyed, production and secretion of insulin becomes insufficient to regulate blood glucose levels and manifest diabetes develops. In most patients, beta cell destruction is caused by cytotoxic T lymphocytes as part of an autoimmune process [32]. Type 1 diabetes is associated with other autoimmune diseases like autoimmune thyroid disease, primary adrenal insufficiency, autoimmune gastritis, and coeliac disease [34].

*Type 2 diabetes* is caused by a combination of genetic and environmental factors. Many patients have an inherited disposition for inadequate beta cell function as well

as a propensity for decreased insulin sensitivity. Type 2 diabetes is associated with obesity, hypertension, and lipid disorders, as part of the metabolic syndrome. It is also associated with non-alcoholic fatty liver disease [35]. Type 2 diabetes is initially characterised by peripheral insulin resistance and compensatory hyperinsulinemia. Eventually, beta cell compensation is insufficient, and diabetes develops [32].

*Acute and late complications:* Diabetes patients may develop severe complications due to excessive fluctuations in blood glucose levels. Acute hypo- or hyperglycaemia can be life-threatening, while long-term hyperglycaemia may lead to microvascular late complications like retinopathy, nephropathy, and neuropathy, and macrovascular complications like cerebrovascular, cardiovascular and peripheral arterial diseases [32,36,37]. Neuropathy is the most prevalent late complication, affecting 50% with long-term diabetes [32]. Diabetic neuropathy can be classified into 1) diffuse neuropathy; 2) mononeuropathy; and 3) radiculopathy/polyradiculopathy. The diffuse neuropathies are the most common and include the sub-groups distal symmetrical polyneuropathy and autonomic neuropathy [36,37].

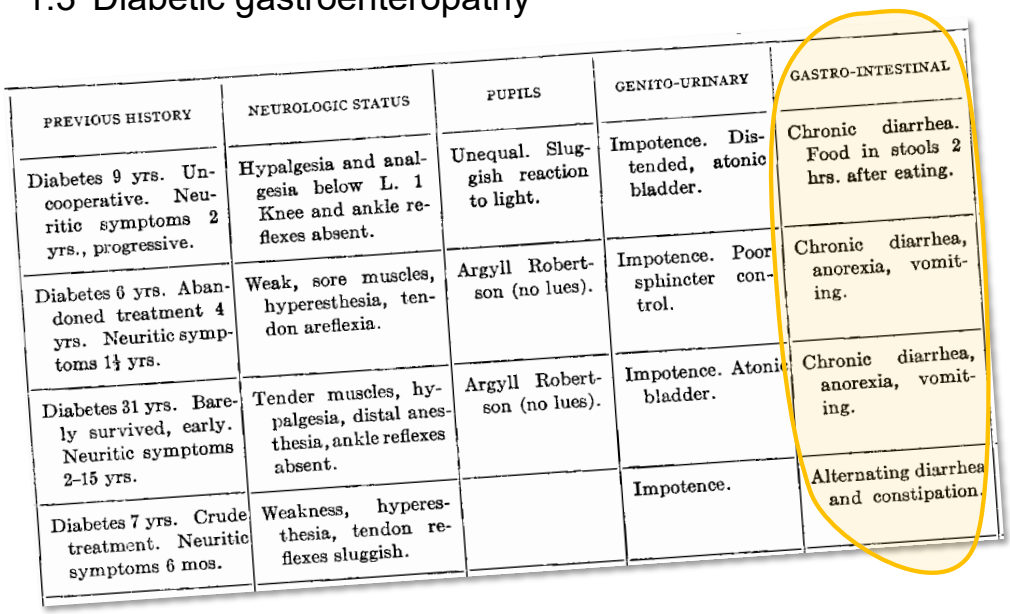
### 1.2.1 Diabetic autonomic neuropathy

Autonomic neuropathy may be present in more than 10% of patients with type 2 diabetes upon diagnosis, whereas it is normally thought to arise after 10 years in type 1 diabetes. It is also prevalent in prediabetes [5,38,39]. Autonomic neuropathy is a potentially severe late complication associated with both increased morbidity and mortality [39–41]. Autonomic neuropathy may affect both the parasympathetic and sympathetic nervous system, leading to a a myriad of symptoms, depending on the affected organ. The early identification of cardiac autonomic neuropathy is of special importance to initiate preventive measures against major cardiovascular events [40]. Autonomic neuropathy may also lead to disturbances in urogenital function, alter thermoregulation through sudomotor dysfunction, reduce the awareness of hypoglycaemic events, and affect motility and secretion of the gastrointestinal tract, gallbladder and bile ducts (Table 1) [36,37,40–42].

| Table 1: Clinical manifestations of autonomic neuropathy | |
|---|---|
| Cardiovascular | Orthostatic hypotension |
| | Orthostatic tachycardia |
| | Resting tachycardia |
| | ↓ heart rate variability |
| | Exercise intolerance |
| | Sudden death (arrhytmias, silent myocardial infarction) |
| Gastrointestinal | Oesophageal dysmotility → reflux and/or dysphagia |
| | Delayed gastric emptying |
| | Altered motility and secretion → diarrhoea and/or constipation |
| | ↓ anorectal sensitivity → faecal incontinence |
| | Gallbladder dysmotility (diabetic cholecystoparesis) |
| Urogenital | Urinary bladder dysfunction (diabetic cystopathy) |
| | Female sexual dysfunction (↓ libido, dyspareunia, ↓ lubrication) |
| | Male sexual dysfunction (erectile dysfunction, ↓ libido, altered ejaculation) |
| Sudomotor dysfunction | Dry skin |
| | ↑ sweating (hyperhidrosis) |
| | ↓ sweating (anhidrosis or hypohidrosis) |
| | Gustatory sweating (sweating after meals) |
| Other | Hypoglycaemia unawareness |
| | Altered pupillary function |
| | Anemia |

Long-term hyperglycaemia is central in the development of neuropathy, especially in type 1 diabetes. Other important risk factors are hypertension, hyperlipidaemia, obesity, and smoking [5,37]. The exact mechanisms causing diabetic neuropathy are not fully discovered. Hyperglycaemia might act through several pathways, causing inflammation, neuronal damage by reactive oxygen species (oxidative stress), and/or ischemia from endothelial dysfunction and reduced perineural blood flow [37].

## 1.3 Diabetic gastroenteropathy



| PREVIOUS HISTORY | NEUROLOGIC STATUS | PUPILS | GENITO-URINARY | GASTRO-INTESTINAL |
|---|---|---|---|---|
| Diabetes 9 yrs. Uncooperative. Neuritic symptoms 2 yrs., progressive. | Hypalgesia and analgesia below L. 1 Knee and ankle reflexes absent. | Unequal. Sluggish reaction to light. | Impotence. Distended, atonic bladder. | Chronic diarrhea. Food in stools 2 hrs. after eating. |
| Diabetes 6 yrs. Abandoned treatment 4 yrs. Neuritic symptoms 1½ yrs. | Weak, sore muscles, hyperesthesia, tendon areflexia. | Argyll Robertson (no lues). | Impotence. Poor sphincter control. | Chronic diarrhea, anorexia, vomiting. |
| Diabetes 31 yrs. Barely survived, early. Neuritic symptoms 2–15 yrs. | Tender muscles, hypalgesia, distal anesthesia, ankle reflexes absent. | Argyll Robertson (no lues). | Impotence. Atonic bladder. | Chronic diarrhea, anorexia, vomiting. |
| Diabetes 7 yrs. Crude treatment. Neuritic symptoms 6 mos. | Weakness, hyperesthesia, tendon reflexes sluggish. | | Impotence. | Alternating diarrhea and constipation. |

***Figure 8:*** *A selection from Table III in "Diabetic neuropathy: General review with report of 125 cases" by R. Wayne Rundles (Medicine, 1945).* *Reprinted with permission from Wolters Kluwer Health, Inc. and Copyright Clearance Center.*

The link between diabetes and gastrointestinal symptoms has a long history, with the first reported observations of diarrhoea and delayed gastric emptying in 1912 and 1925, respectively [43,44]. In 1936, Bargen, Bollman and Kepler described the "diarrhea of diabetes" as "numerous and watery but not particularly fatty unlike those of pancreatic diarrhea" [45]. In a landmark publication from 1945, Rundles made a detailed characterisation of complications seen in 125 patients with diabetic neuropathy (Figure 8). He found that 62% had chronic gastrointestinal symptoms, where constipation (42%) was the most common, followed by diarrhoea (22%). Some patients had alternating diarrhoea and constipation, and several also had anorexia, nausea and vomiting. Four of these patients either had delayed gastric emptying or prolonged small bowel transit evaluated by barium studies [46]. A similar observation was made by Martin et al. (1953), finding delayed gastric emptying in nine out of 14 patients with diabetic diarrhoea [47].

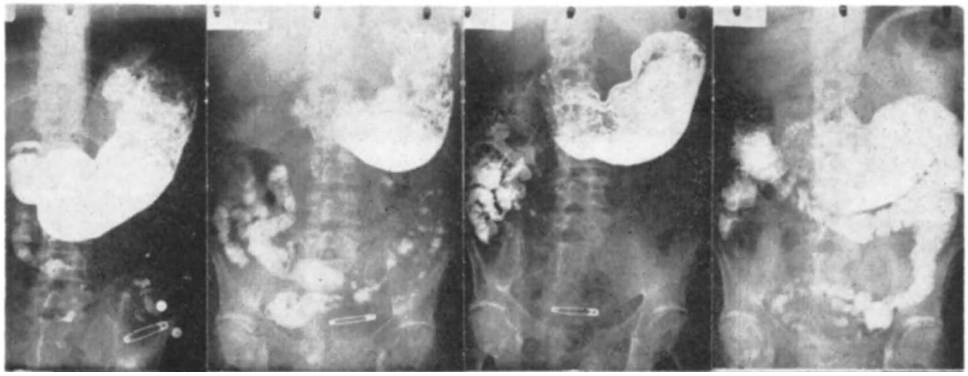


***Figure 9:*** *Abdominal radiographs of a patient with type 1 diabetes and severe gastric retention of a barium sulphate meal. Pictures were taken immediately after meal intake (left to right), after three, six, and 24 hours.*
*Image originally published in "Asymptomatic gastric retention in diabetics (gastroparesis diabeticorum)" by Paul Kassander, Annals of Internal Medicine (Volume 48, Issue 4, Apr 1 1958). Reprinted with permission from The American College of Physicians and Copyright Clearance Center.*

Five years later, Kassander described the "gastroparesis diabeticorum" in a study of 27 diabetes patients, where six (22%) had asymptomatic gastric retention (Figure 9). Due to the similarity with findings made in patients that had undergone vagotomy, Kassander proposed that vagal neuropathy was the most likely cause [47]. In the following years, several important experimental studies were performed, like the ones by Malins and Mayne (1969), Whalen et al. (1969) and Drewes (1971) [45,48,49]. Despite this early enthusiasm, overall research into gastrointestinal complications in diabetes has been relatively limited, especially regarding its intestinal manifestations. Fortunately, the last decade has brought important progress in the field of gastroparesis research and there has also been a slightly increasing interest in intestinal dysfunction [4,50–53].

The terminology commonly used to describe gastrointestinal complications in diabetes, like "autonomic neuropathy of the gut" or "gastrointestinal autonomic neuropathy", reflects the long-term association with autonomic dysfunction. Although autonomic dysfunction is still thought to play an important role in the pathogenesis, recent research, especially within the field of gastroparesis, has discovered findings that do not easily fit under the "autonomic neuropathy umbrella", like alterations to smooth muscle or an imbalance between pro-inflammatory and

anti-inflammatory macrophages [54–56]. Consequently, diabetic gastroenteropathy represents a more inclusive overall term for the gastrointestinal complications in diabetes, and this terminology has gained increased usage during the last years [4,57–59].

In the following sections, I will first describe the clinical features of diabetic gastroenteropathy, giving a brief account of the pathogenesis, before presenting a general approach to diagnostics and treatment. Thereafter, I will describe the three main manifestations, gastroparesis, diarrhoea and constipation, with an emphasis on pathophysiological findings. Diabetic gastroenteropathy may also lead to reflux, dysphagia and faecal incontinence. In addition, diabetes may affect the liver, gallbladder and pancreas. A detailed description of these complications is beyond the scope of this dissertation.

### 1.3.1 Clinical manifestations

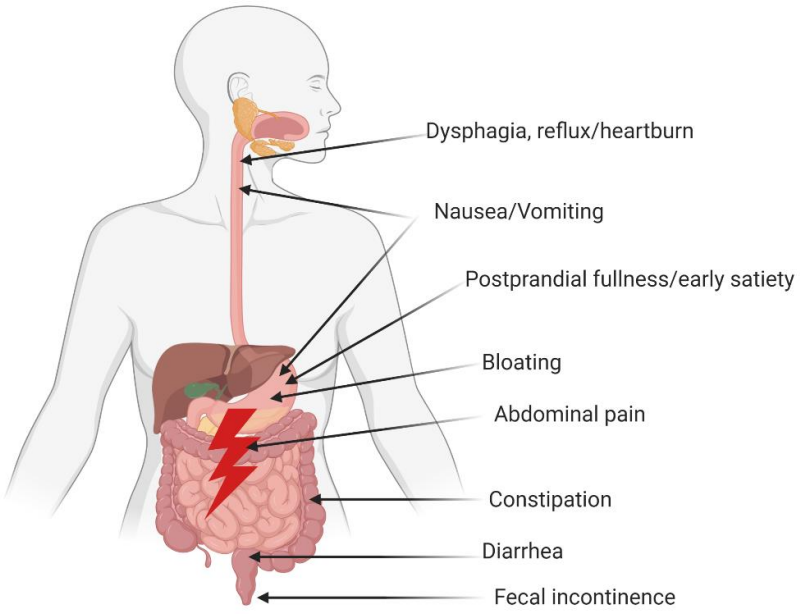



***Figure 10:*** *The various symptoms of diabetic gastroenteropathy and their suspected origin.* *Figure by Meling et al. Curr Diabetes Rev. 2021, published under the CC-BY 4.0 license and reprinted with permission* [57].

Diabetic gastroenteropathy can lead to a variety of symptoms potentially attributable to the entire gastrointestinal tract (Figure 10) [57]. Gastrointestinal symptoms are frequent in diabetes patients, but their prevalence varies considerably between studies, depending on methodology and study population [60,61]. In outpatient clinics, the prevalence may be as high as 68-76%, while community studies have found a prevalence of 40-50% [60,62–67]. In community studies, the most common symptoms are bloating/abdominal distention (12-42%), early satiety (5-32%), reflux/heartburn (14-24%), and nausea (5-23%) [61]. Bowel disturbances like constipation (10-17%), diarrhoea (0-22%), and faecal incontinence (1-10%) are also prevalent [61]. Although findings are not unambiguous, most studies show an increased prevalence of gastrointestinal symptoms in diabetes patients compared to the normal population [61,68–70]. Symptoms are more frequent in women, but it is uncertain whether the prevalence differs between type 1 and type 2 diabetes [57,61]. Patients with gastrointestinal complaints often report reduced quality of life [71,72]. Anxiety and depression are also common in diabetes patients and may both be a cause and a consequence of gastrointestinal symptoms [72–74].

### 1.3.2 Pathogenesis

#### *Autonomic neuropathy*

Given the close interconnection between the autonomic nervous system and the gastrointestinal tract, autonomic neuropathy has long been considered the main cause of gastrointestinal complications in diabetes [46,75]. Motility studies have largely supported an association between autonomic dysfunction, gastric emptying and various other pathophysiological features of gastroparesis like reduced accommodation and antral hypomotility [76–78]. Afferent nerve dysfunction has also been proposed as an explanation for the abdominal pain often troubling these patients [79]. However, studies examining human neural tissue have presented conflicting results, and the focus of gastroparesis research has shifted somewhat away from autonomic neuropathy during the last two decades [4,44].

In diabetic diarrhoea and constipation, the autonomic dysfunction theory is still the most influential. This may partly be explained by the lack of other research, as current evidence is limited, inconclusive and based on old studies, often containing few participants [45,80–85]. As in the stomach, histological findings from the human small bowel and colon are not enterily unambiguous, but a majority of studies identified pathological changes in autonomic neural tissue [43,45,80,81]. The relationship between small bowel transit and autonomic dysfunction is uncertain, with studies finding associations with both delayed and rapid transit, or not finding any association at all [83,86,87]. Looking at colonic transit and autonomic function, results are also contrasting. While one study found prolonged transit in patients with autonomic dysfunction, two others failed to identify any such difference [85,88,89]. Most recently, a wireless motility capsule study found an association between prolonged colonic transit and low cardiac vagal tone [90].

Experimental studies have also been inconclusive. In 1980, Battle et al. investigated intracolonic nerve conduction in 10 healthy controls and 12 insulin-dependent diabetes patients with constipation of varying severity [84]. They found that patients with severe constipation had an absent gastrocolic response after intake of a calory-rich meal. The result was attributed to autonomic dysfunction and supported by the finding that 11 of 12 study patients had clinical features of autonomic neuropathy [84]. Meanwhile, Whalen et al. (1969) investigated intestinal motility in response to intravenous stimulation by adrenergic and cholinergic agents in 13 patients with diabetic diarrhoea. The researchers found intact efferent sympathetic and parasympathetic pathways but signs of impaired afferent sympathetic innervation [48].

### *Enteric neuromuscular alterations*

*Loss of ICCs:* Grover et al. have performed full-thickness biopsy studies from the gastric body and antrum [56,91]. Loss of ICCs was the most frequent finding [91]. The main mechanism behind the ICC-loss is thought to be lack of, or reduced effect from, insulin and insulin-like growth factor 1. Both bind to smooth muscle cells and enteric neurons, leading to secretion of stem cell factor necessary for ICC survival

[4,76]. ICC-loss may lead to dysrhytmias and reduced antral contractility, and is associated with delayed gastric emptying [79,91,92]. Reduced numbers of ICCs have also been found in jejunal, and colonic tissue [44,93].

*Macrophage imbalance:* Histological studies from the stomach have found a disrupted balance between pro-inflammatory (M1) and anti-inflammatory macrophages (M2) [56,79,91]. A potential interpretation of these findings is that increased expression of pro-inflammatory macrophages facilitates ICC loss, while reduction of anti-inflammatory macrophages leaves neural tissue more vulnerable to damage by oxidative stress and inflammation [5,56].

*Loss of nitrergic neurons:* Although just a minor finding in the studies by Grover et al., other studies have found marked loss of enteric neurons in gastric tissue [56,94,95]. Loss of inhibitory nitrergic neurons may cause reduced accommodation and increased pyloric tone, and affect the coordination of gastric peristaltic movements [5]. Chandrasekharan et al. investigated ENS changes in colonic samples from 22 diabetes patients and 42 controls. In the diabetes patients, they found significant loss of inhibitory neurons expressing neuronal nitric oxide synthase and neuropeptide Y. The causative mechanisms for the neuron depletion was most likely oxidative stress and apoptosis [53].

*Smooth muscle alterations:* Histopathological studies from the stomach have found smooth muscle degeneration, fibrosis, and a thickened basal lamina around smooth muscle cells [54,55]. In the colon, circular muscle strips have shown impaired contractility [53]. It has been proposed that diabetes alters the intracellular signaling pathways of intestinal myocytes [4].

### *Other mechanisms*

*Fluctuating glucose levels* influence the gastric emptying rate directly: acute hyperglycaemia delays and acute hypoglycaemia accelerates gastric emptying [96]. Acute hyperglycaemia also inhibits antral contractility and induce gastric dysrhythmias [97]. Chronic hyperglycaemia is a risk factor for developing delayed

gastric emptying [98]. Hyperglycaemia may also affect colonic motility and diminish rectal sensitivity [99,100].

*Bile acid malabsorption* has been proposed as a cause of diabetic diarrhoea, but the studies are few and conflicting [101–103].

### 1.3.3 Differential diagnosis

**Table 2: Alarm features**

| |
|---|
| Age ≥ 45 at debut of dyspepsia; ≥ 55 disturbed bowel movements |
| GI cancer in first grade relative |
| Dysphagia and odynophagia |
| Refractory vomiting |
| Progressive abdominal pain |
| Nocturnal symptoms |
| Involuntary weight loss |
| Fever |
| Signs of gastrointestinal bleeding: visible or occult blood, iron deficiency anemia |
| Signs of inflammation: elevated CRP, ESR, and/or faecal calprotectin |
| Palpable abdominal masses |
| Enlarged lymph nodes |
| Jaundice |

Table by Meling et al. Curr Diabetes Rev. 2021, published under the CC-BY 4.0 license and reprinted and modified with permission. Abbreviations: CRP = C-reactive protein. ESR = erythrocyte sedimentation rate.

Diabetic gastroenteropathy has numerous differential diagnoses [57,61,104]. Diabetes is associated with an increased cancer risk, necessitating vigilance towards alarm features (Table 2) [57,105–110]. Thyroid disease and coeliac disease, associated with type 1 diabetes, may lead to a variety of symptoms, including dyspepsia and disturbed bowel movements [111,112]. A link between inflammatory bowel disease and diabetes has recently been identified, potentially explaining diarrhoea and abdominal pain in some individuals [113–115]. Furthermore, small intestinal bacterial overgrowth (SIBO) may appear in both diabetes types as a consequence of small bowel dysmotility, causing abdominal discomfort, bloating, and diarrhoea [116].

Pancreatic exocrine insufficiency may affect both type 1 and type 2 diabetes, potentially leading to maldigestion and malabsorption, steatorrhea, and abdominal discomfort [22,117–119]. Additionally, diabetes patients have increased risk of developing gallstone disease, causing abdominal pain [120]. Glycogenic hepatopathy, a liver disease mostly seen in type 1 diabetes, could also lead to abdominal pain, in addition to hepatomegaly and elevated liver enzymes [121]. Non-

alcoholic fatty liver disease, meanwhile, is normally asymptomatic, but can lead to complications like liver failure and hepatocellular carcinoma [35,122,123].

Obesity, common in type 2 diabetes, is in itself associated with diarrhoea [124]. Dietary factors may also influence on symptoms, especially foods and beverages containing sugar alcohols. These are substrates for colonic bacterial fermentation leading to excessive gas production and diarrhoea [125,126]. Diabetes patients also use medications where gastrointestinal symptoms are common side effects, like metformin, GLP-1 agonists, antihypertensives, statins, and drugs used for alleviating painful neuropathy [61,64,127,128].

Finally, it can often be difficult to separate manifestations of diabetic gastroenteropathy from functional gastrointestinal disorders like irritable bowel syndrome and functional dyspepsia, frequent causes of symptoms in both diabetes patients and the normal population [129,130]. Long disease duration, a history of challenging glycaemic control, and the presence of other late complications may all increase the likelihood of diabetic gastroenteropathy [57].

### 1.3.4 Diagnostic approach

After ruling out differential diagnoses, the further diagnostic approach depends on the patient's age – higher age makes malignant diseases more likely – and suspected organ affection. However, there is not always a clear connection between each respective symptom and its suspected organ of origin. Patients may also report several concurrent symptoms and display multiregional dysmotility, complicating diagnostics [131–135]. Table 3 proposes diagnostic algorithms for dyspepsia, nausea/vomiting and abdominal pain – common presentations of gastroparesis – and diarrhoea and constipation [59,61,140–142,104,108,109,126,136–139]. Diagnostic algorithms for reflux, dysphagia, and faecal incontinence can be found in our recent publication: Meling et al. (2021) [57]. A more detailed presentation of gastrointestinal motility and function tests are given in chapter 1.4.

**Table 3: Diagnostic algorithm for diabetic gastroenteropathy**

| Symptom | Dyspepsia and nausea/vomiting | Abdominal pain (chronic or recurrent) | Diarrhoea | Constipation |
|---|---|---|---|---|
| Initial tests | Upper endoscopy | Ultrasound LGP (+/- abdominal ultrasound) | Faecal samples: calprotectin, FE-1<br><br>Colonoscopy with biopsies [a] | Treatment trial<br><br>Colonoscopy [a] |
| Further investigation | Gastric emptying scintigraphy<br><br>WMC<br><br>Breath tests<br><br>CT abdomen<br><br>Abdominal ultrasound | CT abdomen<br><br>Endoscopy<br><br>CT angiography | CT/MRI enterography<br><br>Transit time: scintigraphy, WMC<br><br>Breath tests for SIBO<br><br>$^{75}$SeHCAT | Anorectal function tests: HRM, balloon expulsion test<br><br>Barium or MRI defecography<br><br>Transit time: scintigraphy, radiopaque markers, WMC |
| Differential diagnoses | FD<br><br>GERD<br><br>Peptic ulcer<br><br>Drug side effects<br><br>Coeliac disease<br><br>Partial obstruction (gastric outlet/intestinal)<br><br>Cancer (oesophagus, stomach, duodenum)<br><br>CVS/CHS | IBS<br><br>FD<br><br>Drug side effects<br><br>GERD<br><br>Peptic ulcer<br><br>Biliary tract disease<br><br>Pancreatic disease (cancer, pancreatitis)<br><br>IBD<br><br>Ischaemia (cardiovascular, mesenteric) | Drug side effects<br><br>IBS<br><br>Coeliac disease<br><br>Hyperthyroidism<br><br>SIBO<br><br>Pancreatic exocrine insufficiency<br><br>IBD<br><br>Mb. Addison<br><br>Bile acid malabsorption | Drug side effects<br><br>Hypothyroidism<br><br>IBS<br><br>Colorectal cancer<br><br>Neurological disease<br><br>Dyssynergic defecation |

Table by Meling et al. Curr Diabetes Rev. 2021, published under the CC-BY 4.0 license and reprinted and modified with permission. The algorithm is a recommendation based on current knowledge, national guidelines, recent consensus statements, and the authors' own clinical experience. The list of diagnostic modalities and differential diagnoses is not exhaustive. [a] = Initial test in patients with new onset symptoms ≥ 55 years of age; in the rest early during further examination. Abbreviations: WMC = wireless motility capsule. CT = computed tomography. FD = functional dyspepsia. GERD = gastroesophageal reflux disease. CVS/CHS = cyclic vomiting syndrome/cannabinoid hyperemesis syndrome. LGP = liver, gallbladder, and pancreas. IBS = irritable bowel syndrome. IBD = inflammatory bowel disease (including microscopic colitis). FE-1 = faecal elastase-1. MRI = magnetic resonance imaging. SIBO = small intestinal bacterial overgrowth. $^{75}$SeHCAT = $^{75}$Selenium homotaurocholic acid test (for bile acid malabsorption. HRM = high resolution manometry.

### 1.3.5 Diabetic gastroparesis

Gastroparesis is a gastric dysmotility disorder characterised by symptoms like nausea and vomiting, early satiety, postprandial fullness and bloating [143]. Although not traditionally considered a cardinal symptom of gastroparesis, abdominal pain is increasingly recognised as an important clinical feature [144]. Patients may also lose weight and experience aggravated difficulties with glycaemic control [62,145]. In addition to characteristic symptoms and the exclusion of obstructing lesions by upper endoscopy, the gastroparesis diagnosis currently mandates the identification of delayed gastric emptying using a reliable, validated method [146]. Four-hour gastric emptying scintigraphy, gastric emptying breath tests for solids, and wireless motility capsule are currently recommended by guidelines [137,147]. Details of each method are presented in chapter 1.4.

There are no European studies investigating the prevalence of diabetic gastroparesis, but a 2019 US population study found a prevalence of 4.6% in type 1 diabetes and 1.3% in type 2 diabetes, mirroring findings from previous epidemiological studies [148,149]. Some researchers think gastroparesis is underdiagnosed, as only a minority of individuals with symptoms go through gastric emptying tests [76]. As many as 30-50% with long-standing diabetes may have delayed gastric emptying and a large percentage are asymptomatic, as pointed out by Kassander six decades ago [44,47,76]. At the opposite end of the spectrum lies the group with typical gastroparesis-symptoms, but normal or even rapid gastric emptying. According to current criteria, none of these groups qualify as gastroparesis. The latter group is instead called diabetic dyspepsia, but the borderline towards functional dyspepsia is unclear [104,129]. Gastroparesis is associated with other late complications of diabetes like peripheral neuropathy and retinopathy, and with elevated HbA1c levels [5].

*Pathophysiological findings in diabetic gastroparesis*

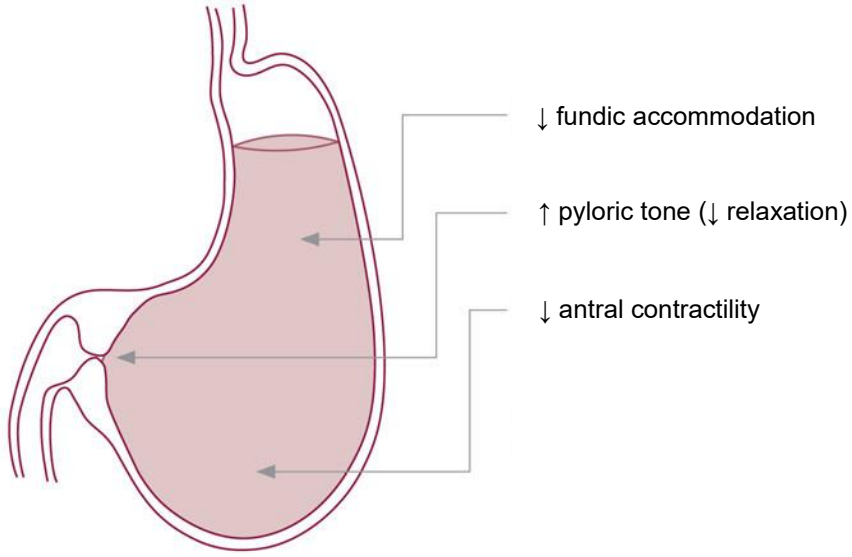



***Figure 11:*** *Reduced fundic accommodation, reduced antral contractility, and increased pyloric tone are three central pathophysiological mechanisms in diabetic gastroparesis. Compared to a healthy stomach, the gastroparetic stomach has a J-shaped configuration caused by dilation of the antrum. Some patients may develop such large stomachs that they may be visible in the lower abdominal quadrants.* *Figure by K. Toverud in Sangnes et al. Tidsskr Nor Laegeforen. 2016, reprinted with permission* [143].

Despite differing study results, gastroparesis is the gastrointestinal diabetes complication where the underlying mechanisms are best mapped. Several elements of normal gastric motility might be affected and delayed gastric emptying can be considered a composite marker for some, but not all, of these changes [52]. Some of the most influential mechanisms are illustrated in Figure 11.

*Reduced fundic accommodation* has been demonstrated using both scintigraphy, gastric barostat and ultrasound [150–152]. Similar to functional dyspepsia, symptoms like early satiety and postprandial fullness are the most likely presenting symptoms of reduced accommodation [17]. Using ultrasound, we have also found that gastroparesis patients have reduced emptying of the proximal stomach [152].

*Antral hypocontractility:* Studies using manometry and wireless motility capsule have demonstrated that patients with diabetic gastroparesis have reduced postprandial antral contractility [153–155]. Ultrasound has shown an enlarged, distended antrum

both during fasting and after meals [152,156]. Antral hypocontractility is one of the most important factors contributing to delayed gastric emptying and may primarily lead to symptoms like nausea and vomiting [79].

*Pyloric sphincter dysfunction* has recently gained a lot of attention as a potential therapeutic target in gastroparesis, after studies using impedance planimetry provided new impetus to the old pylorospasm theory [157–159]. As a possible consequence of pyloric dysfunction, patients may have prolonged antroduodenal transition time [160]. It is likely that pyloric dysfunction contributes to delayed gastric emptying in a sub-group of gastroparesis patients [5].

*Gastric dysrhythmias* can be seen in 75% of gastroparesis patients using cutaneous electrogastrography [79]. Like in the heart, ectopic pacemakers in the stomach may generate rhythms overriding the normal intrinsic slow-wave rhythm or substituting it if the regular pacemaker fails. This may lead to tachygastria (>4 cycles per minute), bradygastria (<2 cycles per minute) or tachybradyarrhythmia. In contrast to normal slow waves, dysrhythmias do not result in gastric contractions and the stomach becomes atonic. The patients may experience nausea [79,161]. Studies have also shown reduced numbers or complete loss of phase III MMCs, especially in the antrum. This might potentially lead to bezoar formation and delayed emptying of nondigestible solids [79,153].

*Intestinal dysmotility:* Several studies have found an association between gastroparesis and small bowel dysmotility [131,153,162,163]. Patients with gastroparesis might also have increased prevalence of slow-transit constipation, but results are not unambiguous [135,164,165].

*Altered visceral sensitivity* is also seen in diabetes and may manifest as either hypersensitivity or hyposensitivity, as demonstrated using gastric barostat and ultrasound meal accommodation test studies, respectively [151,166–168].

### 1.3.6 Diabetic diarrhoea

Diarrhoea lasting more than four weeks is defined as chronic diarrhoea, and is one of the most debilitating symptoms impacting the lives of diabetes patients [125,169]. It is also very prevalent, affecting 11% in a recent community study, compared to 6% in participants without diabetes [170]. Tertiary centre studies have found chronic diarrhoea in 18-41%, all but one finding higher prevalence numbers compared to tertiary centre controls [61]. The diarrhoea may have many causes, like comorbidities, medications and dietary factors. When it is caused by diabetic gastroenteropathy it is called diabetic diarrhoea. Patients typically present with a non-bloody, high-volume, watery stool. It is rarely associated with pain but may be nocturnal and can lead to soiling and faecal incontinence [125,126,171,172]. Diabetic diarrhoea has been associated with long duration of insulin-dependent diabetes and the occurrence of other late complications, especially peripheral neuropathy [125,172].

Few studies have investigated small bowel and colonic motility in diabetic diarrhoea, and most were performed decades ago. Research has mainly focused on the small bowel, while little interest has been devoted to the colon [132,172]. Transit time results have been divergent: Some have found prolonged small bowel transit, others shortened [83,86,172–176]. Most studies demonstrating prolonged transit have shown an association with SIBO, while shortened transit has been associated with autonomic dysfunction [86,175]. There are also those proposing an association between autonomic dysfunction, delayed transit, and SIBO [83,116]. In addition, both Whalen et al., McNally et al. (1969), and Drewes (1971) found that the small bowel had reduced response to distention, while the latter two also found increased frequency and amplitude of peristaltic waves [48,49,177]. Dooley et al. (1988) demonstrated marked alterations in MMC activity [49,82].

### 1.3.7 Diabetic constipation

Chronic constipation is also very prevalent in diabetes. In a recent US community study, 15% of diabetes patients reported chronic constipation [170]. The prevalence

in tertiary centres may be even higher, with numbers ranging from 16-34% [61]. Half of patients experience reduced quality of life due to their bowel symptoms. A similar percentage are dissatisfied with their constipation treatment [178]. Current diagnostic criteria for constipation have moved away from the traditional quantitative definition of less than three bowel movements per week, and now also include symptoms of hard stool consistency, straining and difficulties with evacuating faeces [140]. Constipation is associated with older age, longer diabetes duration, worse glycaemic control, and the occurrence of retinopathy and neuropathy [70,179].

The number of motility studies in diabetes patients with constipation are even fewer than in patients with diarrhoea [132]. In 1990, Wegener et al. found that patients with constipation had prolonged whole-gut transit compared to controls by using indigo carmine to stain the stool [87]. Iber et al. and Jung et al. replicated the findings using radiopaque markers [89,180]. Recent studies have identified links between gastroparesis and slow transit constipation, and between constipation and delayed colonic transit time, but study patients were of mixed aetiology and diabetes patients constituted a minority [135,164,165,174]. A study using the 3D-Transit capsule, demonstrated delayed colonic transit in diabetes patients compared with healthy controls, but only included three patients with constipation [50]. Finally, a wireless motility capsule study found an association between constipation and delayed colonic transit in type 1 diabetes patients, but most patients were asymptomatic [90].

The motility study by Battle et al. has been described previously, finding an absent gastrocolic response in diabetes patients with severe constipation [84]. In a 1998 pilot study, Maleki et al. found that three out of ten constipated diabetes patients had rectal evacuation disorders, equalling the numbers with normal-transit constipation and slow-transit constipation [85]. More recently, Reszczyńska and Kempiński used high-resolution anorectal manometry to demonstrate that diabetes patients with constipation had reduced maximal squeeze pressures and recto-anal pressure gradients, indicating disordered defecation. They also found that patients with constipation had impaired rectal sensitivity [181].

### 1.3.8 Treatment

When treating diabetic gastroenteropathy, we aim to follow a stepwise approach, as illustrated in Figure 12. A comprehensive review of current and future treatment is beyond the scope of this dissertation, but can be found in Meling et al. (2021) [57]. Management of gastrooesophageal reflux and faecal incontinence normally follows traditional guidelines and will not be described in further detail [182,183].

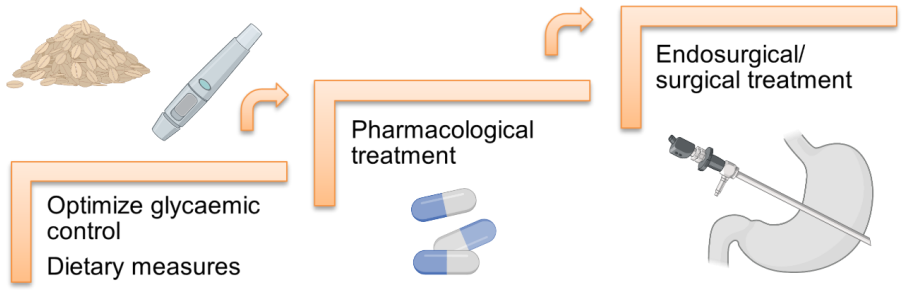



***Figure 12:*** *Proposed treatment approach in diabetic gastroenteropathy.*
*Created by Dag A. Sangnes using Biorender.com.*

*Optimalisation of glycaemic control* is the foundation of treatment, to prevent further progress of late diabetes complications and reduce the influence of blood glucose levels on gastrointestinal motility. In gastroparesis, this is especially important as patients may experience unpredictable nutrient absorption due to delayed gastric emptying and risk inducing hypoglycaemic episodes with regular pre-meal insulin administration [76]. Studies have so far not provided conclusive evidence that long-term control of glycaemia improves upper gastrointestinal symptoms and normalises gastric emptying [98]. However, a recent pilot study found a beneficial effect of glucose sensor-augmented continuous subcutaneous insulin infusion on the number of hypoglycaemic episodes, and time in hypoglycaemia, euglycaemia, and hyperglycaemia. The patients also experienced reduced symptoms [184]. Hybrid closed-loop therapy has also shown promising results in case series, and prospective studies are eagerly awaited [185].

*Dietary measures:* Patients are encouraged to keep a diet with frequent small meals at regular time intervals. They are also recommended to avoid food containing high

amounts of fat, carbonated beverages, alcohol and smoking [5,186]. Reducing the intake of sugar-free sodas can reduce symptoms. However, sufficient fluid intake is important and in constipation, this has a beneficial effect in combination with moderate intake of fibre [187]. High amount of fibre is not recommended, as this delays gastric emptying, leads to bloating, and potentially aggravates constipation [188]. Small-particle sized diets have proven effective for treating gastroparesis in controlled trials [189]. Nutrient drinks can be a valuable addition for some patients. The low FODMAP diet is first-line treatment in irritable bowel syndrome but not yet studied in diabetic gastroenteropathy. It might be an alternative in patients with bloating, abdominal pain, and disturbed bowel movements [57]. Some patients with severe clinical presentations may develop malnutrition and need enteral or parenteral nutrition, or hospitalisations to correct water and electrolyte deficiencies [146].

*Pharmacological treatment* is the next step on the treatment ladder. As there is no current causal therapy for diabetic gastroenteropathy, treatment is mainly aimed at alleviating symptoms and normalizing dysmotility. In gastroparesis, prokinetic drugs like metoclopramide, domperidone, and erythromycin, are first-line choices [57]. Antiemetic drugs like ondansetron may alleviate symptoms. When no secondary causes are identified, opiate antidiarrhoeals like loperamide is the most important treatment for chronic diarrhoea. Constipation is normally treated with osmotic laxatives like polyethylene glycol, contact laxatives like bisacodyl and sodium picosulphate, or novel drugs like linaclotide and prucalopride. The latter may also have a role in treating gastroparesis, while ondansetron can be tried against diarrhoea. Several novel drugs are currently under investigation [57,190].

*Endosurgical/surgical treatment:* Gastroparesis patients refractory for other treatment, may be candidates for advanced endosurgical or surgical treatment. The gastric electrical stimulator (Enterra, Medtronic, Minneapolis, USA) has shown good results in open-label studies, but results have not been replicated in randomised controlled trials [57]. The treatment may still be an option in patients with refractory vomiting [191]. Intrapyloric injections of botulinum toxin also failed to show benefit in controlled trials but may have a role in patients with pyloric dysfunction [5]. Per-

oral pyloromyotomy, also known as gastric per-oral endoscopic myotomy (G-POEM), is an advanced endosurgical procedure splitting the pyloric sphincter muscle down to the serosal layer [192]. So far, results are promising, and large trials are underway. Laparoscopic pyloroplasty has also shown good results [5]. Some patients may end up needing gastrectomy as last-resort treatment [57]. Subtotal colectomy for intractable constipation is only indicated in severe disease refractory for other therapeutic interventions. Concurrent dysmotility in other gastrointestinal segments is a contraindication for surgery [137]. New treatments are being developed, including minimally invasive gastric pacing, and radiofrequency ablation of gastric dysrhythmias [193–195].

## 1.4 Gastrointestinal motility and function tests

Most clinicians treating patients with gastrointestinal symptoms are familiar with the scenario where a patient has normal findings on endoscopical and radiological examinations, despite presenting a severe symptom burden. The next diagnostic step is often investigating gastrointestinal function and motility. This diagnostic field has a long history, and through the years, a myriad of different methods have seen the light of day. Most have ended up collecting dust in a research laboratory, some have found their place in specialised centres, while only a few have achieved extensive clinical use. The reason is most often that they do not meet the following basic principles: 1) the method must measure well-defined parameters with a clear distinction between healthy and sick; 2) it must be standardised, well-validated and give reproducible results; 3) it must be acceptable to both patients and clinicians; and 4) it should be reasonably inexpensive and widely available [196].

Giving a thorough presentation of each gastrointestinal motility and function test is beyond the scope of this dissertation. Besides a presentation of the wireless motility capsule, I will therefore only give a brief introduction to some of the most utilised methods for assessing the stomach, small bowel and colon. For a description of tests used for investigating oesophageal motility and pH or anorectal function, I refer to other sources [136,138,197].

### 1.4.1 Wireless motility capsule

The concept of measuring physiological parameters without the need of invasive, uncomfortable and time-consuming procedures, has long attracted interest inside the field of gastroenterology. The first ingestable pills incorporating transducers for measuring pressure, temperature, and pH were developed already around 1960 [198].

Four decades later, the wireless motility capsule SmartPill® (Medtronic, Minneapolis, USA) was launched. The wireless motility capsule is an indigestible, single-use capsule designed to measure intraluminal pH, pressure and temperature of the stomach, small bowel and colon. Measurement details are presented in Table 4. The capsule is swallowed together with a standardised meal. It has a cylindrical shape, is coated with polyurethane and contains one sensor each measuring pH, pressure, and temperature, one radio frequency transmitter (454 Mhz), one antenna, and two 1.5V batteries [199,200]. It is linked to a portable recorder, which the patients carry close to the abdomen during the five-day examination period. The capsule transmits data signals to the recorder every 20 seconds for the first 24 hours, thereafter every 40 second. Normal battery life is estimated to 120 hours (5 days) [200].

**Table 4: Wireless motility capsule measurement details**

| Parameter | Range | Sensitivity | Measurement frequency | | |
|---|---|---|---|---|---|
| | | | 0-24 h | 24-48 h | >48h |
| pH | 0.05 - 9.0 | ±0.5 | 5 s | 10 s | 2.5 min |
| Pressure | 0 - 350 mmHg | ±5 mmHg when <100 mmHg<br><br>±10% when >100 mmHg | 0.5 s | 1 s | 1 s |
| Temperature | 25 - 49 °C | ±1 °C | 20 s | 40 s | 40 s |

Measurement details as presented by Hasler et al. (2009) [199].

*Gastric emptying:* In 2006, the wireless motility capsule was approved by the United States Food and Drug Administration (FDA) for measuring gastric emptying in patients with suspected gastroparesis. In 2011, the method was equated with gastric emptying scintigraphy and gastric emptying breath tests by the American and European Neurogastroenterology and Motility Societies [201]. Previous studies have found similar diagnostic accuracy as scintigraphy in both healthy participants and patients with gastroparesis, although the total number of head-to-head comparisons are low [202–204]. The wireless motility capsule calculates gastric emptying and other segmental transit times based on stereotypical pH profiles, as shown in Figure 7 (healthy subject) and Figure 13 (diabetic gastroparesis) [23,205]. Several studies have aimed to establish normative transit time values [206]. Results from the largest, most recent, and the only one including European participants are presented in Table 5 [23].

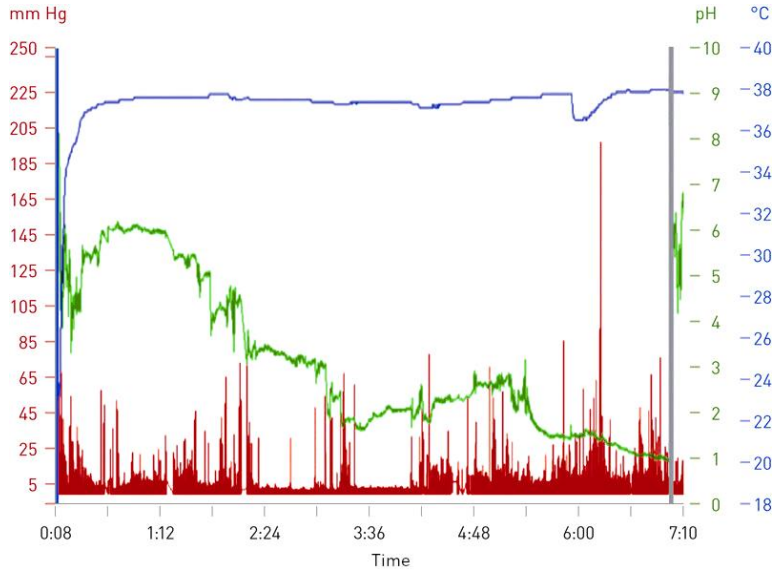



***Figure 13:*** *Wireless motility capsule recording in a patient with diabetic gastroparesis. Compared with the healthy subject in Figure 7, the pH curve (green) decreases more slowly. Gastric emptying (marked by grey) occurs at 7 hours 10 minutes. The capsule recording also shows pressure (red curve) and temperature (blue).* *Figure by Sangnes et al. Tidsskr Nor Laegeforen. 2016, adapted and reprinted with permission* [143].

*Small bowel transit:* The wireless motility capsule is also recommended for the investigation of small bowel transit, but very few studies have compared the method with other diagnostic modalities [137,147,207].

*Colonic and whole gut transit:* Evaluation of colonic transit in patients with suspected slow transit constipation is the other main indication for a wireless motility capsule examination, as approved by the FDA in 2009 [147]. Studies have shown good agreement with radiopaque markers both in healthy individuals and patients with constipation [208–210]. There is also good agreement with scintigraphic whole gut transit, which is often used as a surrogate marker for colonic transit [207].

**Table 5: Wireless motility capsule normative transit time values**

| | |
|---|---|
| Gastric emptying time | 1:45 – 5:00 |
| Small bowel transit time | 2:15 – 8:00 |
| Colonic transit time | 5:00 – 50:30 |
| Whole gut transit time | 10:45 – 68:45 |

Normative values defined by Wang et al. (2015) [23]. Time is given as hours: minutes.

*Other applications:* So far, none of the other physiological measurements captured by the wireless motility capsule have gained widespread clinical usage, partly due to the lack of validation against other methods. In research, most interest has been devoted to the capsule's pressure measurements [9,211]. Studies have investigated gastrointestinal contractility in several disease states, including gastroparesis of various etiologies, diabetes with and without distal symmetrical polyneuropathy, SIBO, obesity, and following Roux-en-Y gastric bypass surgery [29,51,90,130,155,160,162,212–214]. A few studies have also utilised the wireless motility capsule's pH measurements, while the temperature parameter is so far unexplored [200,213–217].

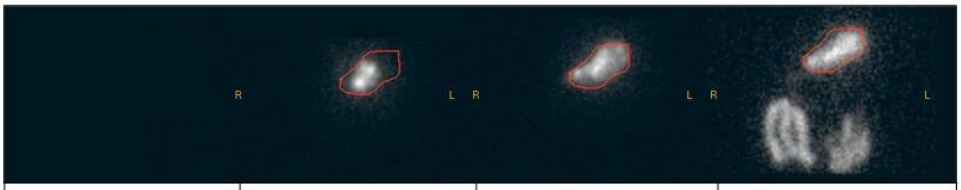
### 1.4.2 Other capsule-based tests

*The Motilis 3D-Transit system* is a new method for determining gastrointestinal transit, where electromagnetic signals from ingested capsules are detected by a magnetic plate attached to the patient's abdomen [218]. In addition to segmental transit times, a software refinement has enabled the 3D-Transit system to identify different colonic motility patterns [219].

*Video capsule endoscopy* (Pillcam®, Given Imaging, Yokneam, Israel) has been firmly established for the evaluation of obscure gastrointestinal bleeding and diseases affecting the small bowel mucosa. Researchers have also assessed its ability to measure regional transit times and motility, but this has so far not been transferred to clinical practice [220].

### 1.4.3 Scintigraphy

In 1966, Griffith et al. described the first method for determining gastric emptying using a radiolabeled solid meal. The researchers incorporated radioactive chromium ($^{51}Cr$) into a meal consisting of eggs and porridge. Thereafter, they conducted half-hourly scans with an automatic scintiscanner until the whole meal had left the stomach [221]. Although methods are refined and radioactive chromium is substituted with technetium-99m ($^{99m}Tc$), the principle behind gastric emptying scintigraphy is largely the same today. Scintigraphy is currently considered the reference standard for measuring gastric emptying. Many different protocols exist, but four-hour studies are considered to be most sensitive for detecting delayed gastric emptying [222]. Less than 10% retention after four hours is considered normal, whereas 10-15% indicate mild, 15-35% moderate, and more than 35% serious gastroparesis [20]. Figure 14 shows the scintigraphic findings in a patient with diabetic gastroparesis. Although less established than gastric emptying studies, scintigraphy can also be used to determine transit times through the small bowel, colon, and whole gut [220].




| Time | 1 hour | 2 hours | 4 hours |
|---|---|---|---|
| Retention | 89% | 78% | 55% |
| Normal values | <90% | <60% | <10% |

***Figure 14:*** *Gastric emptying scintigraphy results in the same patient as in Figure 13. More than half of the radioisotope meal is left in the stomach after four hours, indicating severe gastric retention.* *Figure by Sangnes et al. Tidsskr Nor Laegeforen. 2016, adapted and reprinted with permission* [143].

### 1.4.4 Breath tests

Breath tests have a wide clinical application, including the investigation of SIBO, carbohydrate malabsorption, and pancreatic exocrine insufficiency [223]. The $^{13}$carbon-labelled gastric emptying breath test for solids is one of the main tests for investigating gastric emptying [137,147,224]. The lactulose hydrogen breath test (LHBT) may be used to determine orocaecal transit time, an often-used proxy for small bowel transit [220].

### 1.4.5 Ultrasound

Transabdominal ultrasound (Figure 15) combined with a standardised meal (the ultrasound meal accommodation test) can be used to determine gastric emptying. The method also provides information about fundic accommodation, antral contractility, and pyloric function [17,152,225].

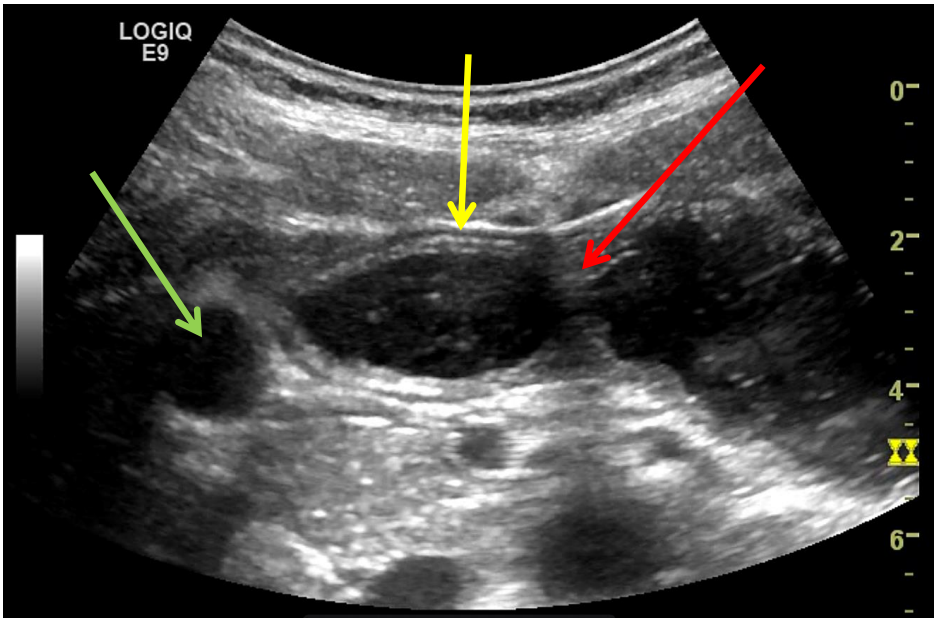



***Figure 15:*** *Transabdominal ultrasound, horizontal section of the antrum: In the middle of the picture, we can see a lumen occlusive contraction (marked by the red arrow) and the layers of the stomach wall (yellow arrow). The duodenal bulb is visible to the left (green arrow).* *Picture by Odd Helge Gilja, reprinted with permission.*

### 1.4.6 Radiopaque markers

The radiopaque marker test is the most used test to evaluate colonic transit in clinical practice. Different protocols exist, utilizing both single and multiple dose administration of capsules, and one or more abdominal radiographs at specified times [137,220]. Radiopaque markers can also be used to investigate gastric emptying [224,226].

### 1.4.7 Other methods

*Manometry* is the reference standard for measuring gastrointestinal contractility. Antroduodenal manometry measures contractile activity in the upper gastrointestinal tract, using a water-perfused or solid-state intraluminal catheter. It may distinguish normal from pathological motility and identify neuropathic or myopathic motility patterns. High-resolution manometry has recently emerged as a diagnostic modality in the small bowel and colon but has so far not gained much usage [137,220].

*Impedance planimetry:* The Endolumenal Functional Lumen Imaging Probe (EndoFLIP®, Crospon Inc., Galway, Ireland) utilises high-resolution impedance planimetry to measure pressure changes, diameter, and volume [227]. Thereby, it may determine wall stiffness or sphincter distensibility, for example in the pylorus [158,227].

*Magnetic resonance imaging* (MRI) is being investigated as a potential method for assessing transit and motility patterns throughout the gastrointestinal tract, while *single photon emission computed tomography* is used in a few centres for evaluating gastric accommodation [137,220].

*Electrogastrography* has experienced a renaissance after the invention of high-resolution electrogastrography. The method enables spatial measurements of abnormalities in the initiation and propagation of gastric slow waves [228].

*Gastric barostat* is validated for investigating gastric accommodation and sensitivity but is mainly used for research. The *satiety drinking test* and the *ultrasound meal accommodation test* might be more patient-friendly alternatives [152,229].

# 2. Aims and hypotheses of the study

## 2.1 Aims

The general aim of the study was to assess the wireless motility capsule's feasibility and accuracy in the investigation of diabetes patients with symptoms suggestive of gastroparesis, diarrhoea and constipation, the three main manifestations of diabetic gastroenteropathy. Specific aims of the study:

*1.1:* Assess the wireless motility capsule's diagnostic performance compared to gastric emptying scintigraphy.

*1.2:* Assess the interrater-reliability for the wireless motility capsule.

*1.3:* Identify the optimal cut-off value for delayed gastric emptying.

*1.4:* Compare symptom severity between patients with rapid, normal and delayed gastric emptying.

*2.1:* Investigate if gastrointestinal transit times differ between diabetes patients with and without diarrhoea.

*2.2:* Measure intraluminal pH levels and intestinal contractility and find out if these measures differ between patients with and without diarrhoea.

*2.3:* Investigate if patients with diarrhoea have more autonomic dysfunction.

*3.1:* Investigate if gastrointestinal transit times differ between diabetes patients with and without constipation.

*3.2:* Investigate if patients with constipation have reduced intestinal contractility.

*3.3:* Compare transit times and contractility parameters between diabetes patients with and without constipation, and healthy controls.

## 2.2 Hypotheses

*H1:* Wireless motility capsule has high diagnostic accuracy for evaluating gastric emptying in the investigation of diabetic gastroparesis.

*H2:* Diabetes patients with rapid or delayed gastric emptying have more symptoms than patients with normal gastric emptying.

*H3:* Diabetes patients with diarrhoea have altered gastrointestinal transit times.

*H4:* Diabetes patients with diarrhoea have altered intraluminal pH levels, reduced contractility, and autonomic dysfunction.

*H5:* Diabetes patients with constipation have delayed colonic transit and reduced intestinal contractility compared to diabetes patients without constipation, and healthy controls.

# 3. Material and methods


***Figure 16:*** *DIAGAS study logo.*
*Figure by Dag A. Sangnes*

We have performed the cross-sectional observational study "Comparison of new diagnostic tests in the investigation of suspected gastroparesis (DIAGAS)" (original Norwegian title: "Sammenligning av nye diagnostiske tester i utredning av mistenkt gastroparese", project leader Georg Dimcevski) (Figure 16). The study was conducted between 2014 and 2018 at the Department of Medicine, Haukeland University Hospital, Bergen, Norway. The investigation of healthy participants using wireless motility capsule has been performed in collaboration with two other studies: "Fluid overload and motility disturbances in the small intestine – characterisation of the effects of an activating GUCY2C mutation" (project leader Hilde Løland von Volkmann), and "SMARTNORM: Evaluating normal gastrointestinal physiology using the wireless motility capsule SmartPill™" (project leader Jan Gunnar Hatlebakk) [230].

## 3.1 Study population

Two groups were included in the study: diabetes patients (all three papers), and healthy controls (paper III). The exclusion criteria were similar for both groups: age below 18 years; current pregnancy or breastfeeding; previous surgery affecting the gastrointestinal tract (except appendectomies); active malignancy (any cancer not in complete remission for the last six months); and lack of ability to comply with the study protocol, including not stopping prohibited medications (specified below).

### 3.1.1 Diabetes patients

Inclusion criteria were type 1 diabetes or type 2 diabetes, chronic gastrointestinal symptoms of more than six months duration, and a normal upper endoscopy in the previous 24 months. Patients came from all of Norway and were included prospectively when they were admitted for diagnostic evaluation at Haukeland University Hospital. They stayed three days at the hospital. Patients were interviewed

and examined by a physician, had routine laboratory tests, and underwent autonomic function tests, and gastrointestinal motility and function tests. Questionnaires were sent out in advance and collected at hospital admittance.

### 3.1.2 Healthy controls

Before inclusion, healthy volunteers were screened for gastrointestinal symptoms using modified Rome III questionnaires. They were also interviewed by a clinical investigator to rule out diseases or use of medications potentially influencing test results. Besides wireless motility capsule examinations, the healthy volunteers did not undergo any of the other examinations in the study protocol.

## 3.2 Laboratory tests

*Blood samples:* haemoglobin, leukocytes with differential, reticulocytes, thrombocytes, sodium, potassium, calcium, chloride, creatinine, albumin, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, glycated haemoglobin, thyroid stimulating hormone, and free thyroxine.

*Urine samples:* creatinine, and albumin/creatinine ratio.

*Stool samples:* faecal calprotectin, and faecal elastase-1.

## 3.3 Gastrointestinal motility and function tests

We performed simultaneous wireless motility capsule and gastric emptying scintigraphy measurements. Both tests are presented in chapter 1.4, while Methodological considerations are addressed in chapter 5.2. We also conducted the ultrasound meal accommodation test. Results from this test are not included in this dissertation, but a full description and results can be found in Steinsvik et al. (2021) [152]. Before the tests, all participants had to stop specified medications, as described in paper I. They were also discouraged from smoking, drinking alcohol, and commence strenuous physical activity during the whole wireless motility capsule

examination. All motility and function tests were commenced at 09:00 AM, after participants had fasted for a minimum of eight hours. Diabetes patients were connected to glucose insulin infusions while fasting or undergoing examinations, with a target blood glucose level of 4-10 mmol/L.

### 3.3.1 Gastric emptying test protocol

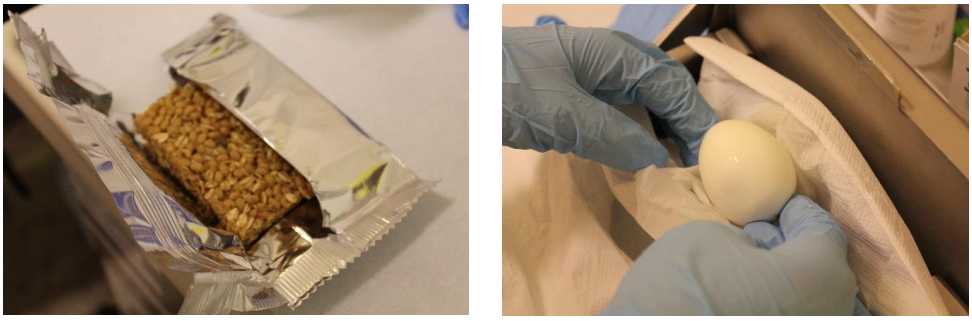


***Figure 17:*** *The meal consisted of one Smartbar (left) and a boiled egg radiolabeled with Tc-99m-nanocolloid.* *Photographs by Dag A. Sangnes.*

We utilised a meal combining the standardised nutrient bar developed for the wireless motility capsule test (SmartBar, Medtronic) and a boiled egg radiolabeled with Tc-99m-nanocolloid (Figure 17). The nutrient bar contains 260 kilocalories (kcal; 66% carbohydrate, 17% protein, 2% fat, 3% fiber), and the egg contains on average 90 kcal (1.1% carbohydrate, 13% protein, 11% fat, 0% fiber). The participants could drink 120 mL still water together with the meal. After meal intake, they ingested the wireless motility capsule, and we immediately started scintigraphic imaging. The participants fasted for an additional six hours but were allowed to drink another 100 mL still water. After six hours, dietary restrictions were lifted.

### 3.3.2 Wireless motility capsule

Upon conclusion of the scintigraphy, the rest of the wireless motility capsule (Figure 18) examination was conducted while participants were ambulant. After five days, they returned the receiver in a pre-stamped protected box and results were downloaded to a secure computer. We used MotiliGI software version 3.0 (Medtronic) to analyse results. Each test was analysed by two different investigators, both of whom were blind to the other's interpretation.

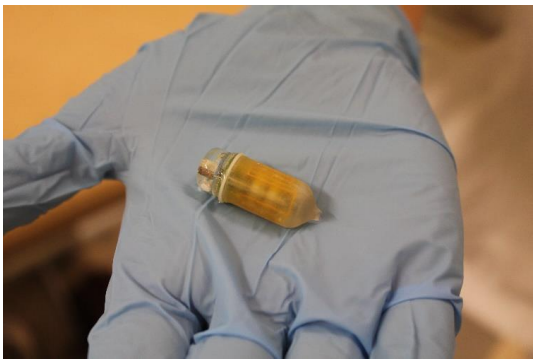


**Figure 18:** *The wireless motility capsule measures 26.8 x 11.7 mm. Photo by Dag A. Sangnes.*

Transit times were calculated after defining the following landmarks: 1) capsule ingestion: a sudden rise in temperature from room temperature to 37°C, normally accompanied by a pH drop and a pressure spike; 2) pylorus: a sharp pH rise (normally >3 pH units) lasting more than 10 min, 3) the ileocaecal junction: a pH drop (normally >0.5 pH units), also lasting more than 10 min; and 4) capsule expulsion: a sudden temperature drop, often associated with a loss of signal. Based on these landmarks, we measured gastric emptying time (capsule ingestion – pylorus), small bowel transit time (pylorus – ileocaecal junction), colonic transit time (ileocaecal junction – capsule expulsion), and whole gut transit time (capsule ingestion – capsule expulsion) [23].

In paper II, we also evaluated gastrointestinal pH levels, and the contractility parameters motility index, contractions per minute, and ileocaecal junction pressure. In addition to median pH levels during gastric emptying time, small bowel transit time, and colonic transit time, we assessed median pH for the following sub-segments: antrum (last 15 min before pylorus), duodenum (first 15 min after pylorus), ileum (last 15 min before the ileocaecal junction), caecum (first 15 min after the ileocaecal junction), and rectum (last 15 min before capsule expulsion). Delta pylorus was defined as the difference between duodenal and antral pH, and delta ileocaecal junction as the difference between caecal and ileal pH. Motility index and contractions per minute were measured for each organ. For measuring the ileocaecal junction pressure, we utilised the method developed by Chander Roland et al. (2014): the highest pressure measured the last 4 min before the ileocaecal junction pH drop [212].

In paper III, we also evaluated motility index and contractions per minute in the small bowel and colon, and in the following sub-segments: duodenum (first 60 min after the pylorus), ileum (last 60 min before the ileocaecal junction), caecum (first 60 min after the ileocaecal junction), and rectum (last 60 min before capsule expulsion).

### 3.3.3 Gastric emptying scintigraphy

We performed simultaneous anterior and posterior planar scintigraphy of the upper abdomen using a double-headed camera system (Siemens e.cam; Siemens Healthineers, Erlangen, Germany), taking pictures at 0 min, 0.5 h, 1 h, 2 h, 3 h, and 4 h (Figure 19). We used Segami Oasis 1.9.4.9 (Segami Corporation, Columbia, USA) to demarcate a region of interest on the 0-min picture of the stomach. Thereafter, we copied the region of interest onto pictures taken at the other time-points (illustrated in Figure 14), before we calculated retention rates at each time-point.

***Figure 19:*** *The gamma camera used for gastric emptying scintigraphy (Siemens e.cam; Siemens Healthineers, Erlangen, Germany).Photo by Dag A. Sangnes.*

## 3.4 Autonomic function tests

We investigated cardiovascular autonomic function by assessing heart rate variability, baroreflex sensitivity, and orthostatic hypotension. We measured resting heart rate variability and baroreflex sensitivity with the Heart Rhythm Scanner PE using the Biocom 5000 Bluetooth ECG Recorder (Biocom Technologies, Poulsbo, USA). Orthostatic blood pressure measurements were performed using Welch Allyn ProBP 3400 (Welch Allyn Inc., Skaneateles Falls, USA). A detailed description of the heart rate variability protocol is given in paper I, while protocols for baroreflex sensitivity and orthostatic hypotension examinations are given in paper II.

## 3.5 Questionnaires

We used the following validated questionnaires: Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM), Gastrointestinal Symptom Rating Scale (GSRS), Hospital Anxiety and Depression Scale (HADS), and Eysenck Personality Questionnaire (EPQ). Results from the EPQ are so far not published, and the questionnaire will not be described any further.

### 3.5.1 PAGI-SYM

PAGI-SYM measures upper gastrointestinal symptoms occurring during the last two weeks. The 20 items are graded on a six-point scale from zero (no symptoms) to five (very serious symptoms). PAGI-SYM can be grouped into six subscores: 1) nausea/vomiting; 2) fullness/early satiety; 3) bloating; 4) upper abdominal pain; 5) lower abdominal pain; and 6) heartburn/regurgitation. The Gastroparesis Cardinal Symptom Index (GCSI) is the average of subscores 1-3 [231,232].

### 3.5.2 GSRS

GSRS assesses upper and lower gastrointestinal symptoms occurring during the last week. The questionnaire includes 15 questions, each graded from zero points (no discomfort) to six points (very severe discomfort). The questions can be categorised into five scales: abdominal pain, reflux, indigestion, diarrhoea, and constipation [233,234]. In paper II, we utilised the diarrhoea scale, defining a score ≥4 points as diarrhoea. Patients scoring <4 points were used as controls. In paper III, we used the constipation scale, also defining 4 points as a cut-off between cases and controls.

### 3.5.3 HADS

HADS is a screening instrument for identifying clinically significant cases of anxiety and depression in patients undergoing investigation or treatment for somatic diseases. The questionnaire has 14 questions: seven regarding anxiety; seven regarding depression. Each question is graded from zero to three points. Cases of anxiety and depression were defined as a sum score ≥11 points on each respective subscale [235].

## 3.6 Statistical analysis

We assessed normality by examining skewness, kurtosis, and Q-Q plots, and performing the Shapiro Wilk's test. When fulfilling criteria for normality, we stated continuous variables as mean (standard deviation), and calculcated differences between two groups using the independent samples *t*-test, and between multiple groups using one-way independent analysis of variance (ANOVA). We corrected the ANOVA using Welch's F and performed Games-Howell post-hoc tests. We used Pearson's product-moment correlation ($r$) to examine associations between normally distributed continuous variables.

When not fulfilling criteria for normality, we stated continuous variables as median (interquartile range), and calculated differences between two groups using the Mann-Whitney U test, and between multiple groups using the Kruskal Wallis test. We performed post-hoc sub-group analyses using Mann-Whitney U test with Bonferroni correction. We used Spearman's rank order correlation ($r_s$) to examine associations between non-normally distributed continuous variables.

We stated categorical variables as *n* (%) and assessed the differences between them using Pearson's chi-square test (paper I and paper II), and Fisher's exact test (paper III). In paper I, we assessed the wireless motility capsule's diagnostic performance by calculating sensitivity, specificity, positive and negative predictive values, accuracy, positive and negative likelihood ratios, and a receiver operating characteristics (ROC) curve. The optimal cut-off value was identified by calculating the maximum Youden's index. We calculated Cohen's kappa measure of agreement ($\kappa$) both in paper I and paper II.

Statistical significance was defined as $p \leq 0.05$ in all three papers. Analyses were performed using IBM SPSS Statistics (IBM Corporation, Armonk, USA) versions 25 (paper I) and 27 (paper II and paper III). In paper II, we also calculated effect size estimates using Microsoft Excel version 2102 (Microsoft Corporation, Redmond, USA). For full details regarding effect size estimates, please refer to the Statistical analysis section in paper II.

## 3.7 Ethics approval

The study was conducted in accordance with the Nuremberg Code and the World Medical Association's Helsinki Declaration. The DIAGAS study was approved by the Western Norway Regional Medical Ethics Committee (2015/58), while the study of healthy participants was approved by the South-Eastern Norway Regional Medical Ethics Committee (2014/2222; 2019/28472). Prior to study-related procedures, all participants submitted oral and written consent. Ethical considerations are discussed in chapter 5.3.

# 4. Results

## 4.1 Paper I

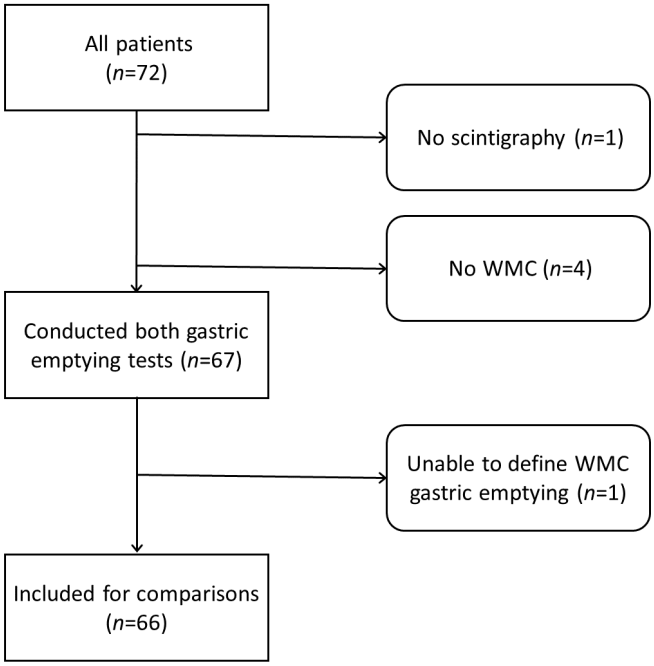



***Figure 20:*** *Paper I inclusion flowchart.*
*Figure by Sangnes et al. Neurogastroenterol Motil 2020, reprinted and modified with permission.*

*Abbreviations: WMC, wireless motility capsule.*

This paper presents the comparison of wireless motility capsule and 4-hour gastric emptying scintigraphy, the current reference standard for measuring gastric emptying. After exclusions, we included 66 patients for comparisons. An inclusion flowchart is presented in Figure 20. We found that gastric emptying measured with wireless motility capsule correlated $r_s$=0.74 ($p$<0.001) with 4-hour scintigraphy. Area under the curve for the receiver operating characteristics (ROC) curve was 0.95 ($p$<0.001). Using the standard 300-minute cut-off value for delayed gastric emptying, sensitivity was 0.92, specificity 0.73, accuracy 0.80, and Cohen's kappa κ=0.61 ($p$<0.001). Agreement between the two examiners were κ=0.97 ($p$<0.001). By using ROC curve coordinates, we found that 385 minutes was the optimal cut-off value for delayed gastric emptying in this patient group, yielding a sensitivity of 0.92, specificity 0.83, accuracy 0.86, and κ=0.72 ($p$<0.001). Finally, we found no difference in total PAGI-SYM score, GCSI, nor any of the subscores when comparing patients with rapid, normal, and delayed gastric emptying.

## 4.2 Paper II

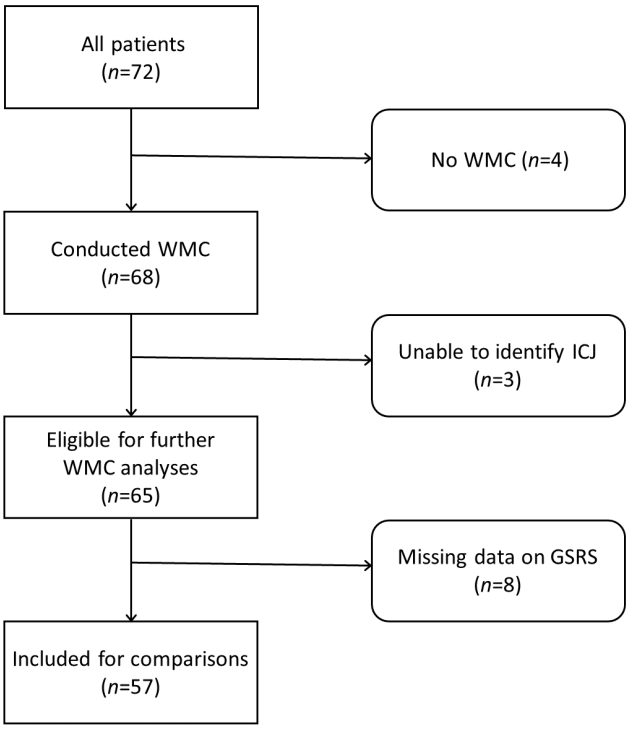



***Figure 21:*** *Paper II inclusion flowchart.*
*Figure by Sangnes et al. J Intern Med. 2021, reprinted and modified with permission.*

*Abbreviations: WMC, wireless motility capsule. ICJ, ileocaecal junction, GSRS, Gastrointestinal Symptom Rating Scale.*

This paper presents gastrointestinal transit, pH levels, contractility parameters and autonomic function test results in diabetes patients with and without diarrhoea. After exclusions, 57 patients were included for comparisons. An inclusion flowchart is presented in Figure 21. We found that 17 patients (30%) had diarrhoea. They had slower gastric emptying (21:46; 4:14, hours: minutes, $p$=0.03), and faster colonic transit (18:37; 54:25, $p$<0.001) than controls. They also had higher pH levels in the antrum (2.4; 1.2, $p$=0.009), caecum (7.3; 6.4, $p$=0.008), and whole colon (7.1; 6.7, $p$=0.05), and smaller pH difference across the pylorus (3.3; 4.9, $p$=0.004), and ileocaecal junction (0.6; 1.0, $p$=0.009). We found no differences in intestinal contractility. Neither did we find any difference in autonomic function between cases nor controls, but diastolic blood pressure drop during ortostatic tests correlated $r_s$=−0.34 ($p$=0.04) with colonic transit time.

## 4.3 Paper III

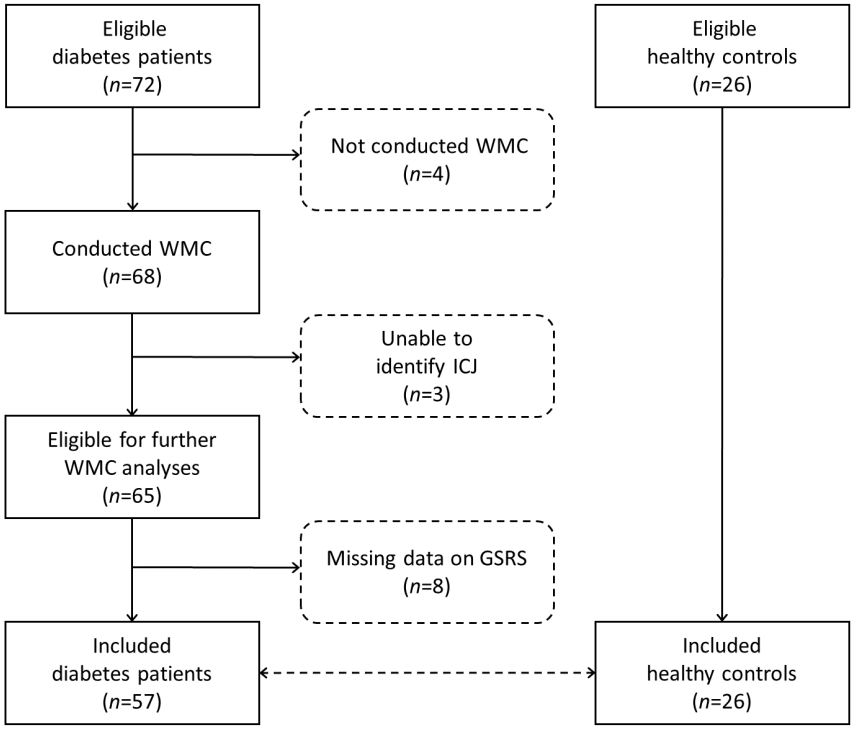



***Figure 22:*** *Paper III inclusion flowchart.* *Figure by Sangnes et al. United European Gastroenterol J. 2021, reprinted with permission. Abbreviations: WMC, wireless motility capsule. ICJ, ileocaecal junction, GSRS, Gastrointestinal Symptom Rating Scale.*

This paper presents gastrointestinal transit and contractility in diabetes patients with and without constipation, and in healthy controls. After exclusions, 57 patients and 26 healthy controls were included in the study. An inclusion flow-chart is presented in Figure 22. We found no difference in transit times when comparing diabetes patients with and without constipation. Patients with constipation (66:15, $p$=0.03), and without constipation (71:16, $p$<0.001) both had slower whole gut transit than healthy controls (35:55). We also found a correlation ($r_s$=-0.32, $p$=0.01) between small bowel motility index and constipation symptoms, but we found no association with colonic contractility.

# 5. Discussion

In this study, we have evaluated the wireless motility capsule's role in the investigation of diabetic gastroenteropathy. In paper I, we found that the wireless motility capsule had high diagnostic accuracy for identifying delayed gastric emptying in diabetes patients with suspected gastroparesis, but we found no association between gastric emptying and patient reported symptoms. In paper II, we found that patients with diabetic diarrhoea had slower gastric emptying and faster colonic transit, compared with controls. They also had changes in intraluminal pH levels, but not in intestinal contractility or autonomic function. In paper III, we found no difference in colonic transit or any other transit time, when comparing diabetes patients with and without constipation. Constipation was associated with reduced small bowel, but not colonic contractility. We also found that diabetes patients, regardless of constipation, had slower whole gut transit than healthy controls.

## 5.1 Clinical considerations

### 5.1.1 Measurement of gastric emptying

Despite its mandatory role in gastroparesis diagnostics, the necessity of determining gastric emptying is controversial. This is due to several factors, where the questionable relationship with symptoms is the most important. In paper I, we found no difference in symptoms between patients with rapid, normal, and delayed gastric emptying, disproving our hypothesis. We found similar results in a previous study using breath tests and radiopaque markers [224]. In another study, we found that patients with normal and delayed emptying had similar symptom profiles at baseline and after three years [72]. A systematic review and meta-analysis, however, found an association between gastric emptying and early satiation/fullness in diabetes patients, but not with nausea, vomiting, abdominal pain and bloating [236].

Also questioning the use of gastric emptying measurements, is the finding that gastric emptying results have high intra-individual variability [129]. If the results change from one examination to another, this may potentially lead to a reclassification from

gastroparesis to normal emptying, and vice versa [129,237]. However, these findings are also controversial, with other studies showing stable gastric emptying after 12 and 25 years follow-up [238,239]. Consequently, some writers argue that there should be a defined distinction between gastroparesis and mildly delayed gastric emptying. Horowitz et al. have proposed that the gastroparesis-diagnosis is reserved for those with delayed emptying more than three standard deviations from the normal range [44]. This is a valid argument given that almost one in three patients with functional dyspepsia have mildly delayed gastric emptying. At the same time, there are many asymptomatic patients with severely delayed gastric emptying, as exemplified by Kassander's "gastroparesis diabeticorum" [47]. If using today's symptom-defined criteria, these patients would fall outside the gastroparesis definition. Yet, one possible pathophysiological explanation is that they initially experienced gastrointestinal symptoms, perhaps even visceral hypersensitivity, but because of disease progression, they gradually developed hyposensitivity caused by increased destruction of sensory neurons.

In our opinion, the use of strict cut-off values for gastric emptying and rigid symptom criteriae, may have led gastroparesis research into a blind-track. As diabetic gastroparesis is caused by many pathophysiological mechanisms, targeting these separately may prove more beneficial than just aiming towards normal gastric emptying, as discussed in chapter 6.2. Nevertheless, gastric emptying measurements continue to play a role in examining diabetes patients with suspected gastroparesis. This is most important in patients experiencing difficulties with blood glucose regulation, as gastric emptying may be responsible for 35% of post-prandial variation in blood glucose levels [44]. Clinically, we have often experienced that treating gastric dysmotility has led to improved glycaemic control, including reduced numbers of hypo- and hyperglycaemic episodes. Studies investigating the long-term effect of gastric electrical stimulation, have also shown a beneficial effect on glycaemic control [240,241]. In collaboration with researchers from Denmark, we are currently in the process of initiating a treatment study, investigating the effect of peroral pyloromyotomy on glycaemic control. Another argument for gastric emptying measurements, is to determine oral drug absorption, which can be delayed in patients

with gastroparesis [44]. However, we believe that gastric emptying measurements should be part of a more comprehensive evaluation, also considering concurrent dysmotility in other parts of the gastrointestinal tract, as will be discussed in chapter 5.1.3.

### 5.1.2 Measurement of small bowel and colonic transit

Gastrointestinal transit time measurements have traditionally played a peripheral role in the investigation of chronic diarrhoea [242]. Based on the results presented in paper II, transit studies may deserve a more prominent role in the diagnostic algorithm of diabetic diarrhoea. We found that patients with diabetic diarrhoea had slower gastric emptying and faster colonic transit than controls, confirming our hypothesis. We also observed a tendency towards faster small bowel transit in patients with diarrhoea, but our study may have been underpowered to detect a significant difference. Findings from older studies investigating transit in diabetic diarrhoea can roughly be grouped in two: 1) slow small bowel transit and an association with SIBO, and 2) fast small bowel transit and an association with neuropathy [86,175]. More recently, an association between slow small bowel transit and SIBO has been found using wireless motility capsule, although no studies have been performed in diabetes [29]. There are limited data regarding colonic transit in patients with diabetic diarrhoea.

As we have advocated elsewhere in the dissertation, treatment of diabetic gastroenteropathy should to a larger extent be individualised based on diagnostic findings. In diabetic diarrhoea, an early stratification into slow and fast intestinal transit could guide further investigations and direct treatment. As indirect tests for SIBO without simultaneous transit time measurements have unsatisfactory diagnostic accuracy, some writers recommend a test-and-treat regime with antibiotics [171]. Due to the increasing antibiotic resistance, we would rather recommend postponing treatment until the patient has undergone adequate testing, including determination of intestinal transit. In the opposite group with fast transit, some patients require potent opiates to control their diarrhoea. As these drugs have abuse potential, dose titration

until normalised transit times could be an objective measurement of treatment efficacy.

In the diagnostics of constipation, transit time measurements traditionally have a more central role than in diarrhoea, and slow colonic transit has long been considered the main pathophysiological mechanism behind diabetic constipation. However, our results in paper III, did not support this hypothesis. As discussed in the paper, our findings might have several explanations, including the unspecific nature of gastrointestinal symptoms and the co-occurrence of psychiatric comorbidities. We consider that the most likely cause of our findings might be that rectal evacuation disorders are more prevalent than slow transit constipation in diabetes, showing a similar distribution like in primary constipation [243]. Unfortunately, we did not perform tests of anorectal motility and sensitivity in this study, but we have previously shown that diabetic neuropathy may be associated with rectal hyposensitivity [244]. Considering that the autonomic nervous system has an essential role in controlling the process of defecation, it seems plausible that diabetic neuropathy may lead to evacuation disorders. Although finding support in a recent study, there is a need of further studies investigating the role of evacuation disorders in the pathophysiology of diabetic constipation [181].

### 5.1.3 Multiregional dysmotility

In paper III, we also found that both diabetes groups, regardless of constipation symptoms, had slower gastric emptying and whole-gut transit compared to healthy controls. In paper II, patients with diabetic diarrhoea and rapid colonic transit, had increased likelihood of having delayed gastric emptying. In so far unpublished data, we found that more than 25% of symptomatic diabetes patients had abnormal transit through two or more gastrointestinal segments. Overall, our findings imply that diabetic gastroenteropathy is a pan-enteric motility disorder. This interpretation is supported by findings from other motility studies, as well as the identification of similar histopathological alterations in both the stomach, small bowel, and colon [134,216,245–247].

The multi-organ affection in diabetic gastroenteropathy might be an explanation for the often-poor specificity of gastrointestinal symptoms. At the same time, it strengthens the argument for examining more than one segment at once. For instance, in patients presenting symptoms suggestive of both gastroparesis and diarrhoea, a wireless motility capsule examination could spare the patients of additional tests, as opposed to gastric emptying scintigraphy or gastric emptying breath tests. In patients with multiregional dysmotility, pharmacological treatment could also be tailorised by transit findings. An example is patients with concurrent gastroparesis and fast-transit diarrhoea, where both ondansetron and clonidine may reduce nausea and vomiting, reduce stool volume and frequency, and normalise intestinal transit [248–250].

### 5.1.4 Measurement of pH and contractility

The clinical utility of the wireless motility capsule's pH measurements is so far undefined. In paper II, we found that patients with diarrhoea had alterations in gastrointestinal pH levels. To our knowledge, no previous studies have demonstrated similar findings in patients with diabetic diarrhoea. Our results should be confirmed and elaborated in follow-up studies before pH measurements are incorporated into regular diarrhoea workup. However, there are some additional justifications for measuring pH in diabetes patients: one is their increased likelihood of developing SIBO, associated with elevations in both gastric and small bowel pH; another is the link with autoimmune atrophic gastritis, which may lead to elevated gastric pH [29,251].

Even though we failed to reveal any major contractility derangements in patients with diarrhoea and constipation, we cannot rule out that these measurements may come useful when evaluating diabetes patients with suspected dysmotility. Previous studies have shown that the wireless motility capsule's contractility measurements might identify clinically relevant pathology [90,130,160,162]. However, as we discuss in chapter 5.2.3, the method might need some refinement to fulfil its potential.

### 5.1.5 The association with autonomic dysfunction

Because of the long-term association between diabetic diarrhoea and autonomic neuropathy, we hypothesised that patients with diarrhoea had more autonomic dysfunction. Somewhat surprisingly, we only managed to find minimal changes in orthostatic blood pressure and no differences in neither heart rate variability nor baroreflex sensitivity in these patients. In paper II, we have discussed possible explanations, where we consider pathological alterations to the ENS to be the most likely cause. The sympathetic nervous system is equally represented throughout the gastrointestinal tract, but the parasympathetic nervous system's innervation is most dense in the proximal and distal parts. Consequently, the intestines may have an increased dependency on intact ENS function, increasing its vulnerability for diabetes induced damage. Another explanation may be the control group, which in this study consisted of diabetes patients with gastrointestinal symptoms, but without diarrhoea. To further elucidate the possible link between autonomic dysfunction and diarrhoea, a third control group of matched diabetes patients without gastrointestinal symptoms would be needed.

Currently, there are no ideal tests for measuring gastrointestinal autonomic function [252,253]. In this study, we utilised tests for measuring heart rate variability, baroreflex sensitivity and orthostatic blood pressure. These are all validated for assessing cardiovascular autonomic function, which is often used as a proxy for gastrointestinal autonomic function. Both we and others have previously shown associations between cardiovascular and gastrointestinal autonomic dysfunction [244,254].

## 5.2 Methodological considerations

### 5.2.1 Measurement of gastric emptying

In contrast to the radioisotope marked meal used in gastric emptying scintigraphy, the wireless motility capsule empties from the stomach with a phase III MMC [9]. The frequency of phase III MMCs varies between individuals, and in diabetes patients

with autonomic neuropathy they may be absent [153]. Combined with antral hypomotility, as seen in gastroparesis, emptying of indigestible solids may therefore be unpredictable [52]. Despite this, the wireless motility capsule demonstrated very high diagnostic accuracy for evaluating gastric emptying, compared to scintigraphy. When increasing the cut-off value for delayed emptying from 300 to 385 min, we found an even higher specificity and accuracy without compromising on sensitivity. We also found a near-perfect inter-rater agreement. The capsule software also provides automatic analyses of segmental transit times, correlating very strongly with manual determination of gastric emptying, but having an error rate of 25%.

Our results strengthens previous findings that the wireless motility capsule can be considered equal to the current reference standard, 4-hour gastric emptying scintigraphy [202,204]. The wireless motility capsule has also shown similar accuracy as breath tests, the second-most widespread method for investigating gastric emptying [255]. The wireless motility capsule's main benefit compared to these tests, is the ability to measure transit throughout all gastrointestinal segments during one examination. This may have important clinical consequences. Furthermore, the wireless motility capsule has a standardised protocol that includes its own meal. In contrast, gastric emptying scintigraphy protocols may differ between centres both regarding implementation and meal composition [202,222]. So far, the capsule has limited availability, but the total costs are comparable to other methods, especially considering that the initiation can take place in tandem with regular half-hour visits at the outpatient clinic [196].

### 5.2.2 Measurement of small bowel and colonic transit

Manual identification of gastric emptying is normally uncomplicated due to the characteristic increase in pH levels across the pylorus, as shown in Figure 7 (page 22). The transition across the ileocaecal junction, may be more difficult to identify, as the differences in pH may be subtle. To compensate for this, the capsule software calculates the combined small bowel and colonic transit time, yet this marker is mainly useful as a pseudomarker for colonic transit. When correctly identified,

however, the pH drop corresponds well with the transition between the small bowel and colon [200]. In so far unpublished data, we found very strong correlations between small bowel ($r_s$=0.963, $p$<0.001) and colonic ($r_s$=0.997, $p$<0.001) transit times defined by two different examiners. The automatic software analyses also correlated very strongly with manual determination of colonic transit ($r_s$=0.991, $p$<0.001), but weakly with small bowel transit ($r_s$=0.496, $p$<0.001), mirroring findings from previous studies [23]. The software failed to identify the ileocaecal junction in 28%, compared to 4% in manual analyses.

Similar to gastric emptying, scintigraphy is considered the reference standard for measuring small bowel transit, but the method has much lower availability than its more renowned sibling. Furthermore, the technique lacks standardisation, exposes patients to radiation, is time-consuming, and demands specialised personnel. Scintigraphy is also limited by its lack of specific anatomical landmarks to identify the ileocaecal junction. The protocols measuring small bowel transit as a percentage of colonic filling at six hours, without correcting for gastric emptying, are vulnerable for misinterpretation in patients with delayed gastric emptying [137,147]. A similar limitation applies to the lactulose hydrogen breath test (LHBT). Lactulose is an osmotic laxative which may delay gastric emptying and accelerate small bowel transit. In patients with SIBO, it may be prematurely metabolised by small bowel bacteria, leading to falsely short transit time results [137,147]. When accounting for all limitations, the wireless motility capsule stands out positively compared to other methods for examining small bowel transit time. However, our study was not designed to compare the capsule's diagnostic performance against neither small bowel scintigraphy nor LHBT, and only one previous validation study has been performed [207]. Further research is therefore required to conclude what is the ideal test for measuring small bowel transit.

As we did not perform head-to-head comparisons between the wireless motility capsule and any of the two preferred methods for measuring colonic transit, scintigraphy and radiopaque markers, we are unable to draw strong conclusions regarding the capsule's role in colonic transit time measurements. Previous studies

have, however, demonstrated good correlation with both scintigraphy and radiopaque markers [207–210]. None of the available methods fulfil all desired criteria for an ideal motility test, but given its low cost, good patient tolerance, and easy implementation into clinical practice, the radiopaque marker test has undisputedly gained the largest usage. Compared to scintigraphy and the wireless motility capsule, the method provides less accurate results. Both scintigraphy and radiopaque markers have issues regarding standardisation, they are time-consuming, and expose patients to radiation. In comparison, the wireless motility capsule is well standardised, quick to initiate and interpret, and do not require radiological examinations except for the rare occations where capsule retention is suspected (0.33% according to postmarketing analyses) [256]. However, compared to radiopaque markers, the test is more expensive and currently has much lower availability.

### 5.2.3 Measurement of pH and contractility

The wireless motility capsule's ability to perform pH and contractility measurements is one of its most exciting features. So far, normative data are provided for these parameters from the stomach, small bowel, and colon, as well as for the pH difference across the pylorus and ileocaecal junction, and for the last 15 minutes before capsule expulsion [23,257]. In contrast to the electromagnetic 3D-Transit system, in which every movement of the capsule is tracked by the external magnetic plate, the intraluminal location of the wireless motility capsule is only approximate, except when it passes the pylorus or ileocaecal junction. Consequently, the capsule is unable to measure regional transit, as well as provide accurately located pH and contractility measurements. This is a limitation of the method, which we attempted to overcome in paper II and III by using explorative temporal measurements to define the regions of interest. In paper II, our use of 15-minute measurements to investigate the pH levels in the regions adjacent to the pylorus and ileocaecal junction, are most likely adequately accurate for its purpose, and correspond with the chosen time intervals used in the reference paper by Wang et al. (2015) [23].

The 60-min time windows used for contractility measurements in paper III may have been too inaccurate to identify any relevant pathology, possibly also explaining why we did not find any differences in colonic contractility between the groups. Another important limitation of the capsule is that it only has one pressure sensor and is floating freely inside the lumen. Thus, in contrast to the fixed manometry catheters, the capsule may move back-and-forth. It is only able to measure contractility at a single recording site and might not identify propagating pressure waves seen with manometry. Studies comparing the wireless motility capsule and antroduodenal manometry, found that the contractility patterns were most different in the fundus, which may be explained by the larger lumen and lower amplitude of contractions [9]. In the antrum, the two modalities showed similar patterns, demonstrating close correlation for the identification of individual antral contractions [9]. The wireless motility capsule was also able to detect phase III MMCs in both the stomach and small bowel [211]. There are currently no studies validating the wireless motility capsule's contractility measurements against small bowel or colonic manometry. Given that manometric examinations are limited by reduced patient tolerance, are cumbersome and time-consuming, demands expertise to interpret, and has little availability beyond specialised centres, it is necessary with further research into more patient-friendly, non-invasive methods for investigating intestinal contractility [196].

### 5.2.4 Other methodological considerations

*Gastric emptying test protocol:* To be able to perform simultaneous wireless motility capsule and gastric emptying scintigraphy tests, we had to make some adjustments to the standard meal, as described in Chapter 3.3.1. The addition of an extra 90 kcal may have led to a slight increase in gastric emptying time in the diabetes patients. Given that this affected both tests equally, results from the diagnostic test comparison in paper I are likely unaffected. However, we cannot rule out that the difference in gastric emptying between patients and healthy controls presented in paper III might have been smaller if the caloric content of the meals had been equal.

*Questionnaires:* The GSRS questionnaire is well-validated for investigating upper and lower abdominal symptoms and is frequently utilised in studies. Its main limitation is the lack of a predefined cut-off value. In paper II, we chose a cut-off value of ≥4 points to define cases with diarrhoea; those scoring <4 points were used as controls. The cut-off value corresponded to the 75$^{th}$ percentile and was meant to be conservative, to ensure that the case group consisted of true positive cases with diarrhoea. The risk of this approach was that we got too many false negatives: patients with diarrhoea falsely classified as controls. We attempted to control this by making post-hoc Kappa analyses, and performing correlation analyses between the continuous variables, both showing good agreement. When calculating results for paper III, we utilised a similar approach.

## 5.3 Ethical considerations

Our study has some ethical concerns. As part of the standardised wireless motility capsule protocol, participants had to stop certain medications before and during the examination. There are good reasons for this: proton pump inhibitors would, for instance, lead to falsely elevated pH levels, while opioids delay gastrointestinal transit. Furthermore, the drugs listed are not vital but prescribed as symptomatic treatment. Nevertheless, it is not unproblematic to stop treatment for twelve days in patients with severe reflux, or eight days in patients with excruciating neuropathic pain. Some of the tests included in the study could be stressful for the patients, like the potential provocation of retching during ingestion of the capsule, or the discomfort associated with prolonged fasting. Fasting may be challenging for diabetes patients, given the risk of developing hypoglycaemia, but we attempted to control this by keeping patients connected to glucose insulin infusions. Scintigraphy also exposes patients to a small dose of ionising radiation. Finally, although patients were informed that participation in the study was voluntary, and everyone could withdraw their consent at any time without consequences for further treatment, we cannot rule out that some of the patients felt an obligation to participate.

## 5.4 Study limitations

Limitations regarding the wireless motility capsule, gastric emptying protocol, and questionnaires have been addressed in chapter 5.2. A discussion of additional study limitations will be addressed briefly in this chapter:

*Study design:* The study was an experimental, cross-sectional observational study, and was not designed to assess causality.

*Study population:* The diabetes population consisted of more women, more patients with type 1 diabetes, and patients referred for investigation at a tertiary centre. Consequently, our findings may not be representative for diabetes patients in the community. Healthy controls had a lower percentage of women compared to diabetes patients, potentially introducing a bias caused by gender differences in transit times.

*Statistics:* We did not perform an a priori power analysis and our study may have been underpowered for detecting some relevant differences. In paper III, we performed multiple comparisons, increasing the risk for Type I errors. To the contrary, the groups with diarrhoea and constipation were relatively small, increasing the risk of Type II errors.

*Other limitations:* To avoid selection bias, we included patients with comorbitities. Of ethical reasons, we also let patients continue their regular medications, except for those prohibited by the test protocol. We attempted to control for this by making group comparisons, without finding any relevant differences.

# 6. Conclusions and future perspectives

## 6.1 Conclusions

In this study, we have used wireless motility capsule to investigate diabetes patients with gastrointestinal symptoms and suspected gastroenteropathy. In three papers, we have evaluated the main manifestations of diabetic gastroenteropathy: gastroparesis, diarrhoea, and constipation. In gastroparesis, gastric emptying measurements are mandatory, and confirming our hypothesis, we found that the wireless motility capsule had high diagnostic accuracy compared to the current reference standard, gastric emptying scintigraphy. However, we were unable to find any difference in symptoms comparing patients with rapid, normal, and delayed gastric emptying. In patients with diarrhoea, we found slower gastric emptying and faster colonic transit compared to controls. Patients with diarrhoea also displayed several alterations in gastrointestinal pH levels, but they had no difference in intestinal contractility and only minor alterations in autonomic function. In patients with constipation, we found no difference in transit times compared to patients without constipation, disproving our hypothesis that diabetic constipation was mainly caused by slow colonic transit. Neither did we find any difference between the groups in colonic contractility, but we found an association between constipation and reduced small bowel contractility. Finally, we found that both diabetes groups, with and without constipation, had slower whole gut transit compared to healthy controls.

### 6.1.1 Clinical implications

*Diabetic gastroparesis:* Wireless motility capsule may be considered similar to gastric emptying scintigraphy for investigating gastric emptying. When dysmotility in more than one gastrointestinal segment is suspected, wireless motility capsule can be used, to save the patient from unnecessary examinations.

*Diabetic diarrhoea:* One should consider giving transit time measurements a more prominent role in the diagnostics of diabetic diarrhoea, to separate the groups with

fast and slow transit. These findings may direct further investigations and influence treatment.

*Diabetic constipation:* In patients with constipation, other causes should be considered before carrying out transit time measurements.

## 6.2 Future perspectives

In ingestable capsules, battery time has always been a limiting factor leading to compromises in functionality to minimise power consumption [258]. Improved battery time may remove the wireless motility capsule's need to reduce the measurement frequency after the first 24 hours of the examination [199,258]. Combined with new sensor technology, enhanced battery capacity may also allow multiple pressure sensors and the sensing of other parameters like electrolytes, gases, metabolites, and enzymes [258]. A merge of current technology, combining the features of the wireless motility capsule and the 3D-Transit capsule, would also be a major diagnostic advancement. In a pilot study, researchers at Aalborg University Hospital have recently tested this in one healthy volunteer, and results are currently awaiting publication (AM Drewes, personal communication, august 2021). Given the success of the 3D-Transit system in refining the software to allow more detailed analyses of colonic motility patterns, a similar upgrade of the wireless motility capsule software, could also enhance the method's diagnostic capabilities [218]. We are currently collaborating on several projects working towards an improvement of the diagnostic ability of the wireless motility capsule.

By implementing detailed clinical phenotyping using different diagnostic modalities, treatment could be more specific. We have already discussed the use of wireless motility capsule measurements to stratify patients with diarrhoea. Other examples are the use of impedance planimetry to identify patients with pyloric dysfunction suitable for endosurgery, the use of ultrasound to select patients needing fundic relaxants to improve accommodation, or the use of electrogastrography to identify gastric dysrhythmias potentially treatable with radio frequency ablation [152,158,159,195].

The wireless motility capsule might also be further developed, in order to identify pyloric dysfunction by measuring antroduodenal transition time [160].

Despite its large prevalence and high morbidity, diabetic gastroenteropathy is less recognised than many other late diabetes complications. In paper II, we illustrated this by demonstrating that 30% of our study patients had diarrhoea, but only 7% used antidiarrhoeal medications. Diabetes patients is followed up by many professions, and it is important that all of these increase their recognition of diabetic gastroenteropathy. In research, knowledge is still limited regarding the pathogenetic and pathophysiological mechanisms causing diabetic gastroenteropathy. This is most pressing when it comes to intestinal diabetes complications. It is worrying that the most groundbreaking studies into diabetic diarrhoea were performed between 1945 and 1970. We plan to build on the knowledge gained in this study in a follow-up study investigating different pathophysiological mechanisms potentially contributing to diabetic diarrhoea, including dysmotility, neural dysfunction, dysbiosis, bile acid malabsorption, and pancreatic exocrine insufficiency. In diabetic constipation, there is also a critical lack of studies, especially regarding the role of anorectal dysfunction. Hopefully, increased pathophysiological knowledge may facilitate the transition towards targeted treatment.

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# 8. Papers I - III

Received: 7 August 2019 | Revised: 5 November 2019 | Accepted: 12 November 2019

DOI: 10.1111/nmo.13771

ORIGINAL ARTICLE

Neurogastroenterology & Motility NGM WILEY

# Wireless motility capsule compared with scintigraphy in the assessment of diabetic gastroparesis

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**Funding information**
Dag A. Sangnes has received a PhD Scholarship grant from the Western Norway Regional Health Authority. The study has otherwise been funded by Haukeland University Hospital.

## Abstract

**Background:** Gastroparesis is a potentially severe late complication of diabetes mellitus. Today, delayed gastric emptying (GE) is mandatory for establishing the diagnosis. In this study, we compared wireless motility capsule (WMC) with gastric emptying scintigraphy (GES).

**Methods:** Seventy-two patients (49 women) with diabetes mellitus (59 type 1) and symptoms compatible with gastroparesis were prospectively included between 2014 and 2018. Patients were simultaneously examined with GES and WMC. Symptoms were assessed with the Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM) questionnaire. All patients were on intravenous glucose-insulin infusion during testing.

**Key Results:** WMC and GES correlated $r = .74$, $P < .001$. Compared to GES, WMC at ordinary cutoff for delayed GE (300 minutes) had a sensitivity of 0.92, specificity 0.73, accuracy 0.80, and Cohen's kappa $\kappa = 0.61$ ($P < .001$). By receiver operating characteristics (ROC), the area under the curve was 0.95 ($P < .001$). A cutoff value for delayed GE of 385 minutes produced sensitivity 0.92, specificity 0.83, accuracy 0.86, and Cohen's kappa $\kappa = 0.72$ ($P < .001$). Inter-rater reliability for GE time with WMC was $r = .996$, $\kappa = 0.97$, both $P < .001$. There was no difference in symptom severity between patients with normal and delayed GE.

**Conclusions & Inferences:** Our findings demonstrate the applicability of WMC as a reliable test to assess gastric emptying in diabetic gastroparesis showing very high inter-observer correlation. By elevating the cutoff value for delayed emptying from 300 to 385 minutes, we found higher specificity without reducing sensitivity.

KEYWORDS

diabetes mellitus, gastric emptying, gastric emptying scintigraphy, gastroparesis, wireless motility capsule

## 1 | INTRODUCTION

Diabetic gastroparesis is a condition characterized by upper gastrointestinal (GI) symptoms and delayed gastric emptying (GE) without gastric outlet obstruction.[1] In addition to potentially debilitating symptoms of nausea, vomiting and upper abdominal pain, the condition may have profound implications for the patients' ability to regulate their blood glucose levels.[2,3] Delayed GE is associated with both short- and long-term hyperglycemia.[4] Gastroparesis may also influence the absorption of oral medications, emphasizing the need for reliable, inexpensive, and accessible tests for measuring GE.[5]

Gastric emptying scintigraphy (GES) has long been considered gold standard for evaluating GE in both research and clinical practice.[6] By radiolabeling a liquid or solid meal and tracking it by a gamma camera, the method gives a physiological, quantitative measurement of GE.[7] Unfortunately, a number of local variants of the test exist, both in terms of meal composition, and duration and frequency of imaging.[6,8] The radiation dosage also limits its applicability in certain patient groups.[9] Moreover, the availability of gamma cameras is reduced, in part due to high acquisition costs.

The wireless motility capsule (WMC; SmartPill, Medtronic) measures pH, pressure, and temperature throughout the GI tract, thereby providing the means for calculating GE.[10] WMC has since 2009 been approved by The United States Food and Drug Administration for the investigation of suspected gastroparesis and has in previous studies shown good agreement with scintigraphy.[8,11] However, there are few studies validating WMC against GES, highlighting the need for further research. To our knowledge, this is the first European study comparing the two methods in a cohort of diabetes patients with suspected gastroparesis.

The primary aim of this study was to assess the diagnostic reliability of WMC compared to GES for the measurement of GE. We also wanted to determine the WMC test's inter-rater reliability and identify the optimal cutoff value for delayed GE by WMC. A secondary aim was to identify proportions with rapid, normal, and delayed gastric emptying by the two methods. We also aimed to illuminate why some patients presented inconsistent test results (one positive/one negative), by comparing with those showing delayed emptying on both tests. Finally, we wanted to compare symptom severity between patients with rapid, normal, and delayed gastric emptying.

**Key Points**

- Gastroparesis is an important complication of diabetes mellitus, and detecting delayed gastric emptying is currently mandatory for establishing the diagnosis.
- Examining gastric emptying in a cohort of symptomatic diabetes patients, wireless motility capsule showed substantial agreement with scintigraphy.
- We found no differences in symptom severity between patients with normal and delayed gastric emptying by any of the tests.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

Seventy-two patients (49 women) with diabetes mellitus (DM) and symptoms consistent with gastroparesis were prospectively included between 2014 and 2018 (Table 1). Patients were recruited from all over Norway after being referred to Haukeland University Hospital for diagnostic evaluation. They were previously examined with upper endoscopy to rule out obstructing lesions or other pathology explaining their symptoms. Patients under 18 years of age and pregnant or breastfeeding women were not included in the study. During examinations, all patients were admitted to the hospital where they, in addition to tests and questionnaires, gave blood samples and were interviewed and examined by a physician. Medications potentially altering GI motility were paused in advance and during the study: proton pump inhibitors (seven days in advance), histamine $H_2$-receptor antagonists, opioid analgesics, nonsteroidal anti-inflammatory drugs, antidiarrheal drugs, prokinetic agents, and antiemetic drugs (3 days), laxatives (2 days), and other antireflux medications (24 hours).

### 2.2 | Gastric emptying tests

After an overnight fast of minimum 8 hours, GES and WMC testing were initiated simultaneously at 09:00 AM. Patients first consumed a standardized 260 kilocalorie (kcal; 66% carbohydrate, 17% protein, 2% fat, 3% fiber) nutrient bar (SmartBar, Medtronic), and a boiled egg (90 kcal; 1.1% carbohydrate, 13% protein, 11% fat, 0% fiber) radiolabeled with Tc-99m-nanocolloid.[12] Then, the WMC was swallowed, and scintigraphic imaging commenced immediately afterward. During the meal, patients could drink 120 mL of water. After swallowing the WMC, they fasted for another six hours, but were allowed to drink an additional 100 mL of water. During the fasting and examination period, all patients were on intravenous glucose-insulin infusion with frequent blood glucose measurements by finger-prick. Target levels were 4-10 mmol/L, and patients received intravenous glucose if they fell below 4 mmol/L.

#### 2.2.1 | Gastric emptying scintigraphy

Simultaneous anterior and posterior planar scintigraphy of the upper abdomen (1 minute per view) were performed on a double-headed camera system (Siemens e.cam; Siemens Healthineers). Pictures were taken at 0, 30 minutes, 1, 2, 3, and 4 hours in accordance with current guidelines.[13] Images were quantified using Segami Oasis 1.9.4.9 (Segami Corp., Inc) by drawing a region of interest around the outline of the stomach at 0 minutes, which was

then copied onto images taken at other time-points (Figure 1). Gastric retention was quantified as the root mean square of the counts in the anterior and posterior regions of interest relative to the acquisition at 0 minutes.[13]

Normal retention value for GES at 4 hours is <10%.[6] Retention at 4-hour GES can be graded into mild (10%-15%), moderate (15%-35%), and severe (>35%).[14] Normative retention values for other time-points are given in Table 2.

### 2.2.2 | Wireless motility capsule

WMC is a 26.8 × 11.7 mm, non-digestible, single-use capsule, containing sensors for pH, temperature and pressure, a battery and a transmitter.[10,15] After activation, it transmits data to a portable receiver, which the patient carries close to the body during the entire examination.[15] Our patients were instructed to return the receiver after 5 days, whereupon data were downloaded to a personal computer using a USB docking device.

WMC transit times were calculated using MotiliGI software (Medtronic). WMC gastric emptying time (WMC GET) was defined as the time between capsule ingestion and passage through the pylorus, as marked by a rapid rise of >3 pH units (Figure 1). Delayed WMC GET is defined as >300 minutes (5 hours), severely delayed WMC GET >720 minutes (12 hours).[10,16,17] In cases of uncertainty, results were based on a consensus of two or more examiners. To calculate inter-rater reliability, all tests were re-analyzed by a different examiner, blinded for previous results. We also compared with automatically generated results by the MotiliGI software.

## 2.3 | Autonomic function tests

Cardiac autonomic function was assessed by a simple five-minute supine heart rate variability (HRV) recording, using the Heart Rhythm Scanner PE (Biocom Technologies). The system investigates both time and frequency domain parameters, and has been described and validated in detail elsewhere.[18] All recordings were performed in a fasting state by the same trained technician. The HRV recordings were reviewed offline by the second author, and minor editing (missing or misplaced beats) was performed. Recordings with persistent ectopic activities or frank arrhythmias were excluded from subsequent analyses.

## 2.4 | Questionnaires

Patients' symptoms were evaluated by the validated questionnaire Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM).[19] PAGI-SYM can be grouped into six subsets (Table 4), where the average of subset 1-3 make up the Gastroparesis Cardinal Symptom Index (GCSI).[20]

**TABLE 1** Clinical characteristics

| Variables | Results |
|---|---|
| All patients, n | 72 |
| Gender (♀/♂), n | 49/23 |
| Diabetes type (1/2), n | 59/13 |
| Employment status (on disability benefits/employed/student/retired), n | 47/14/3/7 |
| Marital status (single/married or cohabitant), n | 23/48 |
| Age, y | 50 (19) |
| Diabetes duration, y | 27 (22) |
| Symptom duration, y | 4 (8) |
| BMI, kg/m$^2$ | 25.9 (7.5) |
| Smoking (never/current/previous), n | 22/23/27 |
| Alcohol (0/<1/1-7/>7 units/wk), n | 26/24/17/4 |
| Comorbid conditions (per patient), number | 7 (6) |
| All medications (per patient), number | 8 (7) |
| Opioid users, n (%) | 19 (26%) |
| Diabetes treatment | |
| Insulin, n (%) | 64 (89%) |
| Insulin pump, n (%) | 27 (38%) |
| CGM, n (%) | 7 (10%) |
| Metformin, n (%) | 10 (14%) |
| GLP-1 agonists, n (%) | 3 (4%) |
| SGLT-2 inhibitors, n (%) | 3 (4%) |
| DPP-4 inhibitors, n (%) | 2 (3%) |
| Other antidiabetic medication, n (%) | 2 (3%) |
| Late complications | |
| All complications (0/1/≥2), n | 20/18/34 |
| Retinopathy, n (%) | 40 (56%) |
| Nephropathy, n (%) | 20 (28%) |
| Polyneuropathy, n (%) | 34 (47%) |
| Diabetic wounds, n (%) | 8 (11%) |
| Cardiovascular disease, n (%) | 7 (10%) |
| Any other complication, n (%) | 11 (15%) |
| Blood glucose values | |
| P-Glucose at test start, mmol/L | 9.2 (4.3) |
| HbA1c, mmol/mol | 65 (21) |
| Heart rate variability | |
| Mean HR at rest, BPM | 74.1 (21.1) |
| SDNN, ms | 21.5 (18.6) |
| RMSSD, ms | 12.2 (16.1) |

*Note:* Data are given as median and interquartile range unless otherwise indicated. Frequencies are given as n and valid percent.

Abbreviations: BMI, body mass index; CGM, continuous glucose monitor; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose co-transporter-2; DPP-4, dipeptidyl peptidase-4; HbA1c, glycated hemoglobin; HR, heart rate; BPM, beats per minute; SDNN, standard deviation of NN intervals (inter-beat intervals where artifacts are removed); RMSSD, root mean square of successive RR interval differences.

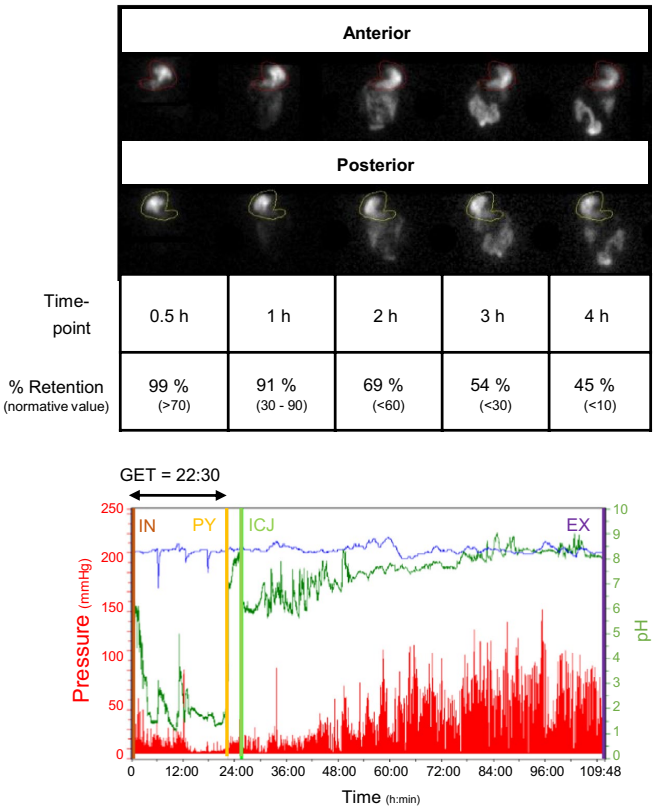


**FIGURE 1** GES (top) and WMC results from a patient with diabetic gastroparesis. Both tests showed severe delay in gastric emptying, with 45% retention on 4-hour GES and a GET of 22 h 30 min. Abbreviations: GES, gastric emptying scintigraphy. WMC, wireless motility capsule. GET, gastric emptying time. IN, capsule ingestion. PY, pylorus. ICJ, ileocecal junction. EX, capsule expulsion

**TABLE 2** Gastric emptying by GES and WMC

| Variables (normative values) | Median (IQR) | Rapid | Normal | Delayed |
|---|---|---|---|---|
| GES (% retention) | | | | |
| GES 30 min (>70) | 91 (13) | 7 (10.0%) | 63 (90.0%) | – |
| GES 1 hour (30 - 90) | 75 (28) | 3 (4.2%) | 53 (74.6%) | 15 (21.1%) |
| GES 2 hours (<60) | 35 (41) | – | 51 (71.8%) | 20 (28.2%) |
| GES 3 hours (<30) | 15 (34) | – | 47 (66.2%) | 24 (33.8%) |
| GES 4 hours (<10) | 5 (19) | – | 43 (60.6%) | 28 (39.4%) |
| WMC (min) | | | | |
| GET (105-300) | 350 (1397) | 0 | 32 (47.8%) | 35 (52.2%) |

*Note:* Data are given as n (%) unless otherwise indicated. Normative values for GES from Abell et al (2008); for WMC from Wang et al (2015).[6,10]

Abbreviations: GES, gastric emptying scintigraphy; GET, gastric emptying time; IQR, interquartile range; WMC, wireless motility capsule.

## 2.5 | Statistical analysis

Results are stated as median (interquartile range, IQR). We treated sum scores from questionnaires as continuous variables. Spearman's rank-order correlation test was used for estimation of associations between continuous variables. Differences between groups were evaluated by Mann-Whitney *U* test for continuous variables and Pearson's chi-square test with Yates' continuity correction for categorical variables. For assessing the diagnostic performance of WMC compared to GES, we calculated correlation, sensitivity, specificity, positive and negative predictive values, accuracy, positive and negative likelihood ratios, Cohen's kappa measure of agreement, and a receiver operating characteristics (ROC) curve. To find the optimal cutoff value for GE by WMC, we calculated the maximum Youden's

index. $P \leq .05$ was defined as the level of statistical significance. Analyses were performed using IBM SPSS Statistics (Ver. 25, IBM Corporation).

### 2.6 | Ethical considerations

The study was approved by The Western Norway Regional Medical Ethics Committee (2015/58) and was conducted in accordance with the Declaration of Helsinki. Participants received oral and written information, and signed an informed consent prior to any study-related procedures.

## 3 | RESULTS

The study flowchart is shown in Figure 2. Detailed clinical characteristics are given in Table 1. Due to suspected capsule retention during test analysis, one patient was examined with an abdominal radiograph at her local hospital upon our request. No capsule was identified. Except for worsening of symptoms in some patients due to pause of medication, no other test related adverse events were reported during the study.

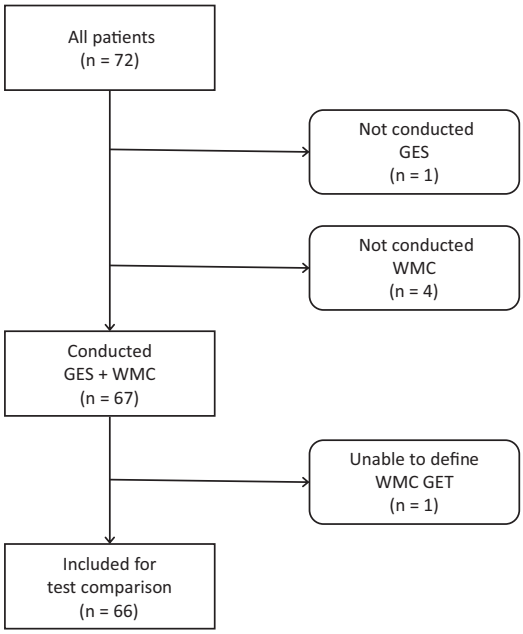


**FIGURE 2** Study flowchart. Abbreviations: GES, gastric emptying scintigraphy. WMC, wireless motility capsule. GET, gastric emptying time

### 3.1 | Diagnostic test comparison

WMC and 4-hour GES correlated $r = .74$ ($P < .001$). Calculating the ROC curve, we found an area under the curve (AUC) of 0.95 ($P < .001$, 95% CI 0.89-1.00). The ROC curve is depicted in Figure 3. We identified 385 minutes as the optimal cutoff value for delayed WMC GET (Youden's $J = .75$). Detailed measures of accuracy for both WMC GET cutoff values are presented in Table 3.

Inter-rater correlation for identifying WMC GET between the two examiners was $r = .996$, while agreement was Cohen's kappa $\kappa = .97$ (95% CI 0.90-1.00), both $P < .001$. MotiliGI calculated WMC GET in 51 patients (75.0%). Correlation between examiner 1 and MotiliGI was $r = .967$, Cohen's kappa $\kappa = .96$ (95% CI 0.88-1.00), both $P < .001$. Correlation between examiner 2 and MotiliGI was $r = .965$ and agreement $\kappa = .92$ (95% CI 0.81-1.00), both $P < .001$.

### 3.2 | Gastric emptying test results

Median GE values and proportions with rapid, normal, and delayed GE are presented in Table 2. Using the 300 minutes cutoff, WMC identified 35 patients (52.2%) with delayed GE, compared to 28 patients (39.4%) with 4-hour GES, $\chi^2$ (1) = 23.86, $P < .001$. With the 385 minutes cutoff value, 31 patients (46.3%) had delayed WMC GET, compared to 4-hour GES, $\chi^2$ (1) = 32.21, $P < .001$. Twenty-seven (40.3%) had severely delayed WMC GET, compared to 10 (14.1%) with GES, $\chi^2$ (1) = 9.48, $P < .01$. Severe retention by WMC and 4-hour GES had an agreement of $\kappa = .34$ ($P < .001$, 95% CI 0.14-0.54). Five patients had mild (7.0%) and 13 (18.3%) moderate retention by GES.

In patients with Type 1 diabetes mellitus (T1DM), median WMC GET was 611 minutes (2372 minutes); in Type 2 diabetes mellitus (T2DM), it was 229 minutes (155 minutes), $P = .01$. Using the ordinary 300 minutes cutoff value, 32 out of 55 (58%) T1DM patients had delayed WMC GET; the same proportion in T2DM was 3 out of 12 (25%), $\chi^2$ (1) = 3.12, $P = .08$. With the 385 minutes cutoff value, 31 (56%) with T1DM and 0 with T2DM had delayed GE, $\chi^2$ (1) = 10.42, $P < .01$. Median retention at 4-hour GES was 8% (22%) in patients with T1DM; in T2DM, it was 2% (4%), $P = .02$. Using GES, 27 out of 59 (47%) with T1DM and only 1 out of 13 (8%) with T2DM had delayed GE, $\chi^2$ (1) = 5.19, $P = .02$.

Making a cross-tabulation of test results, we found that 23 patients (35%) had delayed emptying in both 4-hour GES and WMC GET, while 11 (17%) had normal GES and delayed WMC GET. Only two patients (3%) had delayed GES and normal WMC GET, this group being too small for further statistical comparisons. In Table 4, we have compared selected clinical characteristics, symptom scores, gastric emptying test results, blood glucose values, and heart rate variability parameters (HRV) between those with consistent GE test results (both tests delayed; true positives) and those with inconsistent results (normal GES and delayed WMC GET; false positives).

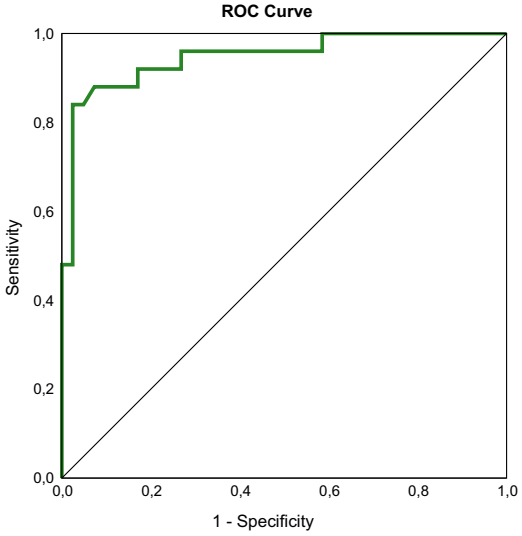


**FIGURE 3** ROC curve for WMC GET compared to 4-hour GES showing an AUC of 0.95 ($P < .001$, 95% CI 0.89-1.00). Abbreviations: ROC, receiver operating characteristics. WMC, wireless motility capsule. GET, gastric emptying time. GES, gastric emptying scintigraphy. AUC, area under the curve. CI, confidence interval

### 3.3 | Symptom scores

Table 5 contains results for GCSI, PAGI-SYM, and all subsets, including a comparison between patients with normal and delayed GE by WMC (300 minutes cutoff) and GES at 4 hours. We found no difference between patients with normal and delayed emptying at any WMC GET cutoff values or GES time-points, both looking at each diabetes type separately and all patients combined. There was no difference in symptom severity between patients with normal and severe gastric retention at any of the tests. Neither WMC GET nor GES at any time point correlated with PAGI-SYM, GCSI or any of its subsets. Furthermore, we found no difference in symptoms between patients with normal and rapid GE. Finally, there was no difference in symptom severity between patients with T1DM and T2DM.

## 4 | DISCUSSION

In this prospective study, we aimed to validate WMC against GES in a patient cohort with DM and symptoms compatible with gastroparesis. We found a strong correlation between WMC and 4-hour GES, $r = .74$ ($P < .001$). With the standard cutoff value of 300 minutes, both sensitivity (0.92) and specificity (0.73) for identifying delayed GE were high, and the two methods showed substantial agreement demonstrated by Cohen's kappa $\kappa = .61$ ($P < .001$). These results are similar to previous studies comparing WMC and GES, where Kuo et al found a correlation between WMC GET and 4-hour GES of $r = .73$ and Lee et al found a device agreement of $\kappa = .61$ in the diabetes subgroup.[8,11] However, in the latter study overall agreement was only moderate when also including patients without DM. In comparison with other methods for determining gastric emptying, WMC has a similar diagnostic accuracy to $^{13}$carbon-labeled gastric emptying breath tests for solids (GEBT) and is far superior to gastric emptying of radiopaque markers (ROMs).[21,22] Other methods have not gained widespread usage outside research settings.[16]

**TABLE 3** Measures of diagnostic accuracy

| Parameters | WMC GET (cutoff 300 min) | WMC GET (cutoff 385 min) |
|---|---|---|
| Sensitivity | 0.92 (0.74-0.99) | 0.92 (0.74-0.99) |
| Specificity | 0.73 (0.57-0.86) | 0.83 (0.68-0.93) |
| Positive predictive value | 0.69 (0.57-0.79) | 0.78 (0.64-0.87) |
| Negative predictive value | 0.93 (0.79-0.98) | 0.94 (0.81-0.98) |
| Accuracy | 0.80 (0.69-0.89) | 0.86 (0.76-0.94) |
| Positive likelihood ratio | 3.43 (2.04-5.76) | 5.39 (2.72-10.68) |
| Negative likelihood ratio | 0.11 (0.03-0.42) | 0.10 (0.03-0.37) |
| Cohen's kappa (κ) | 0.61 (0.43-0.79, $P < .001$) | 0.72 (0.55-0.89, $P < .001$) |

*Note:* Data are given as number (95% confidence interval) unless otherwise indicated.

Abbreviations: GET, gastric emptying time; WMC, wireless motility capsule.

We also found a near perfect inter-rater correlation ($r = .996$, $P < .001$) and Cohen's kappa ($\kappa = .97$, $P < .001$) for identifying WMC GET. For the evaluation of delayed GE, our findings indicate a high diagnostic accuracy of WMC, with interpretation of results being examiner independent. Interestingly, the correlations between each examiner and the MotiliGI software for estimating GET were also very strong. However, in as many as 25% of tests the software did not manage to calculate GET, compared to the one patient where manual analysis failed to make an estimation. Until further refinement of the software, manual test analysis is therefore essential.

Current normative transit time values for WMC are based on a study by Wang et al, examining 215 healthy, asymptomatic volunteers.[10] To identify the optimal cutoff value for delayed GE in our symptomatic DM cohort, we used ROC curve coordinates to find the maximum Youden's index. A value of 385 minutes increased the specificity to 0.83 without reducing sensitivity. Cohen's kappa was also increased to $\kappa = .72$ ($P < .001$). Consequently, by elevating the cutoff value, the risk of identifying false positives is reduced. One might therefore argue for the establishment of separate cutoff values for symptomatic diabetes patients, although we recommend further follow-up studies to confirm our findings.

At both cutoff values, a larger proportion of patients had delayed GE by WMC than GES. Lee et al propose a reasonable explanation for this discrepancy in the different physiological mechanisms used by the two tests: While GES examines the emptying of a gradually dissolving solid meal, the indigestible WMC is expelled from the

**TABLE 4** Comparison of groups with false and true positive WMC GET results

| Variables | GES normal/ WMC delayed | Both delayed | *P*-value |
|---|---|---|---|
| Clinical characteristics | | | |
| Age, y | 55 (16) | 38 (18) | <.01 |
| Diabetes duration, y | 31 (21) | 24 (18) | .08 |
| Symptom duration, y | 12 (16) | 6 (8) | .21 |
| BMI, kg/m$^2$ | 25.1 (7.9) | 23.1 (6.1) | .27 |
| Symptom scores | | | |
| 1) Nausea/vomiting | 1.7 (2.7) | 2.0 (2.0) | .33 |
| 2) Fullness/early satiety | 2.3 (2.3) | 3.3 (1.8) | .56 |
| 3) Bloating | 3.0 (2.0) | 3.3 (2.9) | .89 |
| 4) Upper abdominal pain | 3.0 (2.5) | 2.3 (2.4) | .76 |
| 5) Lower abdominal pain | 4.0 (2.0) | 2.3 (1.8) | .06 |
| 6) Heartburn/ regurgitation | 1.6 (3.4) | 1.5 (1.7) | .56 |
| GCSI | 2.2 (2.1) | 2.9 (1.6) | .74 |
| PAGI-SYM (total) | 2.9 (2.2) | 2.6 (1.3) | .64 |
| Gastric emptying tests | | | |
| GES 4 hours, % | 5 (4) | 26 (36) | <.001 |
| WMC GET, min | 611 (811) | 2737 (2155) | <.001 |
| Blood glucose values | | | |
| P-Glucose at test start, mmol/L | 7.8 (3.3) | 9.5 (4.9) | .44 |
| HbA1c, mmol/mol | 62 (11) | 72 (37) | .09 |
| Heart rate variability | | | |
| Mean HR at rest, BPM | 79.8 (19.1) | 79.3 (23.1) | .98 |
| SDNN, ms | 23.8 (20.7) | 17.6 (12.6) | .92 |
| RMSSD, ms | 10.6 (15.0) | 10.9 (8.3) | .90 |

*Note:* In the table, we have compared patients with normal 4-hour GES and delayed WMC GET (false positives, left column) with patients with delayed emptying on both tests (true positives). Data are given as median and interquartile range unless otherwise indicated.

Abbreviations: BMI, body mass index; BPM, beats per minute; GCSI, Gastroparesis Cardinal Symptom Index; GES, gastric emptying scintigraphy; GET, gastric emptying time; HbA1c, glycated hemoglobin; HR, heart rate; PAGI-SYM, Patient Assessment of Upper Gastrointestinal Symptom Severity Index; P-Glucose, plasma glucose; RMSSD, root mean square of successive RR interval differences; SDNN, standard deviation of NN intervals (inter-beat intervals where artifacts are removed); WMC, wireless motility capsule.

stomach by the returning phase III of the migrating motor complex (MMC). In addition to measuring GE, the WMC may therefore also measure impairment of the MMC and dyscoordination of gastric and small bowel motility, leading the authors to argue that the WMC in fact has higher sensitivity for detecting gastroparesis than GES.[11] Indeed, passage of the WMC does not occur before >90% of the meal has emptied.[8] As underlined by Kloetzer et al, WMC is therefore able to provide information about both gastric fasting and fed-state.[17] Interestingly, doing subgroup analyses, Lee et al found the same proportions with delayed emptying by both tests in diabetes patients.[11] The overall difference in their study was thus driven by the higher proportion with delayed emptying by WMC in the non-diabetic group.[11] To better understand the discrepancies in test results between the two methods, we compared patients with false-positive (normal GES and delayed WMC GET) and true-positive (both delayed) test results (Table 4). While glucose levels, HRV parameters, symptom scores, and clinical characteristics except for age were similar in both groups, the median WMC GET was more than 35 hours longer in the true positive group. This finding further bolsters the argument for increasing the cutoff value for delayed emptying in diabetes patients.

Wireless motility capsule also identified a higher proportion of patients with severe retention than GES. In this respect, we only found a fair agreement between the two methods ($\kappa$ = .34, $P$ < .001), similar to previous studies.[11] The most likely explanation is that definite cutoff values for severely delayed GET are not clearly established. WMC failed to identify any patients with rapid gastric emptying, while GES found three (4.2%) and seven (10.0%) at the 60 and 30 minutes time-points, respectively. Previous studies also found a higher share with rapid GE using GES.[11] Still, given that 20% of symptomatic diabetes patients may have rapid GE, it was surprising that we did not identify any cases using WMC.[23] Interestingly, the prevalence with delayed GE increased at each GES time point. This underlines the importance of following the recommended protocol of taking pictures until four hours to avoid false-negative tests.[6,14]

Previous studies comparing the symptom severity between patients with normal and delayed GE have shown inconsistent results.[24-26] In this study, we found no difference in PAGI-SYM, GCSI or any of their subsets between patients with normal and delayed GE. Neither did we find any differences comparing patients with normal and rapid emptying. This lack of association between GE and patient-reported symptoms is one of the main challenges in the field of gastroparesis research. The explanation is likely multifactorial. Firstly, patients with suspected diabetic gastroparesis often present a diversity of unspecific symptoms, not only limited to cardinal symptoms of nausea, vomiting, early satiety, fullness, and bloating, but often also abdominal pain, reflux, diarrhea, constipation, and fecal incontinence.[27-30] Adding to the confusion, delayed GE is present in 30%-50% with longstanding diabetes regardless of symptoms, probably as a consequence of autonomic neuropathy.[5,31-33] Secondly, there are multiple pathophysiological alterations associated with diabetic gastroparesis, both locally in the gut and in the autonomic and central nervous system. [28] Some of these, like the loss of interstitial Cells of Cajal, can be directly linked to the development of delayed GE.[34] Others may explain the genesis of gastrointestinal symptoms through different mechanisms, like abnormal central neuronal activity.[35,36] Although mostly

**TABLE 5** Symptom scores and gastric emptying by GES and WMC

| | | GES 4 hours | | | WMC GET 300 min | | |
|---|---|---|---|---|---|---|---|
| **Variables** | **All patients** | **Normal** | **Delayed** | ***P*-value** | **Normal** | **Delayed** | ***P*-value** |
| PAGI-SYM | | | | | | | |
| 1) Nausea/vomiting | 1.7 (2.3) | 1.7 (2.1) | 2.0 (2.0) | .37 | 1.3 (2.1) | 2.0 (2.0) | .49 |
| 2) Fullness/early satiety | 3.3 (1.8) | 3.0 (1.75) | 3.25 (1.5) | .39 | 3.3 (1.5) | 3.3 (2.0) | .72 |
| 3) Bloating | 3.4 (2.4) | 3.5 (2.5) | 3.0 (2.5) | .73 | 3.8 (2.4) | 3.0 (2.5) | .95 |
| 4) Upper abdominal pain | 3.0 (2.5) | 3.5 (2.5) | 3.0 (2.0) | .39 | 3.5 (2.0) | 3.0 (2.5) | .32 |
| 5) Lower abdominal pain | 2.5 (2.5) | 3.0 (3.5) | 2.0 (2.0) | .65 | 2.0 (3.3) | 3.0 (2.0) | .26 |
| 6) Heartburn/regurgitation | 1.6 (2.3) | 2.3 (2.6) | 1.4 (1.7) | .18 | 2.5 (2.6) | 1.6 (1.7) | .30 |
| GCSI | 2.8 (1.5) | 2.8 (1.6) | 2.7 (1.3) | .72 | 2.9 (1.7) | 2.8 (1.9) | .69 |
| PAGI-SYM (total) | 2.5 (1.4) | 2.4 (2.1) | 2.6 (1.3) | .75 | 2.5 (2.1) | 2.6 (1.4) | .94 |

*Note:* Data are given as median and interquartile range unless otherwise indicated.

Abbreviations: GCSI, Gastroparesis Cardinal Symptom Index; GES, gastric emptying scintigraphy; GET, gastric emptying time; PAGI-SYM, Patient Assessment of Upper Gastrointestinal Symptom Severity Index; WMC, wireless motility capsule.

controlled for in studies, the influence of medication side-effects and other comorbidities on gastrointestinal symptoms, can also be a confounder. Finally, more than a quarter of patients with functional dyspepsia, a highly prevalent condition with symptoms mimicking gastroparesis also present with delayed GE.[24] An important goal for future gastroparesis studies must therefore be to identify other biomarkers better correlated to patient-reported symptoms. By expanding focus beyond the pylorus, recent studies have indeed uncovered a possible link between small bowel dysmotility and symptoms suggestive of gastroparesis.[37-39] Here, the WMC may play an important role in further research, providing pH and pressure profiles from gut segments otherwise largely unavailable for examination.[5,40,41]

Nevertheless, as the rate of GE is pivotal in determining postprandial glycaemia, its measurement will still be of great importance in diabetes patients, especially those presenting with unexplained fluctuations in blood glucose levels.[3] Consequently, the latest consensus statement on investigation of gastric motility recommends GE studies to be performed in patients with poorly controlled diabetes.[42] Furthermore, as clinical presentation alone can rarely differentiate between rapid and delayed emptying, it is recommended to determine GE in patients with symptoms compatible with gastroparesis, where upper GI endoscopy has not provided an explanatory diagnosis.[42] This is important, as the two entities of rapid or delayed GE may respond to entirely different therapeutic approaches.[26,43]

Compared to GES and other methods for evaluating gastric emptying, WMC has the great advantage of examining several GI regions during the same test. This is especially relevant in diabetes patients, often presenting multiregional dysmotility.[5,44] In contrast to GES, it does not involve radiation and has a universally standardized meal.[45] Furthermore, conduction of the test requires little training, transit time results are mostly easy to interpret, and the test equipment is not space consuming. It may therefore be suitable for regular out-patient clinics, although its availability is so far mostly limited to tertiary centers.[46] Costs are comparable to GES, both tests being more expensive than GEBT and ROMs.[16,22] However, unlike other GE tests, where patients need to stay in the clinic for at least half a workday, commencing WMC testing rarely takes more than 30 minutes. During the rest of the examination, patients are ambulant. Consequently, the associated loss of productivity is less for both patients and clinicians.

There are some limitations to our study. To make the WMC protocol most similar to clinical practice, we used the standardized cereal bar supplied by the producer. To be able to perform the two GE tests simultaneously, we had to serve a radiolabeled egg as an addendum. This increased the total energy content of the meal by approximately 90 kcal. Higher calorie meals are expected to empty more slowly from the stomach, potentially increasing the proportion of patients with delayed GE. Furthermore, our cohort had a predominance of women and patients with Type 1 DM (Table 2). The gender distribution of gastroparesis between women and men is 4:1, while the cumulative incidence of gastroparesis is higher in Type 1 DM.[47] Still, the higher prevalence of Type 2 DM in the society makes this group underrepresented in the study population. While evaluating the WMC test's inter-rater reliability, we unfortunately did not perform an inter-observer agreement evaluation of GES. Finally, the study was conducted at a tertiary center receiving referrals from secondary healthcare institutions. Accordingly, our patient cohort may be more severely affected by their disease than diabetes patients treated in primary care.

A strength of the study was its prospective design and the simultaneous assessments with WMC and GES, thereby avoiding intra-individual variations in GE. During the study, all patients were admitted to the hospital, where they were on intravenous glucose-insulin infusion during both fasting and testing. Consequently, we were able to avoid major fluctuations in blood sugar levels potentially affecting GE, as well as preventing

iatrogenic hypoglycemia. Finally, our study is the largest prospective study validating the WMC in DM patients, increasing the robustness of our results.

In conclusion, our findings confirm the applicability of WMC as a highly reliable test for determining GE in diabetic gastroparesis diagnostics. By elevating the cutoff value for delayed GE from 300 to 385 minutes, we managed to improve the method's diagnostic accuracy further, possibly implying the need for separate cutoff values in symptomatic diabetes patients.

## ACKNOWLEDGEMENTS

The authors would like to thank Dr Elisabeth Steinsvik for assistance during statistical analysis, Dr Ingrid Nordaas for help with designing the graphical summary, and medical students Revathy Mohanalingam and Athiya Seelan for help in recording data. We also thank the Department of Medicine and Department of Radiology at Haukeland University Hospital for providing research facilities, and we thank all hospital personnel assisting us during the study. Finally, we thank all participating patients.

## CONFLICT OF INTEREST

The authors have no competing interests.

## AUTHOR CONTRIBUTIONS

Georg Dimcevski (GD) is guarantor of the article. Dag A. Sangnes (DS), Eirik Søfteland (ES), Martin Biermann (MBI), Odd Helge Gilja (OHG), and GD contributed to the design of the study. Mattis Bekkelund (MBE), MBI, and DS analyzed the tests. OHG and GD assisted for consensus evaluations. Jakub Frey (JF), MBE, and DS contributed to data entry. DS performed the statistical analysis. DS drafted the manuscript with contributions from MBI, ES, and GD. All authors were involved in critical revisions and approved the final version of the manuscript.

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## DATA AVAILABILITY STATEMENT

Preliminary data from the study was presented at the NeuroGASTRO congress in Istanbul, Turkey, June 4-6, 2015.[40] An abstract from the study was presented at the NeuroGASTRO congress in Lisbon, Portugal, September 5-7, 2019.[48] Full study protocol can be accessed upon request.

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**How to cite this article:** Sangnes DA, Søfteland E, Bekkelund M, et al. Wireless motility capsule compared with scintigraphy in the assessment of diabetic gastroparesis. *Neurogastroenterol Motil*. 2020;32:e13771. https://doi.org/10.1111/nmo.13771

## APPENDIX A

### STARD 2015

| Section & Topic | No | Item | Reported on page # |
|---|---|---|---|
| Title or Abstract | | | |
| | **1** | Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC) | 1 |
| Abstract | | | |
| | 2 | Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts) | 1 |

| Section & Topic | No | Item | Reported on page # |
|---|---|---|---|
| Introduction | | | |
| | 3 | Scientific and clinical background, including the intended use and clinical role of the index test | 2 |
| | 4 | Study objectives and hypotheses | 2 |
| Methods | | | |
| Study design | 5 | Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study) | 2 |
| Participants | 6 | Eligibility criteria | 2 |
| | 7 | On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry) | 2 |
| | 8 | Where and when potentially eligible participants were identified (setting, location and dates) | 2 |
| | 9 | Whether participants formed a consecutive, random or convenience series | 2 |
| Test methods | 10a | Index test, in sufficient detail to allow replication | 3 |
| | 10b | Reference standard, in sufficient detail to allow replication | 2-3 |
| | 11 | Rationale for choosing the reference standard (if alternatives exist) | 2 |
| | 12a | Definition of and rationale for test positivity cutoffs or result categories of the index test, distinguishing prespecified from exploratory | 3 |
| | 12b | Definition of and rationale for test positivity cutoffs or result categories of the reference standard, distinguishing prespecified from exploratory | 2 |
| | 13a | Whether clinical information and reference standard results were available to the performers/readers of the index test | 3 |
| | 13b | Whether clinical information and index test results were available to the assessors of the reference standard | 2 |
| Analysis | 14 | Methods for estimating or comparing measures of diagnostic accuracy | 4 |
| | 15 | How indeterminate index test or reference standard results were handled | 3 |
| | 16 | How missing data on the index test and reference standard were handled | 5 and Figure 2 |
| | 17 | Any analyses of variability in diagnostic accuracy, distinguishing prespecified from exploratory | - |
| | 18 | Intended sample size and how it was determined | 2, 5 and Figure 2 |
| Results | | | |
| Participants | 19 | Flow of participants, using a diagram | Figure 2 |
| | 20 | Baseline demographic and clinical characteristics of participants | Table 1 |
| | 21a | Distribution of severity of disease in those with the target condition | - |
| | 21b | Distribution of alternative diagnoses in those without the target condition | - |
| | 22 | Time interval and any clinical interventions between index test and reference standard | 2 |
| Test results | 23 | Cross-tabulation of the index test results (or their distribution) by the results of the reference standard | 5 |
| | 24 | Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals) | 5, Table 3 and Figure 3 |
| | 25 | Any adverse events from performing the index test or the reference standard | 5 |
| Discussion | | | |
| | 26 | Study limitations, including sources of potential bias, statistical uncertainty, and generalizability | 8 |
| | 27 | Implications for practice, including the intended use and clinical role of the index test | 6-8 |
| Other information | | | |
| | 28 | Registration number and name of registry | 4 |
| | 29 | Where the full study protocol can be accessed | 9 |
| | 30 | Sources of funding and other support; role of funders | 1 |

JIM Original Article

doi: 10.1111/joim.13340

# Diabetic diarrhoea: a study on gastrointestinal motility, pH levels and autonomic function

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**Abstract.** Sangnes DA, Dimcevski G, Frey J, Søfteland E. Diabetic diarrhoea: a study on gastrointestinal motility, pH levels and autonomic function. *J Intern Med.* 2021;**OO:**1-13. https://doi.org/10.1111/joim.13340

**Background.** Chronic diarrhoea is a common, but poorly investigated diabetes complication. Autonomic neuropathy is a leading pathophysiological theory founded on old, small studies. Studies of gastrointestinal motility and pH levels are lacking.

**Objectives.** Using new diagnostic methods, we aimed to find out if diabetic diarrhoea was associated with alterations in gastrointestinal motility, pH levels and autonomic function.

**Methods.** Fifty-seven patients (42 women, 46 type 1 diabetes) were prospectively included. Symptoms were evaluated with the gastrointestinal symptom rating scale, defining $\geq$ 4 points as cases with diarrhoea. Patients scoring $<$ 4 were used as controls. We used the wireless motility capsule to measure gastrointestinal transit times, pH levels and contractility parameters. Autonomic function was assessed by measuring heart rate variability, baroreflex sensitivity and orthostatic hypotension.

**Results.** Seventeen patients (30%) had diarrhoea. Compared with controls, cases had slower gastric emptying (21:46 vs. 4:14, h:min, $p = 0.03$) and faster colonic transit (18:37 vs. 54:25, $p < 0.001$). Cases had increased intraluminal pH in the antrum (2.4 vs. 1.2, $p = 0.009$), caecum (7.3 vs. 6.4, $p = 0.008$) and entire colon (7.1 vs. 6.7, $p = 0.05$). They also had a decreased pH difference across the pylorus (3.3 vs. 4.9, $p = 0.004$) and ileocaecal junction (0.6 vs 1.0, $p = 0.009$). The groups did not differ in autonomic function, but diastolic blood pressure drop correlated $r_s = -0.34$ ($p = 0.04$) with colonic transit time.

**Conclusions.** Patients with diabetic diarrhoea had altered gastrointestinal transit and intraluminal pH levels, but minimal changes in autonomic function. Our results suggest that tests of gastrointestinal function are clinically useful in diabetic diarrhoea.

**Keywords:** autonomic dysfunction; diabetic diarrhoea; diabetic gastroenteropathy; gastrointestinal transit; intraluminal pH levels; wireless motility capsule

**Abbreviation:** GSRS, Gastrointestinal Symptom Rating Scale

## Introduction

Chronic diarrhoea affects more than 10% of diabetes patients and often leads to impaired quality of life [1,2]. Evaluation can be challenging, as diabetes patients are at increased risk for developing other conditions leading to diarrhoea, like coeliac disease, pancreatic exocrine insufficiency and inflammatory bowel disease [3–7]. Diarrhoea may also come from dietary factors or common antidiabetic drugs like metformin and glucagon-like peptide-1 agonists [8–11]. However, in half of all patients, the diarrhoea will be attributed to alterations in intestinal motility and secretion secondary to diabetic gastroenteropathy [12]. Diabetic gastroenteropathy can affect any portion of the gastrointestinal tract, leading to manifestations like oesophageal dysmotility, gastroparesis and intestinal hyper- or hypomotility [11,13,14]. When these patients present with chronic diarrhoea, it has been termed diabetic diarrhoea [12]. Here, the diarrhoea is typically nonbloody and painless, with

a high-volume, watery consistence. It may be nocturnal and can lead to faecal incontinence [1,12].

Although being recognized for almost a century, little is known about the pathophysiological mechanisms behind diabetic diarrhoea [13]. The leading theory of autonomic neuropathy was established after finding high covariance between neuropathy and diarrhoea in case studies and a clinical resemblance with patients who had undergone vagotomy or sympathectomy [15,16]. Later studies are limited in numbers, inconclusive, and there are no studies using new technology for assessing autonomic function [13,15,17–19]. Studies investigating intestinal transit and contractility are also lacking. One explanation may be that these measurements previously have been laborious and patient unfriendly, limiting their availability to specialized centres. Recently, the wireless motility capsule has emerged as a promising method, simultaneously measuring transit times and contractility throughout the gastrointestinal tract whilst patients are ambulant [20]. The capsule also measures pH levels [21]. This is relevant since diarrhoeal disorders are associated with both intraluminal and systemic pH level alterations [22,23]. So far, these measurements are unexplored in diabetic diarrhoea, but there are noteworthy findings from studies on patients with irritable bowel syndrome and small intestinal bacterial overgrowth [24,25].

In this study, our main hypothesis was that diabetes patients with diarrhoea had altered gastrointestinal transit times. We also hypothesized that they had altered intraluminal pH levels, reduced contractility and autonomic dysfunction. To investigate this, we examined a cohort of diabetes patients with gastrointestinal symptoms and suspected gastroenteropathy using wireless motility capsule and autonomic function tests.

## Methods

### *Study population*

Between 2014 and 2018, we prospectively included diabetes patients with symptoms suggestive of gastroenteropathy into a cross-sectional, observational study. All patients had been referred for diagnostic evaluation at a tertiary centre at Haukeland University Hospital, Bergen, Norway. Inclusion criteria were type 1 or type 2 diabetes, age over 18 years and normal upper endoscopy. Exclusion criteria were pregnancy, breastfeeding, active malignancy (defined as any cancer not in complete remission for the last six months) and lack of ability to comply with the study protocol.

Patients were admitted to the hospital during the study, where they were interviewed and examined by a physician, and delivered blood, urinary and faecal samples (Table 1). They were kept on intravenous glucose-insulin infusion during fasting and examinations, with a target glucose level between 4 and 10 mmol/L.

### *Wireless motility capsule*

The wireless motility capsule (SmartPill; Medtronic, Minneapolis, USA) is a 26 × 13 mm indigestible, single-use capsule. It registers temperature (range 25–49°C), pH (0.5–9.0) and pressure (0–350 mmHg) throughout the gastrointestinal tract. During the test, data are transferred to a portable data receiver and afterwards downloaded to a computer. For analysis, we used MotiliGI® software version 3.0 (Medtronic).

We used stereotypical pH profiles to define transit times [21]: Gastric emptying time (capsule ingestion – pylorus), small bowel transit time (pylorus – ileocaecal junction), colonic transit time (ileocaecal junction – capsule expulsion); and whole gut transit time (capsule ingestion – capsule expulsion). Antral pH was defined as median pH for the last 15 min before the pylorus; duodenal pH the first 15 min after the pylorus; ileum the last 15 min before the ileocaecal junction; caecum the first 15 min after the ileocaecal junction; and rectum the last 15 min before capsule expulsion. Delta pylorus was defined as the difference between duodenal and antral pH; delta ileocaecal junction the difference between ileal and caecal pH.

We also measured the motility index and contractions per minute in the whole stomach, small bowel and colon [20]. To determine the ileocaecal junction pressure, we used the method proposed by Chander Roland et al., identifying the maximum pressure for the last 4 min prior to the ileocaecal junction pH drop [25].

All patients had to pause medications potentially altering intestinal function before and during the study. We have specified details in a previous article, together with a description of the test meal and initiation protocol [26]. Patients continued other regular medications, provided doses had been

 

**TABLE 1.** *Clinical characteristics of all diabetes patients and a comparison between patients with diarrhoea and controls*

| Variables | All patients ($n = 57$) | Comparison of groups | | | |
|---|---|---|---|---|---|
| | | Controls ($n = 40$) | Cases ($n = 17$) | $p$ value | Effect size |
| General demographics | | | | | |
| Women, $n$ | 42 (74%) | 30 (75%) | 12 (71%) | 0.73 | 0.05 |
| On disability benefits, $n$ | 36 (64%) | 25 (63%) | 11 (69%) | 0.66 | 0.06 |
| Age, years | 50 (39–56) | 50 (40–56) | 51 (31–57) | 0.57 | 0.08 |
| BMI, kg/m$^2$ | 25.7 (22.1–29.6) | 26.5 (22.1–30.4) | 24.8 (21.5–28.2) | 0.41 | 0.11 |
| Smoking (never/previous/current), $n$ | 18/22/17 | 16/13/11 | 2/9/6 | 0.10 | 0.28 |
| Alcohol (0/<1/1–7/≥7 units/week), $n$ | 20/18/15/3 | 12/12/13/2 | 8/6/2/1 | 0.39 | 0.23 |
| Diabetes status | | | | | |
| Type 1 diabetes, $n$ | 46 (81%) | 32 (80%) | 14 (82%) | 0.84 | 0.03 |
| Diabetes duration, years | 26 (16–37) | 28 (19–39) | 23 (13–31) | 0.10 | 0.22 |
| Late complications (0/1/≥2), $n$ | 17/13/27 | 13/9/18 | 4/4/9 | 0.78 | 0.09 |
| Retinopathy, $n$ (%) | 32 (56%) | 23 (58%) | 9 (53%) | 0.75 | 0.04 |
| Nephropathy, $n$ (%) | 15 (26%) | 10 (25%) | 5 (29%) | 0.73 | 0.05 |
| Polyneuropathy, $n$ (%) | 25 (44%) | 16 (40%) | 9 (53%) | 0.37 | 0.12 |
| Diabetic wounds, $n$ (%) | 7 (12%) | 4 (10%) | 3 (18%) | 0.42 | 0.11 |
| Cardiovascular disease, $n$ (%) | 5 (9%) | 2 (5%) | 3 (18%) | 0.12 | 0.21 |
| Any other complication, $n$ (%) | 9 (16%) | 6 (15%) | 3 (18%) | 0.80 | 0.03 |
| Biochemistry | | | | | |
| B-HbA1c, %/mmol/mol | 8.1 (7.2–9.1) / 65 (55–76) | 8.1 (7.3–8.9) / 65 (56–74) | 8.0 (7.2–10.7) / 64 (55–93) | 0.64 | 0.06 |
| P-Glucose at test start, mmol/L | 9.0 (6.6–11.3) | 8.9 (6.8–11.2) | 9.0 (5.6–12.4) | 0.92 | 0.01 |
| S-TSH, mIE/L | 1.4 (0.8–2.0) | 1.6 (0.9-2.0) | 1.4 (0.8–2.1) | 0.85 | 0.03 |
| P-fT4, pmol/L | 15.8 (14.5–18.9) | 16.3 (14.9–19.4) | 14.7 (13.6–17.8) | 0.050 | 0.27 |
| U-ACR, mg/mmol | 1.6 (0.6–5.2) | 1.0 (0.5–3.6) | 3.5 (0.8–7.3) | 0.09 | 0.24 |
| F-Calprotectin, mg/kg | 16 (15–42) | 15 (15–39) | 18 (15–43) | 0.70 | 0.06 |
| F-Elastase-1, mg/g | 487 (283–500) | 445 (283–500) | 500 (322–500) | 0.12 | 0.23 |

Results are presented as median (quartiles) unless otherwise indicated. Frequencies are given as $n$ (%), where percentages are calculated from the total $n$ in each column. Cases are defined by GSRS diarrhoea score ≥4 points; controls <4. Biochemical reference values as used at Haukeland University Hospital (presented on https://analyseoversikten.no): B-HbA1c, 4.0%–6.0%/20–42 mmol/mol; P-Glucose 4.0–6.0 mmol/L; S-TSH, 0.40–4.50 mIE/L; P-fT4, 8.0–21.0 pmol/L; U-ACR, 0 -2.5 mg/mmol; F-Calprotectin, <50 mg/kg; and F-Elastase-1, <200 mg/g.
Abbreviations: ACR, Albumin to creatinine ratio; B-, Whole blood; F-, Faecal; FT4, Free thyroxine; GSRS = Gastrointestinal Symptom Rating Scale; P-, Plasma; S, Serum; TSH, Thyroid stimulating hormone; U-, Urinary.

stable for 3 months. Intake of alcohol was prohibited, and patients were asked to refrain from smoking and strenuous physical activity.

### *Autonomic function tests*

We assessed heart rate variability at rest and baroreflex sensitivity using the Heart Rhythm Scanner PE and the Biocom 5000 Bluetooth ECG Recorder (Biocom Technologies, Poulsbo, USA). We have described the heart rate variability protocol in a previous paper [27]. To measure baroreflex sensitivity, patients took deep breaths at a rate of five per minute. Thereafter, actual values were compared with predicted normative age-adjusted values by the software. Finally, we assessed orthostatic hypotension using Welch Allyn ProBP 3400 (Welch Allyn Inc., Skaneateles Falls, USA) following a standardized protocol measuring supine, resting blood pressure and standing blood pressure after 1 and 3 min. Orthostatic hypotension was defined as a drop in systolic blood pressure of $\geq$20 mm Hg or diastolic blood pressure $\geq$10 mm Hg from supine to standing position [28].

### *Symptom assessments*

Symptoms were evaluated by physician interview and using the Gastrointestinal Symptom Rating Scale (GSRS), a questionnaire validated for assessing the occurrence and severity of upper and lower gastrointestinal symptoms during the last week [29]. GSRS includes 15 questions, each rated from no discomfort (zero points) to very severe discomfort (six points). Diarrhoea syndrome (hereafter named 'diarrhoea') is derived by taking the mean of the individual symptoms: increased passage of stools, loose stools and urgent need for defecation [29]. We used a cut-off value of $\geq$4 points, corresponding to the 75th percentile, to define cases with diarrhoea. Those scoring <4 were used as controls. We also looked at correlations between diarrhoea score and each wireless motility capsule and autonomic function test parameter.

### *Statistical analysis*

Continuous variables are stated as median (quartiles) and categorical variables as $n$ (%). We used the Mann–Whitney $U$ test to compare two continuous variables, using $r$ as an effect size estimate ($r = z/\sqrt{N}$). To examine associations between continuous variables, we used Spearman's Rank Order Correlation test ($r_s$) with bootstrapped 95% confidence intervals (CI) and the coefficient of determination ($R^2 = r_s$ squared). We used Pearson's chi-square test to compare categorical variables with Cramér's $V$ ($\phi_c$) as an effect size estimate. Agreement was evaluated using Cohen's kappa measure of agreement ($\kappa$). Statistical significance was defined as $p \leq 0.05$. Analyses were performed using IBM SPSS Statistics (Version 27, IBM Corporation, USA), except effect size estimates for the Mann–Whitney $U$ test and $R^2$, which were calculated using Microsoft Excel (Version 2102, Microsoft Corporation, USA). For both $r$ and $\phi_c$, effect sizes can be interpreted using Cohen's criteria (1988): Small effect (>0.10), medium effect (>0.30) and large effect (>0.50) [30].

### *Ethical considerations*

All participants submitted oral and written consent prior to study-related procedures. The study was approved by The Western Norway Regional Medical Ethics Committee (2015/58) and conducted in accordance with the Declaration of Helsinki.

## Results

Seventy-two patients were included in the study, of which 68 were examined with wireless motility capsule. We were unable to identify the ileocaecal junction in three patients, precluding determination of small bowel and colonic transit. Of the remaining 65 patients, eight had missing GSRS data, leaving 57 available for comparisons. An inclusion flowchart is shown in Fig. 1.

### *Clinical characteristics*

Clinical characteristics are presented in Table 1. Fifty patients (88%) used insulin, three (5%) sodium-glucose cotransporter-2 inhibitors, two (4%) glucagon-like peptide-1 agonists, two (4%) dipeptidyl peptidase-4 inhibitors and one (2%) used pioglitazone. Four patients (7%) used antidiarrhoeal medications. A detailed list of medications are provided in Table S1.

We identified 17 (30%) cases with a diarrhoea score $\geq$4 points, compared to 12 (21%) reporting diarrhoea during physician interview, $\kappa = 0.68$, $p < 0.001$. Median score in all patients were 2.7 (0.5–4.0), with no difference between women (2.3, 0.6–4.0) and men (2.7, 0–5.0, $p = 0.81$, $r = 0.03$), nor between type 1 diabetes (2.8, 0.7–4.1) and type 2 diabetes (2.0, 0–4.0, $p = 0.46$, $r = 0.10$). Those with one or more late diabetes complications scored 3.0 (0.8–4.3), those without 0.7 (0–3.5), $p = 0.06$,

 

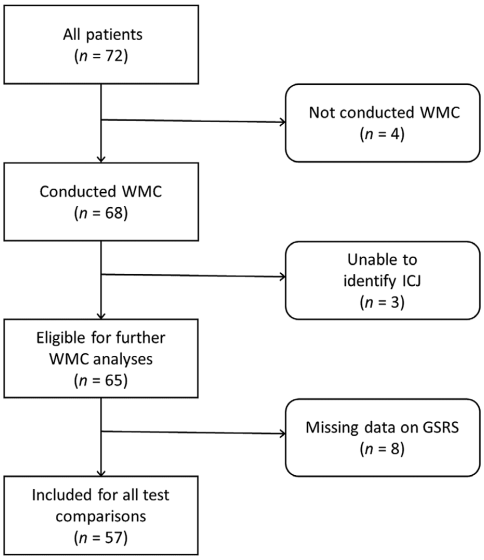


**FIGURE 1** Inclusion flow chart.

$r = 0.25$. Cases and controls did not differ in age, BMI, diabetes duration, HbA1c, faecal elastase-1, nor faecal calprotectin levels.

*Transit times, pH levels and contractility parameters*

A comparison of transit times, pH levels and contractility parameters between cases and controls are presented in Table 2. Transit times are also displayed in Fig. 2, pH levels in Fig. 3. Correlations between all wireless motility capsule measurements and the continuous GSRS diarrhoea score are shown in Table S2.

We found that cases had slower gastric emptying ($p = 0.03$) and faster colonic transit ($p < 0.001$) than controls. We found no difference in small bowel transit ($p = 0.11$) nor whole gut transit ($p = 0.16$). Colonic transit correlated with the diarrhoea score, $p = 0.006$.

We found that cases had increased antral pH ($p = 0.009$) and decreased pH difference across the pylorus ($p = 0.004$). Cases also had increased colonic pH ($p = 0.05$), increased caecal pH ($p = 0.008$) and decreased pH difference across the ileocaecal junction ($p = 0.009$). Antral pH ($p = 0.02$), ileal pH ($p = 0.03$), caecal pH ($p = 0.006$) and pH differences across the pylorus ($p = 0.001$) and ileocaecal junction ($p = 0.04$) all correlated with diarrhoea scores.

We found no correlations between transit times and pH in the stomach ($r_s = 0.02$, 95% CI −0.24–0.28, $R^2 = 0.0\%$, $p = 0.86$), small bowel ($r_s = 0.10$, 95% CI −0.16–0.34, $R^2 = 1.0\%$, $p = 0.46$), nor colon ($r_s = -0.14$, 95% CI −0.37–0.12, $R^2 = 2.0\%$, $p = 0.32$). There was no correlation between pH difference across the ileocaecal junction and colonic transit time, $r_s = 0.13$, 95% CI −0.12–0.38, $R^2 = 1.7\%$, $p = 0.34$.

We found no difference between cases and controls in any of the contractility parameters, all $p > 0.23$. Neither did we identify any significant correlations with the GSRS diarrhoea score, all $p > 0.35$.

*Autonomic function tests*

In Table 3, we present a comparison of autonomic function tests between cases and controls, as defined by the GSRS cut-off value. Correlations between autonomic function test parameters and the GSRS diarrhoea score are shown in Table S3. In cases, we found a trend towards increased diastolic blood pressure drop at 3 min, $p = 0.054$. We found no difference in any of the other parameters (all $p > 0.10$) and no significant correlations (all $p > 0.10$). Thirteen controls (33%) and eight cases (57%) had orthostatic hypotension, $\chi^2$ (1) = 2.65, $p = 0.10$, $\phi_c = 0.22$. Of all autonomic function test parameters, only diastolic blood pressure drop at 0 min correlated significantly ($p = 0.04$) with colonic transit time, Table S4.

## Discussion

In this study we aimed to investigate the association between diabetic diarrhoea, intestinal motility, pH levels and autonomic dysfunction. By examining diabetes patients with wireless motility capsule, we found that patients with diarrhoea had slower gastric emptying and faster colonic transit than controls. They also had an increased pH level in the stomach's antrum, caecum and entire colon and decreased pH difference across the pylorus and ileocaecal junction. We found a moderate negative correlation between diastolic blood pressure drop and colonic transit time, but no other associations between diabetic diarrhoea and autonomic dysfunction.

**TABLE 2.** *Wireless motility capsule measurements of transit times, pH levels and contractility parameters: a comparison of diabetes patients with diarrhoea and controls*

| Variables/location, unit | Controls | Cases | *p* value | Effect size |
|---|---|---|---|---|
| Transit times | | | | |
| Stomach, h:min | 4:14 (3:11–19:26) | 21:46 (3:58–47:12) | 0.03 | 0.29 |
| Small bowel, h:min | 4:44 (3:51–6:03) | 3:36 (2:24–6:52) | 0.11 | 0.21 |
| Colon, h:min | 54:25 (22:56–78:11) | 18:37 (7:23–35:08) | <0.001 | 0.49 |
| Whole gut, h:min | 72:44 (38:11–105:32) | 57:05 (31:59–74:07) | 0.16 | 0.19 |
| pH levels | | | | |
| Stomach (whole) | 1.6 (1.1–2.8) | 1.6 (1.4–3.6) | 0.45 | 0.10 |
| Antrum | 1.2 (0.8–1.8) | 2.4 (1.5–2.9) | 0.009 | 0.35 |
| Delta pylorus | 4.9 (3.6–5.4) | 3.3 (2.3–4.4) | 0.004 | 0.38 |
| Small bowel (whole) | 7.4 (7.0–7.6) | 7.1 (6.6–7.7) | 0.35 | 0.12 |
| Duodenum | 6.2 (5.6–6.6) | 5.9 (4.8–6.5) | 0.25 | 0.15 |
| Ileum | 7.7 (7.3–7.8) | 7.8 (7.4–8.4) | 0.19 | 0.17 |
| Delta ICJ | 1.0 (0.7–1.5) | 0.6 (0.3–0.9) | 0.009 | 0.35 |
| Colon (whole) | 6.7 (6.2–7.0) | 7.1 (6.7–7.3) | 0.05 | 0.26 |
| Caecum | 6.4 (5.9–6.9) | 7.3 (6.7–7.7) | 0.008 | 0.35 |
| Rectum | 7.5 (7.0–7.9) | 7.4 (6.4–7.8) | 0.23 | 0.16 |
| Contractility parameters | | | | |
| Gastric MI, mmHg·s/min | 40.2 (27.0–65.2) | 42.6 (32.8–75.0) | 0.61 | 0.07 |
| Gastric Ct, number/min | 1.1 (0.8–1.7) | 1.2 (0.8–2.0) | 0.58 | 0.07 |
| Small bowel MI, mmHg·s/min | 136.0 (84.5–226.1) | 182.7 (106.4–266.6) | 0.23 | 0.16 |
| Small bowel Ct, number/min | 3.9 (2.3–5.2) | 4.1 (2.8–6.3) | 0.38 | 0.12 |
| ICJ pressure, mmHg·s/min | 40.6 (25.1–62.9) | 39.0 (23.9–75.8) | 0.62 | 0.07 |
| Colonic MI, mmHg·s/min | 148.6 (104.8–254.3) | 132.7 (88.5–259.8) | 0.77 | 0.04 |
| Colonic Ct, number/min | 1.3 (1.1–2.0) | 1.7 (1.0–2.7) | 0.50 | 0.09 |

Results are presented as median (quartiles). Cases are defined by GSRS diarrhoea score ≥4 points; controls <4. Transit times, pH variables and contractility parameters are defined in the Methods section.
Abbreviations: Ct, Contractions; GSRS, Gastrointestinal Symptom Rating Scale; ICJ, Ileocaecal junction; MI, Motility index.

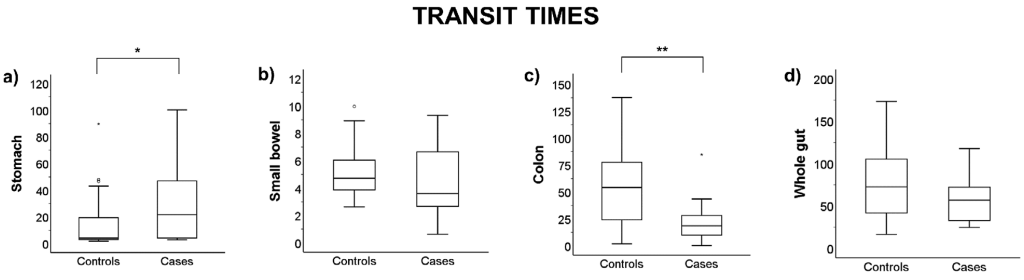


**FIGURE 2** Box-plots showing regional transit times in controls and cases. Statistical significance of $p \leq 0.05$ are marked by *; $p < 0.01$ are marked by **. Results are given as median (quartiles). Transit times (hours: minutes): (a) Stomach: 4:14 (3:11–19:26) in controls versus 21:46 (3:58-47:12) in cases, $p = 0.03$; (b) Small bowel: 4:44 (3:51–6:03) versus 3:36 (2:24-6:52), $p = 0.11$; (c) Colon: 54:25 (22:56–78:11) versus 18:37 (7:23–35:08), $p < 0.001$; Whole gut: 72:44 (38:11–105:32) versus 57:05 (31:59–74:07), $p = 0.16$.

 

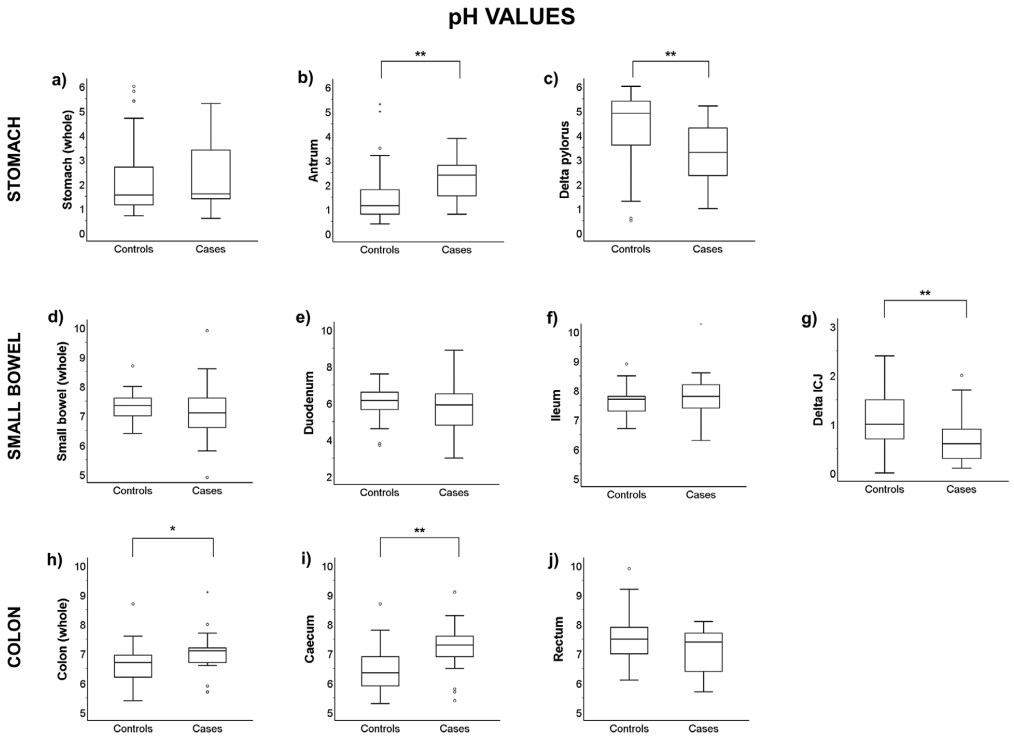


**FIGURE 3** *Box-plots showing regional pH levels in controls and cases. Statistical significance of* $p \leq 0.05$ *are marked by *;* $p < 0.01$ *are marked by **. Results are given as median (quartiles). Stomach pH levels: (a) Stomach (whole): 1.6 (1.1–2.8) in controls versus 1.6 (1.4–3.6) in cases,* $p = 0.45$*; (b) Antrum: 1.2 (0.8–1.8) versus 2.4 (1.5–2.9),* $p = 0.009$*; (c) Delta pylorus: 4.9 (3.6–5.4) versus 3.3 (2.3–4.4),* $p = 0.004$*. Small bowel pH levels: (d) Small bowel (whole): 7.4 (7.0–7.6) versus 7.1 (6.6–7.7),* $p = 0.35$*; (e) Duodenum: 6.2 (5.6–6.6) versus 5.9 (4.8–6.5),* $p = 0.25$*; (f) Ileum: 7.7 (7.3–7.8) versus 7.8 (7.4–8.4),* $p = 0.19$*; (g) Delta ICJ: 1.0 (0.7–1.5) versus 0.6 (0.3–0.9),* $p = 0.009$*. Colonic pH levels: (h) Colon (whole): 6.7 (6.2–7.0) versus 7.1 (6.7–7.3),* $p = 0.05$*; (i) Caecum 6.4 (5.9–6.9) versus 7.3 (6.7–7.7),* $p = 0.008$*; (j) Rectum 7.5 (7.0–7.9) versus 7.4 (6.4–7.8),* $p = 0.23$*. Abbreviation: ICJ = Ileocaecal junction.*

Previous studies of intestinal dysmotility in diabetic diarrhoea have shown divergent results [31–36]. Some have found an association between diabetic diarrhoea, prolonged transit time and small intestinal bacterial overgrowth [31,33,34]. Others have found results similar to ours, with shortened intestinal transit, some also identifying a correlation with autonomic dysfunction [12,32,35,36]. Theoretically, autonomic dysfunction may induce intestinal dysmotility through several pathways. Loss of inhibitory input through damaged sympathetic innervation could explain the rapid transit seen in our diarrhoea patients [17]. Stimulation of alpha-adrenergic receptors on enterocytes is also important for intestinal fluid absorption, and autonomic dysfunction could lead to increased colonic fluid levels and watery diarrhoea [1,13]. Alterations in the sympathetic and parasympathetic nervous systems have been found in several human pathological studies [17,37]. Despite this, Whalen and colleagues demonstrated intact efferent autonomic function in patients with diabetic diarrhoea when investigating intestinal motility in response to intravenous stimulation by adrenergic and cholinergic agents [38]. They did, however, find reduced pain response to intrajejunal balloon distention, indicating afferent dysfunction [38]. Similar findings have been made in the oesophagus,

 

**TABLE 3.** *Autonomic function tests: a comparison of diabetes patients with diarrhoea and controls*

| Variable, unit | Controls | Cases | *p* value | Effect size |
|---|---|---|---|---|
| Heart rate variability (time-domain measures) | | | | |
| Mean heart rate, bpm | 74.1 (66.8–86.3) | 71.3 (64.2–84.4) | 0.63 | 0.07 |
| Mean NN | 802.8 (689.9–939.6) | 841.4 (745.7–948.5) | 0.51 | 0.11 |
| SDNN, ms | 24.6 (12.7–35.0) | 20.1 (15.0–30.7) | 0.70 | 0.06 |
| RMSSD, ms | 15.8 (6.9–26.9) | 14.0 (11.7–21.1) | 0.64 | 0.07 |
| Heart rate variability (frequency-domain measures) | | | | |
| Total power, $ms^2$ | 67.8 (21.2–272.8) | 80.0 (5.1–219.1) | 0.59 | 0.08 |
| Very low frequency, $ms^2$ | 54.1 (19.5–132.3) | 60.6 (13.8–129.1) | 1.00 | 0.00 |
| Low frequency, $ms^2$ | 26.5 (4.9–54.7) | 30.0 (4.3–68.5) | 0.84 | 0.03 |
| High frequency, $ms^2$ | 10.6 (4.1–48.8) | 14.3 (3.4–34.2) | 0.92 | 0.02 |
| LF norm, nu | 58.6 (39.1–78.6) | 62.8 (45.1–74.2) | 0.69 | 0.06 |
| HF norm, nu | 41.4 (21.4–61.0) | 37.2 (25.9–54.9) | 0.69 | 0.06 |
| LF/HF ratio | 1.4 (0.7–3.7) | 1.7 (0.8–3.0) | 0.66 | 0.07 |
| Baroreflex sensitivity | | | | |
| Standard deviation of HR | 3.3 (2.2–5.1) | 4.2 (2.2–4.4) | 0.92 | 0.02 |
| Maximal variance of HR | 11.0 (5.2–16.0) | 6.9 (5.0–11.3) | 0.28 | 0.16 |
| Mean variance of HR | 6.8 (3.0–11.5) | 4.8 (3.2–8.1) | 0.52 | 0.09 |
| E/I ratio | 1.09 (1.03–1.18) | 1.07 (1.04–1.14) | 0.74 | 0.05 |
| Orthostatic tests | | | | |
| 30:15 ratio | 1.06 (1.03–1.19) | 1.06 (1.03–1.11) | 0.47 | 0.11 |
| Resting systolic BP | 122 (112–134) | 126 (115–138) | 0.16 | 0.19 |
| Resting diastolic BP | 75 (66–82) | 77 (65–84) | 0.64 | 0.06 |
| Systolic BP drop at 0 min | 3 (-3–15) | 25 (-1–31) | 0.32 | 0.17 |
| Diastolic BP drop at 0 min | 3 (-4–8) | 10 (2–16) | 0.10 | 0.27 |
| Systolic BP drop at 1 min | 2 (-4–18) | 3 (-8–21) | 0.97 | 0.01 |
| Diastolic BP drop at 1 min | 1 (-6–6) | 2 (-6–11) | 0.55 | 0.08 |
| Systolic BP drop at 3 min | 2 (-4–12) | 9 (1–27) | 0.10 | 0.22 |
| Diastolic BP drop at 3 min | -1 (-7–6) | 4 (-1–18) | 0.054 | 0.26 |

Results are presented as median (quartiles). Cases are defined by GSRS diarrhoea score ≥4 points; controls <4.
Abbreviations: BP, Blood Pressure; Bpm, Beats per minute; E/I ratio, Expiration/Inspiration ratio; GSRS, Gastrointestinal Symptom Rating Scale; HF norm, nu, High frequency normalized units; HR, Heart Rate; LF/HF ratio, low-frequency/high-frequency ratio; LF norm, nu, Low frequency normalized units; RMSSD, Root mean square of successive RR interval differences; SDNN, Standard deviation of NN intervals (inter-beat intervals where artefacts are removed).

duodenum and rectum, whilst gastric barostat studies have found the opposite in diabetic gastroparesis: visceral hypersensitivity [39–41]. Studies utilizing cardiac autonomic function tests in patients with diabetic gastroenteropathy, have also provided conflicting results [36,42,43].

In this study, we were unable to find any differences between cases and controls in heart rate variability or baroreflex sensitivity. Neither did we find any correlations between these parameters and diarrhoea score. We did, however, find a trend towards an increased orthostatic blood pressure drop in cases. In addition, we found a moderate negative correlation with colonic transit time. These results could indicate a possible impairment of the sympathetic nervous system, although in such case, we would have expected to find differences in the high frequency spectres of the heart rate variability as well [28,44]. Overall, our results imply that other mechanisms than autonomic dysfunction are more prominent in the pathophysiology of diabetic diarrhoea. One explanation for our findings, could be that some patients in the comparator group also had enteric dysmotility. All patients had gastrointestinal symptoms and a clinical suspicion of gastroenteropathy, but controls differed with respect to not reporting diarrhoea. To

 

investigate this further, we found that a small proportion of controls had slow-transit constipation, as defined by GSRS and prolonged colonic transit [21,29]. However, excluding these patients did not alter the statistical significance of our original results.

Another pathophysiological theory potentially explaining our findings, is the loss of enteric neurons [17]. Through the production of nitrogen monoxide, these neurons have an important inhibitory effect on gastrointestinal peristalsis, and their depletion may lead to accelerated transit [1]. Apoptosis of enteric glial cells may aggravate neuronal loss [1]. Another possible mechanism may be reduced synthesis of sodium hydrosulphide, which acts as an inhibitor of intestinal smooth muscles [45]. There are conflicting results regarding the role of bile acid malabsorption in diabetic diarrhoea, but the theory has recently gained new impetus [12,46]. Increased levels of colonic bile acids might explain diarrhoea through several mechanisms, including a direct stimulatory effect on motility [47]. Small intestinal carbohydrate malabsorption may accelerate colonic transit through an increased fluid load, but short-chain fatty acids produced by fermentation of carbohydrates, slow down transit [48]. Additional mechanisms possibly contributing to dysmotility are neuroendocrine dysregulation, alterations of smooth muscle cells and loss of interstitial cells of Cajal [17]. Interestingly, the effect of hyperglycaemia is somewhat paradoxical: whilst chronic hyperglycaemia is central in the development of enteric neuropathy, and hence leads to accelerated transit, acute hyperglycaemia leads to delayed transit throughout the entire gastrointestinal tract [13,14,17].

Our study is the first to report intestinal pH alterations in patients with diabetic diarrhoea. Previously, this has been investigated in asymptomatic type 1 diabetes patients with peripheral neuropathy, finding decreased colonic pH levels and an increased pH difference across the ileocaecal junction compared to healthy controls [49,50]. Similar findings have been demonstrated in irritable bowel syndrome [24]. Normally, the pH level decreases more than one unit across the ileocaecal junction as a consequence of the more acidic environment in the caecum compared to the ileum [21]. This is mostly due to bacterial fermentation and production of short-chain fatty acids [49]. The magnitude of the ileocaecal pH drop has therefore been suggested as a proxy for the degree of fermentation in the proximal colon [51]. This may be increased in carbohydrate malabsorption or with heightened intake of fibre or other nonabsorbable sugars, the latter being a common cause of diarrhoea in diabetes [8,11,48]. When our cases had a decreased ileocaecal pH drop and an increased intracolonic pH profile than controls, this may reflect another microbial profile [21,49]. A number of factors may influence microbial composition, including diet, stool consistency, intestinal transit times and bile acids [52,53]. Theoretically, bile acid malabsorption may lead to colonic pH alterations directly, but this is so far not reported in studies. Different types of nutrients can influence pH levels indirectly, where increased production of ammonium in high protein-diets may lead to an alkaline intracolonic milieu [52]. In contrast to fermentation of carbohydrates, protein fermentation is most pronounced in lower parts of the colon, thus being a less likely cause of our caecal pH findings [53]. The interrelationship between intestinal transit and pH levels may be unpredictable: when colonic transit is rapid, pH levels may increase as bacteria have less time to ferment carbohydrates. At the same time, rapid transit may induce a shift towards lactate production, potentially lowering pH levels [52]. In this study, we found no association between pH levels and transit times.

Another possible explanation for our findings of a more alkaline caecal micromilieu may be altered activation of receptors facilitating bicarbonate secretion [54]. Interestingly, a study administering linaclotide to patients with irritable bowel syndrome with constipation, increased caecal pH, reduced colonic transit time and improved symptoms [51]. Linaclotide exerts its effect through increased luminal secretion of chloride and bicarbonate, in next case leading to increased efflux of water [51]. Ileocaecal valve dysfunction could lead to a decreased pH drop across the ileocaecal junction, as shown in patients with Crohn's disease who had undergone ileocaecal resection. Compared to controls, patients had increased pH in the caecum, whilst ileal pH levels were similar [55]. Ileocaecal valve dysfunction has also been associated with bacterial overgrowth [25]. However, we did not find any differences in ileocaecal junction pressure between cases and controls. Neither did we find any other differences in contractility parameters, but this should be explored in more detail in future studies. New studies are also needed to investigate the many potential causes of pH level alterations in diabetic diarrhoea,

 

including characterization of the microbiome and tests for bile acid malabsorption and bacterial overgrowth.

Previous studies have shown that wireless motility capsule examinations have large therapeutic consequences, providing new diagnoses in 50% of patients and changing treatment in 75% [56]. Our results also suggest that tests of gastrointestinal motility and pH levels have a role in the evaluation of diabetic diarrhoea, potentially guiding medical treatment. As an example, the patient with slow small bowel transit secondary to bacterial overgrowth, needs a different therapeutic approach than the patient with rapid colonic transit caused by enteric neuropathy. Many diabetes patients also have concurrent dysmotility in more than one gastrointestinal segment, evidenced by our diarrhoea patients having both delayed gastric emptying and rapid colonic transit [12,35,56]. Here, motility testing may help to tailorize pharmacological treatment [13,35,57,58]. Furthermore, alterations in pH levels or changes in luminal water content may affect intestinal drug delivery and absorption, being especially relevant for the release of active substances from drugs with controlled release formulations [14]. Although not yet investigated in diabetes, intestinal pH level alterations may also be linked to visceral sensitivity [59]. Finally, and crucially, the attention to this underreported and undertreated diabetes complication should be increased in health care providers. It is worrying that 30% of our study patients had diarrhoea, but only 7% used antidiarrhoeal medications.

There are some methodological considerations regarding our study. We used a validated questionnaire to assess bowel function [29]. As there are no predefined dichotomous cut-off values for the GSRS diarrhoea syndrome, we chose to define $\geq$4 points as cases with diarrhoea. This cut-off value was intentionally conservative, to maximize sensitivity for detecting true diarrhoea cases. A post hoc Kappa analysis, demonstrated a substantial agreement between our chosen cut-off for diarrhoea and clinical information gathered from physician interviews. Additionally, we performed correlation analyses showing similar results, thus strengthening our findings. Furthermore, exact localization of the wireless motility capsule is only possible when it passes the pylorus, ileocaecal junction or is expelled from the body [60]. The definition of gastrointestinal subsegments is therefore based on temporal measurements in relation to these physiological landmarks. We utilized pH measurements 15 min before and after the pylorus and ileocaecal junction to determine pH in the adjacent subsegments, similar to the reference study by Wang and colleagues [21]. Other studies have used 30-min measurements or split the intestines into quartiles [49,50,61]. Compared to these approaches, 15-min measurements are preferential in patients with rapid transit. Due to the large variance in transit times, it also has an advantage over the quartile approach when it comes to interindividual comparisons. As stabilized pH values for >10 min is a criterion for manually determining the physiological landmarks, and the capsule has a negligible lag phase for detecting pH changes, 15-min measurements are likely sufficient [60]. Nevertheless, we support further validation studies to establish a consensus. Lastly, to investigate the association between diabetic diarrhoea and autonomic dysfunction, we measured heart rate variability, baroreflex sensitivity and orthostatic hypotension [28]. These are validated methods for assessing cardiac autonomic function and often used as a proxy for visceral autonomic neuropathy due to the lack of ideal tests for evaluating gastrointestinal autonomic function [27,62]. We have previously demonstrated an association between impaired rectal sensitivity, indicating autonomic neuropathy, and reduced cardiac autonomic function [40]. Others have also found an association between cardiac autonomic neuropathy and gastric vagal neuropathy [63].

Our study had some limitations. Being an exploratory study, we did not perform an a priori power analysis, but our main findings still had moderate effect sizes. However, our study may have been underpowered to identify a minor difference in small bowel transit. We also included patients having comorbidities or using drugs associated with diarrhoea (Table S1). Due to their frequency, excluding these patients would potentially introduce a selection bias. To assess eventual influence from comorbidities, we compared GSRS scores, only finding a marginally lower free thyroxine in diarrhoea patients (Table S1). Since the difference between groups was within the biological variation of free thyroxine, and both groups were in an euthyroid state, we find this unlikely to have had an influence on symptoms [64]. As for medications, we found higher diarrhoea scores in patients using opioids and antiepileptic drugs, both drug classes common in the treatment of painful neuropathy.

 

Considering this, we find it unlikely that our main findings could be explained by medications.

The main strength of our study was the use of state-of-the-art technology to assess gastrointestinal motility, pH levels and autonomic function. To our knowledge, this is the largest experimental study to date investigating diabetic diarrhoea. Whilst similar studies often have a retrospective design, we used prospective inclusion. Thereby we limited potential biases and were able to standardize patient characterization using structured interviews, review of medicine lists and measurement of biochemical parameters. Another strength was the measurement of faecal calprotectin and faecal elastase-1 to exclude previously undiagnosed inflammatory bowel disease and pancreatic exocrine insufficiency, respectively.

To conclude, we found that patients with diabetic diarrhoea had slower gastric emptying, faster colonic transit and altered gastrointestinal pH levels. Overall, our findings do not support the association between diabetic diarrhoea and autonomic dysfunction. Our results add increased knowledge to a field largely devoid of research for the last two decades. Hopefully, they provide the groundwork for further studies into the pathophysiology of diabetic diarrhoea. Our study also proves that measurement of transit times and intestinal pH levels can be a valuable guide for individualized treatment and may warrant a more central role in the evaluation of diabetic diarrhoea.

### Acknowledgements

The authors would like to thank M. Bekkelund for assistance with wireless motility capsule test analyses. We also thank Haukeland University Hospital for providing research facilities, all the hospital personnel assisting us during the study, and all participating patients.

### Conflict of Interest

The authors have no competing interests.

### Author Contributions

Eirik Søfteland (ES) is guarantor of the article. Dag A. Sangnes (DS), Georg Dimcevski (GD) and ES designed the study. DS and ES analysed the tests. Jakub Frey (JF) and DS contributed to data entry. DS performed the statistical analysis. All authors were involved in drafting of the manuscript. All authors approved the final version of the manuscript.

### Funding

Dag A. Sangnes has received a PhD Scholarship grant from the Western Norway Regional Health Authority. The study has otherwise been funded by Haukeland University Hospital.

### Data Availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

### Prior Presentation

An abstract from the study was presented at the NeuroGASTRO congress in Lisbon, Portugal, September 5–7, 2019.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supporting information ■

 

**JIM-21-0222 – R1**

# Diabetic diarrhoea: a study on gastrointestinal motility, pH levels and autonomic function

## Electronic supplementary material

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# Tables

**Supplementary Table 1 |** Medications associated with diarrhoea and their relation to diarrhoea scores

| Organ system, drug class | *n* (%) | Comparison of diarrhoea scores | | | |
|---|---|---|---|---|---|
| | | Not using medication | Using medication | *p* value | Effect size |
| Diabetes and endocrine | | | | | |
| Corticosteroids | 8 (14%) | 2.7 (0.7-4.0) | 2.3 (0-4.7) | 0.85 | 0.03 |
| Sex hormones | 9 (16%) | 2.7 (0.7-4.0) | 1.3 (0-4.5) | 0.52 | 0.09 |
| Metformin | 9 (16%) | 2.5 (0.4-4.3) | 2.7 (1.0-3.3) | 0.97 | 0.01 |
| Thyroid hormones | 14 (25%) | 2.7 (0.3-4.0) | 2.3 (0.5-4.5) | 0.95 | 0.01 |
| Cardiovascular | | | | | |
| ACEI/ARB | 18 (32%) | 2.7 (0.3-4.3) | 2.0 (0.7-3.8) | 0.86 | 0.02 |
| Antiplatelet drugs | 13 (23%) | 2.7 (0.7-4.0) | 1.7 (0-4.3) | 0.49 | 0.09 |
| Beta-blockers | 10 (18%) | 2.7 (0.7-4.3) | 2.2 (0-3.3) | 0.48 | 0.09 |
| Calcium channel blockers | 8 (14%) | 2.7 (0.5-4.0) | 2.5 (0.2-4.6) | 0.97 | 0.00 |
| Lipid-lowering agents | 25 (44%) | 3.0 (0.4-4.0) | 2.0 (0.5-4.3) | 0.88 | 0.02 |
| Loop diuretics | 6 (11%) | 2.7 (0.7-4.0) | 0.3 (0-3.3) | 0.14 | 0.20 |
| Thiazides | 6 (11%) | 2.7 (0.3-4.0) | 2.0 (0.7-4.5) | 0.79 | 0.04 |
| Gastrointestinal | | | | | |
| Laxatives | 11 (19%) | 2.7 (0.7-4.1) | 2.0 (0-4.0) | 0.45 | 0.10 |
| Prokinetics | 13 (23%) | 2.7 (0.7-4.3) | 0.7 (0.2-3.8) | 0.38 | 0.12 |
| Proton pump inhibitors | 25 (44%) | 3.0 (0.4-4.6) | 1.7 (0.5-3.8) | 0.19 | 0.17 |
| Neurological and psychiatric | | | | | |
| Anxiolytics | 7 (12%) | 2.0 (0.3-4.0) | 4.0 (2.7-6.0) | 0.07 | 0.24 |
| Antidepressants* | 13 (23%) | 2.7 (0.3-4.3) | 1.7 (0.7-4.0) | 0.91 | 0.02 |
| Antiepileptics | 7 (12%) | 2.0 (0.3-3.8) | 5.0 (1.7-6.0) | 0.04 | 0.27 |
| Hypnotics and sedatives | 11 (19%) | 2.7 (0.7-4.0) | 1.3 (0-5.3) | 0.95 | 0.01 |
| Other medications | | | | | |
| Antihistamines | 14 (25%) | 2.0 (0-4.0) | 2.7 (1.6-4.1) | 0.39 | 0.11 |
| Antineoplastic drugs/immunomodulators | 10 (18%) | 2.0 (0.7-4.0) | 2.8 (0-4.8) | 0.92 | 0.01 |
| Opiates | 13 (23%) | 2.0 (0.2-3.7) | 4.0 (0.8-5.7) | 0.03 | 0.28 |
| Vitamins/minerals | 22 (39%) | 2.0 (0.3-4.0) | 2.7 (0.5-4.2) | 0.78 | 0.04 |

Frequencies are given as *n* (%). Other results are presented as median (quartiles). Medications with frequencies ≤5 were excluded from statistical comparisons, including antidiarrhoeals (*n*=4; 7%), antiemetics (3; 5%), other antacids (4; 7%), NSAIDs (4; 7%) and anti-diabetic medications bar metformin. *All antidepressants were grouped together for statistical purposes, including SSRIs, SNRIs and TCAs. Abbreviations: GSRS = Gastrointestinal Symptom Rating Scale. ACEI = angiotensin-converting enzyme inhibitors. ARB = Angiotensin II receptor blockers. NSAID = Non-steroidal anti-inflammatory drugs. SSRI = Selective serotonin reuptake inhibitors. SNRI = Serotonin-norepinephrine reuptake inhibitor. TCA = Tricyclic antidepressants.

**Supplementary Table 2 |** Wireless motility capsule measurements of transit times, pH levels and contractility parameters: Correlation with diarrhoea scores

| Variables / location | Correlation | 95% CI | | $R^2$ | *p* value |
|---|---|---|---|---|---|
| | | Lower | Upper | | |
| Transit times | | | | | |
| Stomach | 0.23 | -0.02 | 0.48 | 5.3% | 0.08 |
| Small bowel | -0.22 | -0.47 | 0.07 | 4.8% | 0.10 |
| Colon | -0.36 | -0.59 | -0.08 | 13.0% | 0.006 |
| Whole gut | -0.05 | -0.29 | -0.20 | 0.3% | 0.74 |
| pH levels | | | | | |
| Stomach (whole) | 0.17 | -0.11 | 0.42 | 2.9% | 0.22 |
| Antrum | 0.32 | 0.04 | 0.57 | 10.2% | 0.02 |
| Delta pylorus | -0.43 | -0.61 | -0.22 | 18.5% | 0.001 |
| Small bowel (whole) | 0.03 | -0.24 | 0.31 | 0.1% | 0.84 |
| Duodenum | -0.26 | -0.50 | 0.00 | 6.8% | 0.051 |
| Ileum | 0.29 | 0.02 | 0.54 | 8.4% | 0.03 |
| Delta ICJ | -0.27 | -0.48 | -0.001 | 7.3% | 0.04 |
| Colon (whole) | 0.23 | -0.04 | 0.48 | 5.3% | 0.08 |
| Caecum | 0.36 | 0.12 | 0.58 | 13.0% | 0.006 |
| Rectum | -0.02 | -0.28 | 0.26 | 0.0% | 0.89 |
| Contractility parameters | | | | | |
| Gastric MI | 0.03 | -0.22 | 0.27 | 0.1% | 0.81 |
| Gastric Ct | 0.04 | -0.22 | 0.30 | 0.2% | 0.78 |
| Small bowel MI | 0.13 | -0.14 | 0.39 | 1.7% | 0.35 |
| Small bowel Ct | 0.06 | -0.20 | 0.34 | 0.4% | 0.64 |
| ICJ pressure | -0.05 | -0.34 | 0.25 | 0.3% | 0.73 |
| Colonic MI | -0.02 | -0.32 | 0.27 | 0.0% | 0.89 |
| Colonic Ct | 0.02 | -0.24 | 0.29 | 0.0% | 0.88 |

Correlations are between each given parameter and the continuous GSRS diarrhoea score and presented as Spearman's correlation coefficient ($r_s$). Transit times, pH variables and contractility parameters are defined in the Methods section. Abbreviations: CI = Confidence interval. $R^2$ = Coefficient of determination. ICJ = Ileocaecal junction. MI = Motility index. Ct = Contractions. GSRS = Gastrointestinal Symptom Rating Scale.

**Supplementary Table 3** | Autonomic function tests: Correlation with diarrhoea scores

| Variable | Correlation | 95% CI | | $R^2$ | *p* value |
|---|---|---|---|---|---|
| | | Lower | Upper | | |
| Heart rate variability (time-domain measures) | | | | | |
| Mean heart rate | 0.02 | -0.32 | 0.38 | 0.0% | 0.93 |
| Mean NN | -0.01 | -0.38 | 0.32 | 0.0% | 0.94 |
| SDNN | -0.20 | -0.48 | 0.14 | 4.0% | 0.23 |
| RMSSD | -0.03 | -0.31 | 0.29 | 0.1% | 0.84 |
| Heart rate variability (frequency-domain measures) | | | | | |
| Total power | -0.16 | -0.45 | 0.17 | 2.6% | 0.34 |
| Very low frequency | -0.21 | -0.51 | 0.14 | 4.4% | 0.19 |
| Low frequency | -0.08 | -0.39 | 0.26 | 0.6% | 0.65 |
| High frequency | -0.13 | -0.42 | 0.21 | 1.7% | 0.45 |
| LF norm | 0.04 | -0.24 | 0.32 | 0.2% | 0.79 |
| HF norm | -0.04 | -0.32 | 0.24 | 0.2% | 0.79 |
| LF/HF ratio | 0.05 | -0.24 | 0.34 | 0.3% | 0.79 |
| Baroreflex sensitivity | | | | | |
| Standard deviation of HR | -0.14 | -0.44 | 0.20 | 2.0% | 0.39 |
| Maximal variance of HR | -0.25 | -0.51 | 0.06 | 6.3% | 0.13 |
| Mean variance of HR | -0.27 | -0.55 | 0.06 | 7.3% | 0.10 |
| E/I ratio | -0.26 | -0.55 | 0.06 | 6.8% | 0.11 |
| Orthostatic tests | | | | | |
| 30:15 ratio | -0.10 | -0.41 | 0.22 | 1.0% | 0.60 |
| Resting systolic BP | 0.02 | -0.36 | 0.34 | 0.0% | 0.93 |
| Resting diastolic BP | 0.08 | -0.28 | 0.41 | 0.6% | 0.66 |
| Systolic BP drop at 0 min | 0.25 | -0.17 | 0.60 | 6.3% | 0.17 |
| Diastolic BP drop at 0 min | 0.21 | -0.17 | 0.54 | 4.4% | 0.23 |
| Systolic BP drop at 1 min | 0.02 | -0.38 | 0.40 | 0.0% | 0.89 |
| Diastolic BP drop at 1 min | 0.15 | -0.20 | 0.48 | 2.3% | 0.41 |
| Systolic BP drop at 3 min | 0.25 | -0.13 | 0.59 | 6.3% | 0.16 |
| Diastolic BP drop at 3 min | 0.27 | -0.07 | 0.60 | 7.3% | 0.13 |

Correlations are between each given parameter and the continuous GSRS diarrhoea score and presented as Spearman's correlation coefficient ($r_s$). Abbreviations: SDNN = Standard deviation of NN intervals (inter-beat intervals where artefacts are removed). RMSSD = Root mean square of successive RR interval differences. LF norm = Low frequency normalized. HF norm = High frequency normalized. LF/HF ratio = Low frequency/high frequency ratio. HR = Heart rate. E/I ratio = Expiration/inspiration ratio. BP = Blood pressure. $R^2$ = Coefficient of determination. GSRS = Gastrointestinal Symptom Rating Scale.

**Supplementary Table 4** | Autonomic function tests: Correlation with colonic transit time

| Variable | Correlation | 95% CI | | $R^2$ | *p* value |
|---|---|---|---|---|---|
| | | Lower | Upper | | |
| Heart rate variability (time-domain measures) | | | | | |
| Mean heart rate | -0.07 | -0.40 | 0.26 | 0.5% | 0.69 |
| Mean NN | 0.06 | -0.27 | 0.39 | 0.4% | 0.72 |
| SDNN | -0.05 | -0.34 | 0.31 | 0.3% | 0.77 |
| RMSSD | -0.27 | -0.54 | 0.07 | 7.3% | 0.10 |
| Heart rate variability (frequency-domain measures) | | | | | |
| Total power | 0.004 | -0.29 | 0.37 | 0.0% | 0.98 |
| Very low frequency | 0.11 | -0.20 | 0.44 | 1.2% | 0.50 |
| Low frequency | 0.01 | -0.28 | 0.37 | 0.0% | 0.97 |
| High frequency | -0.19 | -0.46 | 0.16 | 3.6% | 0.25 |
| LF norm | 0.13 | -0.19 | 0.43 | 1.7% | 0.43 |
| HF norm | -0.13 | -0.43 | 0.19 | 1.7% | 0.43 |
| LF/HF ratio | 0.14 | -0.17 | 0.43 | 2.0% | 0.41 |
| Baroreflex sensitivity | | | | | |
| Standard deviation of HR | -0.15 | -0.45 | 0.17 | 2.3% | 0.38 |
| Maximal variance of HR | -0.06 | -0.41 | 0.30 | 0.4% | 0.71 |
| Mean variance of HR | -0.14 | -0.48 | 0.24 | 2.0% | 0.41 |
| E/I ratio | -0.11 | -0.47 | 0.26 | 1.2% | 0.51 |
| Orthostatic tests | | | | | |
| 30:15 ratio | -0.17 | -0.48 | 0.16 | 2.9% | 0.32 |
| Resting systolic BP | -0.28 | -0.53 | 0.002 | 7.8% | 0.10 |
| Resting diastolic BP | -0.24 | -0.52 | 0.12 | 5.8% | 0.17 |
| Systolic BP drop at 0 min | -0.21 | -0.53 | 0.10 | 4.4% | 0.22 |
| Diastolic BP drop at 0 min | -0.34 | -0.61 | -0.004 | 11.6% | 0.04 |
| Systolic BP drop at 1 min | -0.24 | -0.53 | 0.10 | 5.8% | 0.16 |
| Diastolic BP drop at 1 min | -0.22 | -0.51 | 0.11 | 4.8% | 0.20 |
| Systolic BP drop at 3 min | -0.29 | -0.60 | 0.03 | 8.4% | 0.09 |
| Diastolic BP drop at 3 min | -0.28 | -0.58 | 0.06 | 7.8% | 0.10 |

Correlations are between each given parameter and the continuous GSRS diarrhoea score and presented as Spearman's correlation coefficient ($r_s$). Abbreviations: SDNN = Standard deviation of NN intervals (inter-beat intervals where artefacts are removed). RMSSD = Root mean square of successive RR interval differences. LF norm = Low frequency normalized. HF norm = High frequency normalized. LF/HF ratio = Low frequency/high frequency ratio. HR = Heart rate. E/I ratio = Expiration/inspiration ratio. BP = Blood pressure. $R^2$ = Coefficient of determination. GSRS = Gastrointestinal Symptom Rating Scale.

Received: 29 July 2021 | Accepted: 29 September 2021

DOI: 10.1002/ueg2.12169

ORIGINAL ARTICLE

ueg journal WILEY

# Gastrointestinal transit and contractility in diabetic constipation: A wireless motility capsule study on diabetes patients and healthy controls

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**Funding information**

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## Abstract

**Background:** Diabetic constipation is traditionally attributed to slow colonic transit, despite limited evidence. More than half of patients find treatment unsatisfactory. To improve treatment, there is a need for better diagnostic understanding of the condition.

**Objective:** In this wireless motility capsule study, we aimed to investigate gastrointestinal transit and contractility in diabetes patients with and without constipation, and in healthy controls.

**Methods:** We prospectively included type 1 or type 2 diabetes patients with gastrointestinal symptoms. Based on the Gastrointestinal Symptom Rating Scale we distinguished into two groups: with constipation and without constipation. Non-diabetic controls were asymptomatic. All were examined with wireless motility capsule, determining transit times and contractility parameters.

**Results:** 57 patients (42 women, 46 with type 1 diabetes) and 26 healthy controls (14 women) were included. We found no difference in transit times between diabetes patients with and without constipation. Compared to healthy controls (35:55, h:min), whole-gut transit was slower in both diabetes patients with constipation (66:15, $p = 0.03$) and without constipation (71:16, $p < 0.001$). Small bowel motility index correlated $r_s = -0.32$ ($p = 0.01$) with constipation symptoms.

**Conclusions:** Diabetes patients with constipation had similar transit times as those without constipation. Both groups had slower whole-gut transit than healthy controls. Constipation was associated with reduced small bowel, but not colonic contractility. Our results imply that other mechanisms than slow colonic transit may be more important in the pathogenesis of diabetic constipation.

**KEYWORDS**

constipation, diabetes mellitus, gastroenteropathy, motility, transit, wireless motility capsule

## INTRODUCTION

Gastrointestinal symptoms are common in diabetes, and constipation is especially frequent.[1,2] In tertiary centres, up to 60% report constipation, while community studies have found a prevalence of 10%–17%.[1,2] Constipation leads to reduced quality of life in half of the patients, and a similar proportion find the treatment unsatisfactory.[3] Causes may be multifactorial, including dietary factors, medications and comorbid conditions, but is often due to diabetic gastroenteropathy, a dysmotility disorder potentially affecting the entire gastrointestinal tract.[4]

Constipation has traditionally been defined as less than three weekly bowel movements, but recent Rome criteria have also included symptoms of straining, incomplete evacuation, anorectal obstruction, hard faeces or the need of manual stimulation to facilitate defecation.[5] Constipation can be categorised into normal-transit constipation, slow-transit constipation and rectal evacuation disorders.[6] Diabetic constipation has traditionally been associated with slow colonic transit, but this knowledge is based on a limited number of studies, often including few patients suffering from constipation.[7–9] Other studies have been retrospective, registry-based, designed to investigate different hypotheses or contained a mixed constipation cohort, where diabetes patients constituted a minority.[10,11]

The two most established methods for measuring colonic transit are radiopaque markers and colonic scintigraphy, but both have disadvantages, such as radiation exposure, poor standardisation and only providing motility results from one single gastrointestinal segment.[12] The wireless motility capsule, however, is not depending on radiological examinations and measures transit through all gut regions in one test.[13] It also has the added advantage of measuring contractility parameters, such as contractions per minute and the motility index.[14] These measurements might provide valuable information about intestinal motility, but their utility in diabetic constipation is so far undefined.

Consequently, in this study, we hypothesised that diabetes patients with constipation had delayed colonic transit and reduced intestinal contractility compared to diabetes patients without constipation, and healthy controls.

**Key Summary**

**Summarise the established knowledge on this subject**

- Constipation is very frequent in diabetes and often has a large impact on quality of life. Half of all patients find treatment unsatisfactory.
- Diabetic constipation has traditionally been attributed to slow colonic transit, but this knowledge is based on a small number of decades-old studies.

**What are the significant and/or new findings of this study?**

- Using wireless motility capsule, we investigated gastrointestinal transit times and contractility in diabetes patients with and without constipation, and in healthy controls.
- We found no difference in transit between diabetes patients with and without constipation, but both diabetes groups had slower whole-gut transit than healthy controls. We also found an association between constipation and reduced small bowel contractility.
- Our results may indicate that slow colonic transit is less important in the pathogenesis of diabetic constipation than previously believed. When evaluating these patients, clinicians should consider other disease mechanisms.

## MATERIALS AND METHODS

### Study population

The study was a cross-sectional case–control observational study with consecutive inclusion. It was performed at a tertiary centre at Haukeland University Hospital, Bergen, Norway between 2014 and 2018. Two groups were included: diabetes patients and healthy controls. Exclusion criteria for both groups were age < 18 years, breastfeeding or pregnancy, previous major intra-abdominal surgery or inability to adhere to the study protocol.

### Diabetes patients

In the patient group, inclusion criteria were type 1 diabetes or type 2 diabetes, chronic gastrointestinal symptoms (minimum duration >6 months), and a normal upper endoscopy during the last 2 years. Patients were referred from all of Norway for diagnostic evaluation at Haukeland University Hospital. They were admitted for the first 3 days of the study period and were outpatients for the last five. While at hospital, they were evaluated by a physician, delivered blood-, urine- and stool samples (Table 1), and underwent tests of gastrointestinal motility. Questionnaires were distributed in advance and collected at admittance. During fast and examinations, patients received glucose-insulin infusion (target glucose level 4–10 mmol/L).

### Healthy controls

As part of a collaborative study, healthy volunteers were examined with wireless motility capsule.[15] All were screened for gastrointestinal symptoms by modified Rome III questionnaires and interviewed by a clinical investigator (physician or study nurse) to rule out pre-existing conditions or use of drugs potentially affecting gastrointestinal motility.

**TABLE 1** Clinical characteristics of diabetes patients with constipation, without constipation and healthy controls

| Variables | Diabetes | | | Healthy controls | |
|---|---|---|---|---|---|
| | Constipation $n = 15$ | No constipation $n = 42$ | $p$-value | $n = 26$ | $p$-value |
| General demographics | | | | | |
| Women, *n* (%) | 14 (93%) | 28 (67%) | 0.08 | 14 (54%) | 0.03[a] |
| Age, years, mean (SD) | 51 (9) | 47 (13) | 0.19 | 42 (15) | 0.07 |
| BMI, kg/m$^2$, mean (SD) | 28.2 (5.8) | 26.2 (5.8) | 0.29 | 24.0 (2.2) | 0.12 |
| Current smokers, *n* (%) | 2 (13%) | 15 (36%) | 0.08 | - | - |
| Diabetes status | | | | | |
| Type 1 diabetes, *n* (%) | 14 (93%) | 32 (76%) | 0.26 | - | - |
| Diabetes duration, years, mean (SD) | 34 (10) | 24 (13) | 0.009 | - | - |
| Late complications, *n* (%) | 11 (73%) | 29 (69%) | 1.0 | - | - |
| Retinopathy, *n* (%) | 9 (60%) | 23 (55%) | 0.77 | - | - |
| Nephropathy, *n* (%) | 3 (20%) | 12 (29%) | 0.74 | - | - |
| Peripheral neuropathy, *n* (%) | 6 (40%) | 19 (45%) | 0.77 | - | - |
| Diabetic wounds, *n* (%) | 3 (20%) | 4 (10%) | 0.37 | - | - |
| Cardiovascular disease, *n* (%) | 2 (13%) | 3 (7%) | 0.60 | - | - |
| Biochemistry | | | | | |
| B-HbA1c, mmol/mol | 63 (9) | 67 (31) | 0.23 | - | - |
| S-TSH, mIE/L | 1.3 (1.2) | 1.5 (1.0) | 0.33 | - | - |
| P-fT4, pmol/L | 16.8 (5.8) | 15.6 (3.9) | 0.52 | - | - |
| U-ACR, mg/mmol | 0.7 (10.9) | 2.0 (4.7) | 0.17 | - | - |
| F-calprotectin, mg/kg | 34 (24) | 15 (34) | 0.73 | - | - |
| F-elastase-1, mg/g | 473 (149) | 500 (233) | 0.62 | - | - |

*Note*: Results are given as median (IQR) unless otherwise indicated. Frequencies are given as *n* (%), where percentages are calculated from the total *n* in each column. Biochemical reference values as used at Haukeland University Hospital: B-HbA1c, 20–42 mmol/mol; S-TSH, 0.40–4.50 mIE/L; P-fT4, 8.0–21.0 pmol/L; U-ACR, 0–2.5 mg/mmol; F-calprotectin, <50 mg/kg; and F-elastase-1, <200 mg/g.

Abbreviations: ACR, albumin to creatinine ratio; B, whole blood; F, faecal; FT4, free thyroxine; HbA1c, glycosylated haemoglobin; IQR, interquartile range; P, plasma; S, serum; SD, standard deviation; TSH, thyroid stimulating hormone; U, urinary.

[a]Sub-group analyses: higher percentage of women in the group with constipation compared with healthy controls ($p = 0.01$), not compared to the group without constipation ($n = 0.32$).

## Motility capsule testing

The wireless motility capsule (SmartPill®, Medtronic) measures pH, temperature and pressure throughout the gastrointestinal tract (Figure 1). After an overnight fast, the capsule was swallowed together with a 260-kcal nutrient bar (SmartBar®, Medtronic) and 120 mL of water. To achieve simultaneous examination with gastric emptying scintigraphy, diabetes patients also ingested a radiolabelled boiled egg (90 kcal). Prior to the investigation and during the study, participants had to pause medications possibly altering gastrointestinal motility. Full details are presented in a previous article.[16] For data analyses, we used MotiliGI® software version 3.0 (Medtronic).

We measured transit times using standardised definitions: gastric emptying time (capsule ingestion–pylorus), small bowel transit time (pylorus–ileocaecal junction) and colonic transit time (ileocaecal junction–capsule expulsion).[13] Normative cut-off values for colonic transit: rapid (<5:00, h:min), normal (<5:00–50:30) and delayed (>50:30).[13] We also measured the motility index and contractions per minute in the small bowel and colon, and sub-segments: duodenum (first 60 min after the pylorus), ileum (last 60 min before the ileocaecal junction), caecum (first 60 min after the ileocaecal junction) and rectum (last 60 min before capsule expulsion).[14]

## Questionnaires

We assessed constipation symptoms using the Gastrointestinal Symptom Rating Scale (GSRS). GSRS can be split into five syndromes, where constipation is a mean of scores on the individual symptoms: (1) decreased passage of stools, (2) hard stools and (3) feeling of incomplete evacuation.[17] Based on prior studies, we chose a cut-off value ≥ 4 to define constipation.[18] We also performed a

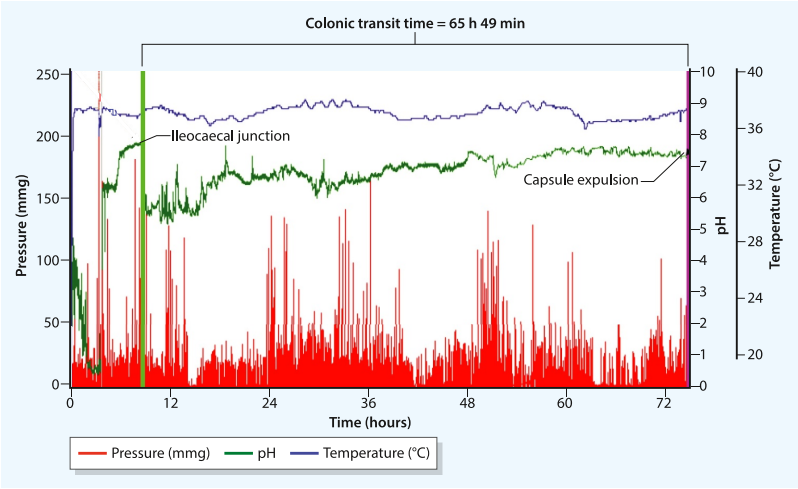


**FIGURE 1** Illustration of a wireless motility capsule recording in a diabetes patient with constipation. The recording shows temperature (°C, top blue curve), pH (middle green curve) and pressure (mmHg, bottom red curve). Colonic transit time is measured from the ileocaecal junction to capsule expulsion, as marked by arrows. In this patient, colonic transit was 65 h 49 min (normal: <5:00–50:30, h:min), indicating slow-transit constipation

psychometric evaluation using the Hospital Anxiety and Depression Scale, where cases of anxiety and depression were defined by a sum score ≥ 11 on the respective subscales.[19]

## Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. The investigation of diabetes patients was approved by The Western Norway Regional Medical Ethics Committee (2015/58), while the study of healthy participants was approved by The South-Eastern Norway Regional Medical Ethics Committee (2014/2222 and 2019/28472). All participants submitted oral and written informed consent.

## Statistical analysis

Normality was assessed by examination of skewness, kurtosis, *Q*–*Q* plots and Shapiro Wilk's test. In cases of normality, continuous variables were stated as mean (standard deviation, SD). Differences between two groups were examined with the independent samples *t*-test. Differences between multiple groups were analysed with one-way independent analysis of variance corrected by Welch's *F* and using Games–Howell *post hoc* test. In cases of non-normality, continuous variables were stated as median (interquartile range, IQR). We used the Mann–Whitney *U* test to compare two, and the Kruskal–Wallis test to compare multiple continuous variables, performing sub-group analyses using Mann–Whitney *U* test with Bonferroni correction. We used Pearson's product-moment correlation ($r$) and Spearman's rank order correlation ($r_s$) to examine associations between normally and non-normally distributed continuous variables, respectively. Categorical variables were stated as *n* (%), and differences between them were assessed using Fisher's exact test. Statistical significance was defined as $p \leq 0.05$. Analyses were performed using IBM SPSS Statistics (Ver. 27, IBM Corporation).

## RESULTS

A total of 72 diabetes patients and 26 healthy participants were included in the study. Of these 68 diabetes patients and all healthy participants were examined with wireless motility capsule. We could not identify the ileocaecal junction in three patients, preventing the determination of small bowel and colonic transit times. Another 8 patients had missing data on the GSRS, leaving 57 available for all comparisons. An inclusion flowchart is shown in Figure 2.

## Clinical characteristics

Clinical characteristics are presented in Table 1. Fifteen diabetes patients (26%) had constipation. Mean constipation score in all patients were 2.6 (SD = 1.5). Women (2.9, SD = 1.5) had more constipation than men (2.0, SD = 1.2), $p = 0.046$. We found no difference between type 1 diabetes (2.6, SD = 1.6) and type 2 diabetes (2.6, SD = 1.2), $p = 0.95$. Patients with constipation had longer diabetes duration than those without constipation ($p = 0.009$). Diabetes duration also correlated with the

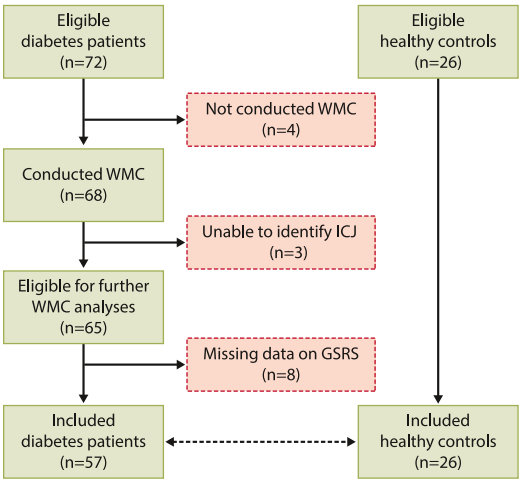


**FIGURE 2** Inclusion flow chart

constipation score ($r$ = 0.38, $p$ = 0.04), but we found no association with age ($p$ = 0.19). Patients with late complications of their diabetes had a constipation score of 2.7 (SD = 1.5); those without complications 2.4 (SD = 1.4), $p$ = 0.40.

Patients with anxiety had more constipation ($p$ = 0.01; Table S1). We found no difference in constipation symptoms when comparing other comorbid conditions. Neither did we find any difference in biochemical parameters (Table 1), nor when looking at medications where constipation is a known side-effect (Table S2).

## Transit times

Table 2 and Figure 3 show transit times in all groups. We found no difference in gastric emptying ($p$ = 0.99), small bowel transit ($p$ = 0.28), colonic transit ($p$ = 0.96) or whole-gut transit ($p$ = 0.69) when comparing diabetes patients with and without constipation. Neither did we find any associations between transit time parameters and the constipation score (all $p > 0.27$).

Healthy controls had faster gastric emptying than both diabetes groups: with constipation ($p$ = 0.003) and without constipation ($p < 0.001$). Healthy controls also had faster colonic transit than diabetes patients without constipation ($p$ = 0.01), but not compared with patients with constipation ($p$ = 0.18). Whole-gut transit was faster in healthy controls than in diabetes patients with constipation ($p$ = 0.03) and without constipation ($p < 0.001$).

In Figure 4, we have presented proportions with delayed, normal and rapid transit in diabetes patients with and without constipation, and in healthy controls. Seven (47%) patients with constipation had delayed colonic transit, while 17 (41%) without constipation had delayed colonic transit, $p$ = 0.75. In comparison, 2 (9%) healthy controls had delayed colonic transit, $p$ = 0.01.

## Contractility parameters

Results from contractility measurements are presented in Table 2. We found that small bowel motility index correlated $r_s$ = −0.32 ($p$ = 0.01) with the constipation score. When comparing the three groups, we found no difference in any of the contractility parameters.

# DISCUSSION

In this study, we investigated gastrointestinal transit and contractility in diabetes patients with and without constipation, and in a group of healthy controls. Contrary to our hypothesis, we found no difference in transit times when comparing diabetes patients with and without constipation. We did, however, find an association between reduced small bowel contractility and constipation symptoms. Compared with healthy controls, both diabetes groups had slower whole-gut transit.

The lack of association between constipation symptoms and transit times found in our study, may have several causes. Firstly, gastrointestinal symptoms are regularly proven to be unspecific markers of organ dysfunction.[20] Exemplifying this, we have previously shown that patients with familial GUCY2C diarrhoea syndrome had increased colonic transit time, despite having four loose stools per day.[15] Constipation is particularly problematic, as the original definition based on stool frequency, correlates poorly with patients' complaints.[21] Instead, patients perceive constipation as a multi-symptom disorder, where straining, hard stool, abdominal discomfort, bloating and the feeling of incomplete evacuation are all equated with infrequent bowel movements.[3] Symptoms like abdominal discomfort and bloating are even more unspecific, also being frequent in gastroparesis and small bowel dysmotility.[4]

Furthermore, there is an overlap in symptoms between rectal evacuation disorders, normal-transit constipation and slow-transit constipation.[3] In primary constipation, rectal evacuation disorders are seen more frequently than slow-transit constipation.[6] The prevalence in diabetes is unknown, but a 1998 pilot-study identified rectal evacuation disorders in 3 out of 10 patients.[22] A recent study supports these findings, demonstrating that constipated diabetes patients had reduced maximal squeeze pressures and recto-anal pressure gradients, and impaired rectal sensitivity.[23] Intact rectal sensitivity is an essential mechanism in the process of defecation, as gradual rectal filling of faeces elicits an urge to defecate.[24] Without sensing this stimulation, the urge to defecate may be attenuated, leading to accumulation of faeces.[21] In patients with refractory functional constipation, 25% had rectal hyposensitivity.[25] Given the potential of diabetic neuropathy for disrupting anorectal sensory pathways, we consider it likely that rectal hyposensitivity is a main mechanism also in diabetic constipation.

On the other hand, there are also findings of visceral hypersensitivity in diabetes.[26] Visceral hypersensitivity is traditionally associated with functional gastrointestinal disorders, but the borderline between diabetic gastroenteropathy and functional disorders may be blurred.[27] In this study, we did not perform tests of visceral

**TABLE 2** Wireless motility capsule measurements of gastrointestinal transit times and contractility parameters: A comparison between diabetes patients with constipation, without constipation and healthy controls

| | Diabetes | | | | | Correlation | |
|---|---|---|---|---|---|---|---|
| **Variable, unit** | **Constipation** | **No constipation** | ***p*-value** | **Healthy controls** | ***p*-value** | **$r_s$** | ***p*-value** |
| Transit times, h:min | | | | | | | |
| Gastric emptying | 4:17 (15:52) | 4:30 (24:51) | 0.99 | 2:58 (1:24) | <0.001[a] | −0.12 | 0.38 |
| Small bowel | 5:08 (1:51) | 4:18 (2:46) | 0.28 | 4:13 (1:37) | 0.16 | 0.15 | 0.27 |
| Colon, mean (SD) | 47:48 (38:00) | 45:59 (33:23) | 0.96 | 28:27 (16:21) | 0.01[b] | 0.11[r] | 0.42 |
| Whole gut, mean (SD) | 66:15 (38:23) | 71:16 (36:33) | 0.69 | 35:55 (16:54) | <0.001[c] | −0.05[r] | 0.70 |
| Motility index, mmHg × s/min | | | | | | | |
| Small bowel (total) | 129.6 (120.4) | 143.4 (154.2) | 0.50 | 111.0 (49.5) | 0.29 | −0.32 | 0.01 |
| Duodenum | 85.3 (72.2) | 86.3 (123.5) | 0.82 | 63.9 (56.5) | 0.33 | −0.25 | 0.06 |
| Ileum | 146.0 (144.8) | 193.3 (306.8) | 0.61 | 182.0 (166.3) | 0.88 | −0.21 | 0.13 |
| Colon (total) | 132.7 (119.7) | 163.3 (173.2) | 0.51 | 160.9 (151.5) | 0.71 | −0.14 | 0.29 |
| Caecum | 104.4 (135.6) | 92.9 (106.5) | 0.90 | 92.1 (159.0) | 0.98 | −0.11 | 0.42 |
| Rectum | 364.0 (435.0) | 246.1 (302.7) | 0.36 | 336.5 (403.9) | 0.34 | 0.13 | 0.35 |
| Contractions per minute, number | | | | | | | |
| Small bowel (total) | 3.8 (2.8) | 3.9 (3.2) | 0.99 | 3.2 (1.1) | 0.77 | −0.19 | 0.17 |
| Duodenum | 2.9 (1.6) | 2.9 (3.2) | 0.80 | 2.2 (1.9) | 0.83 | −0.27 | 0.047 |
| Ileum, mean (SD) | 4.9 (2.2) | 4.4 (2.5) | 0.47 | 4.7 (1.9) | 0.70 | 0.002[r] | 0.99 |
| Colon (total) | 1.5 (1.0) | 1.3 (1.0) | 0.57 | 1.8 (0.7) | 0.21 | −0.08 | 0.55 |
| Caecum | 2.5 (2.6) | 2.5 (2.2) | 0.93 | 3.5 (3.0) | 0.22 | −0.13 | 0.33 |
| Rectum, mean (SD) | 2.4 (1.2) | 1.9 (1.0) | 0.15 | 2.5 (1.1) | 0.08 | 0.15[r] | 0.27 |

*Note*: Results are given as median (IQR) unless otherwise indicated. Correlations are examined between the continuous GSRS constipation score and each wireless motility capsule variable. Correlation coefficients are given as Spearman's $r_s$ unless marked by *r*, indicating Pearson's product-moment correlation (*r*). Sub-group analyses are corrected for multiple comparisons.

Abbreviations: GSRS, Gastrointestinal Symptom Rating Scale; IQR, interquartile range; SD, standard deviation.

[a]Faster gastric emptying time in healthy controls than in diabetes patients with constipation ($p = 0.003$) and without constipation ($p < 0.001$).

[b]Faster colonic transit time in healthy controls than in diabetes patients without constipation ($p = 0.01$), but not compared with patients with constipation ($p = 0.18$).

[c]Faster whole-gut transit time in healthy controls than in diabetes patients with constipation ($p = 0.03$) and without constipation ($p < 0.001$).

sensitivity, meaning that our patient cohort may have been a mix of patients with reduced and increased intestinal sensation. This may result in a different perception of symptoms, and possibly explain the lack of difference in colonic transit between patients with and without constipation.

Another potential explanation, is that the constipation is not caused by diabetes-induced dysmotility but common psychiatric comorbidities, such as anxiety and depression.[28] We have previously demonstrated that mood disorders are prevalent in diabetic gastroparesis, and in this study we found that patients with anxiety had more constipation.[29] Our results are consistent with previous studies.[30] However, the relationship between mental status and gastrointestinal symptoms is likely bidirectional: whereas mood disorders may lead to hypervigilance and altered interpretation of symptoms, they may also be a consequence of the disease burden.[31]

Finally, while not finding any difference in transit times comparing diabetes patients with constipation and without constipation, we found that both groups had slower gastric emptying and whole-gut transit than healthy controls. An interpretation of these results may be that diabetic constipation is a manifestation of a global gastrointestinal dysfunction secondary to diabetic gastroenteropathy. Our results are supported by other transit studies and by histomorphological findings, showing similar alterations in both the stomach and colon, most notably loss of Interstitial Cells of Cajal and enteric neurons.[4,32,33] In addition, hyperglycaemia in itself have been shown to induce dysmotility in the whole gastrointestinal tract.[34]

As a secondary aim, we wanted to examine intestinal contractility using the wireless motility capsule's pressure measurements. Unfortunately, research on intestinal contractility is scarce in diabetic constipation, but a wireless motility capsule study on diabetic gastroparesis patients found blunted colonic contractions compared with healthy controls.[32] Interestingly, we found a moderate correlation between decreased small bowel contractility and constipation

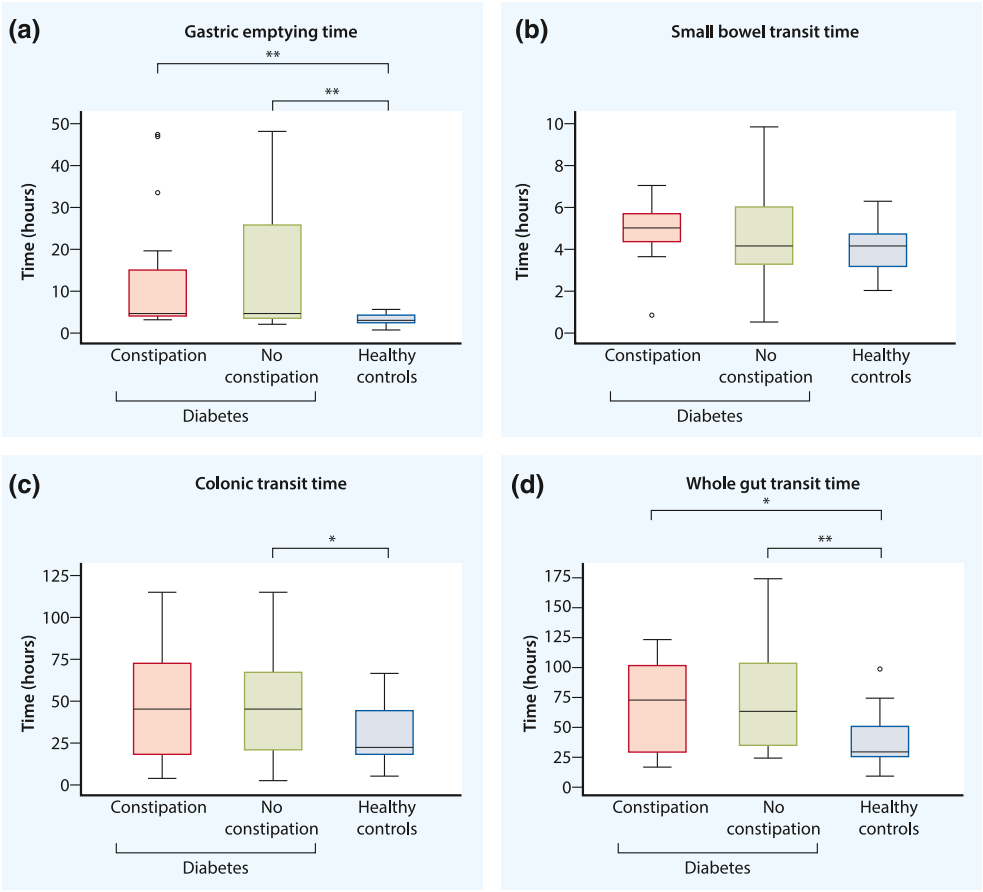


**FIGURE 3** Box-plots showing comparisons of (a) gastric emptying time, (b) small bowel transit time, (c) colonic transit time and (d) whole-gut transit time between diabetes patients with constipation, without constipation and healthy controls. Statistical significance of $p \leq 0.05$ are marked by * and $p < 0.01$ by **. Full results are presented in Table 2. To summarise, we found faster gastric emptying (a) and whole gut transit (d) in healthy controls than in both diabetes groups. We also found faster colonic transit (c) in healthy controls than in diabetes patients without constipation, but found no difference in small bowel transit (b). Neither did we find any difference when comparing transit times between diabetes patients with and without constipation

symptoms, but no association with colonic dysmotility. The interpretation of this finding is uncertain but may lend support to the theory that constipation in diabetes is not caused by isolated colonic dysfunction. The lack of difference in colonic contractility between patients with and without constipation strengthens this argument. However, another explanation may be that the wireless motility capsule has insufficient sensitivity to detect clinically relevant contractility disturbances. Unlike manometry catheters, the capsule floats freely in the lumen and has only one pressure sensor, which complicates the differentiation between different contractility patterns.[32,35] Nevertheless, a study comparing patients with functional constipation, irritable bowel syndrome and healthy controls, was able to identify altered colonic contractility in constipated patients.[36] Considering that the wireless motility capsule has advantages over manometry in availability, ease of use and increased patient comfort, we support head-to-head validation studies to determine its future role in colonic contractility assessments.

Our study was cross-sectional and exploratory and thus not designed to investigate causality. Despite this, our findings may have clinical significance. When so many patients with diabetic constipation experience inadequate treatment, this may indicate that the diagnostics have not identified the causative mechanism behind the symptoms. Slow transit has for long been considered the main mechanism behind diabetic constipation, but other possible explanations have been sparsely investigated. In this paper, we have attempted to discuss some of these potential causes. Of these, evacuation disorders caused by diabetes-induced damage to the neural regulation may be the most likely and merits further

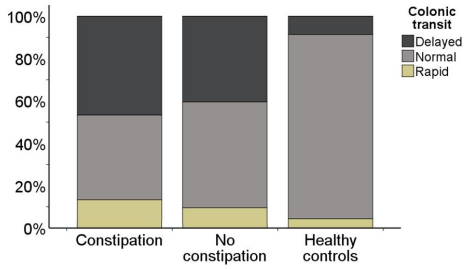


**FIGURE 4** Proportions with delayed, normal and rapid colonic transit in diabetes patients with constipation, without constipation and in healthy controls. Frequencies are given as *n* (%), where percentages are calculated from the total *n* in each group. Constipation ($n = 15$): 7 (47%) delayed; 6 (40%) normal; 2 (13%) rapid. Without constipation ($n = 42$): 17 (41%) delayed; 21 (50%) normal; 4 (10%) rapid. Healthy controls ($n = 23$): 2 (9%) delayed; 20 (87%) normal; 1 (4%) rapid. Proportions were equally distributed in the diabetes groups ($p = 0.75$), both differing from the distribution in healthy controls, $p = 0.01$

investigation. In addition, we have shown that diabetes patients with constipation had higher anxiety levels. Chronic anxiety may further contribute to the development of rectal evacuation disorders.[37] Most likely, diabetic constipation is a heterogeneous disorder. We therefore emphasise the need for a thorough investigation before initiating treatment, which should be individualised based on diagnostic findings. Prokinetic agents may still have a place in treatment but other causes like rectal evacuation disorders and psychiatric comorbidities should be ruled out first, as these require an entirely different approach to treatment than slow-transit constipation.[25,30] When performing gastrointestinal motility testing, our findings also underline the relevance of evaluating more than just colonic transit, as diabetes patients regularly show concurrent affection of multiple gastrointestinal segments.[33] Hopefully, a broader diagnostic approach to patients with diabetic constipation will lead to improved clinical outcomes in these patients.

Our study had some additional limitations. It was conducted at a tertiary centre and most of the patients had type 1 diabetes. Findings may therefore not be representative for diabetes patients in the general population. The sample size of the constipation group was also small, increasing the risk for type II errors. When performing multiple comparisons, as in our study, there is a risk of type I errors. To control for this, we used the Games-Howell and Bonferroni *post hoc* tests when calculating results from normally and non-normally distributed parameters, respectively. As comorbidities associated with constipation are frequent in diabetes patients, excluding these would potentially introduce a selection bias. Of ethical reasons, we also advised patients to continue their regular medications, except those discouraged by the wireless motility capsule protocol. Controlling for the effect of comorbidities and medications, we found no difference in constipation symptoms. Neither did we find any difference in thyroid function tests, faecal calprotectin and faecal elastase-1. Due to the simultaneous investigation with scintigraphy, diabetes patients received a meal with 90 kcal higher caloric content than healthy controls. Although we cannot exclude a minor influence on gastric emptying, we find it unlikely that colonic and whole-gut transit results are affected. The lack of a predefined cut-off value is a limitation of the GSRS questionnaire. To control for this, we performed correlation analyses, without finding any association between constipation symptoms and transit times. Healthy controls were recruited as part of a collaborating study and included a lower proportion of women compared to diabetes patients with constipation. Healthy controls also trended towards a lower mean age. This may have introduced a bias due to gender differences in transit times.[13] Finally, healthy controls did not answer the GSRS but were screened prior to inclusion using modified Rome III questionnaires and clinical interview.

## CONCLUSION

In conclusion, we found that colonic transit did not differ between diabetes patients with and without constipation. Compared to healthy controls, we found delayed whole-gut transit in both diabetes groups, regardless of constipation symptoms. We also found an association between constipation symptoms and decreased small bowel, but not colonic contractility. Overall, our results may imply that diabetes patients with constipation need a more comprehensive diagnostic investigation than transit time studies, and that other factors may be more important in generating constipation symptoms in these patients.

### ACKNOWLEDGEMENTS

The authors would like to thank the Department of Medicine for providing research facilities, and all hospital personnel assisting us during the study. We also thank all participating patients. Dag A. Sangnes has received a PhD Scholarship grant from the Western Norway Regional Health Authority. Katarina Lundervold and Mattis Bekkelund have received grants from the Norwegian Competence Centre for Functional Gastrointestinal Disorders. Katarina Lundervold received funding from the Norwegian Competence Centre for Ultrasound in Gastroenterology and the NeuroSysMed Centre, Haukeland University Hospital. Mattis Bekkelund received a grant from the Norwegian Research Council through the medical student research programme at University of Oslo. The study has otherwise been funded by Haukeland University Hospital.

### CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

### AUTHOR CONTRIBUTIONS

Dag A. Sangnes, Odd Helge Gilja, Georg Dimcevski and Eirik Søfteland designed the study. Dag A. Sangnes, Eirik Søfteland,

Katarina Lundervold, Mattis Bekkelund and Hilde L. von Volkmann performed and analysed the tests and contributed to data entry. Dag A. Sangnes and Katarina Lundervold performed the statistical analysis. Dag A. Sangnes, Katarina Lundervold and Birgitte Berentsen drafted the manuscript with contributions from Odd Helge Gilja, Georg Dimcevski, Eirik Søfteland, Mattis Bekkelund and Hilde L. von Volkmann. All authors approved the final version of the manuscript.

## ETHICS APPROVAL

The study was conducted in accordance with the Declaration of Helsinki. The investigation of diabetes patients was approved by The Western Norway Regional Medical Ethics Committee (2015/58), while the study of healthy participants was approved by The South-Eastern Norway Regional Medical Ethics Committee (2014/2222 and 2019/28472).

## INFORMED CONSENT

All participants submitted oral and written informed consent.

## DATA AVAILABILITY STATEMENT

The datasets generated and analysed during the current study are available from the corresponding author on a reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Sangnes DA, Lundervold K, Bekkelund M, von Volkmann HL, Berentsen B, Gilja OH, et al. Gastrointestinal transit and contractility in diabetic constipation: a wireless motility capsule study on diabetes patients and healthy controls. United European Gastroenterol J. 2021;1–10. https://doi.org/10.1002/ueg2.12169

# Gastrointestinal transit and contractility in diabetic constipation: a wireless motility capsule study on diabetes patients and healthy controls

## Electronic supplementary material

**Supplementary Table 1 |** Comorbid conditions associated with constipation and their relation to GSRS constipation scores

| Organ system, condition | *n* (%) | Constipation scores | | |
|---|---|---|---|---|
| | | Without condition | With condition | *p* value |
| Gastrointestinal | | | | |
| Coeliac disease | 6 (11 %) | 2.0 (2.7) | 2.8 (2.6) | 0.42 |
| Pancreatic disease | 7 (12 %) | 2.2 (2.7) | 2.3 (2.7) | 0.73 |
| Metabolic and endocrine | | | | |
| Obesity | 13 (23 %) | 2.3 (2.6) | 2.0 (2.5) | 0.92 |
| Thyroid disease | 15 (26 %) | 2.0 (2.4) | 3.3 (2.0) | 0.11 |
| Neurological and psychiatric | | | | |
| Anxiety | 6 (11%) | 2.0 (2.3) | 3.7 (1.7) | 0.01 |
| Depression | 8 (14%) | 2.5 (1.4) | 3.2 (1.8) | 0.48 |

GSRS scores are given as median (IQR). Frequencies are given as *n* (%). Abbreviations: GSRS = Gastrointestinal Symptom Rating Scale. IQR = Interquartile range. Cases with anxiety and depression were defined using the Hospital Anxiety and Depression Scale, as described in the Materials and Methods section.

**Supplementary Table 2 |** Medications associated with constipation and their relation to GSRS constipation scores

| Organ system; drug class | *n* (%) | Constipation scores | | |
|---|---|---|---|---|
| | | Not using medication | Using medication | *p* value |
| Cardiovascular | | | | |
| ACEI/ARB | 18 (32%) | 2.3 (2.7) | 2.0 (1.8) | 0.50 |
| Antiplatelet drugs | 13 (23%) | 2.2 (2.7) | 2.7 (2.0) | 0.65 |
| Beta-blockers | 10 (18%) | 2.0 (2.7) | 2.5 (2.6) | 0.99 |
| Calcium channel blockers | 8 (14%) | 2.3 (2.3) | 1.7 (1.2) | 0.09 |
| Lipid-lowering agents | 25 (44%) | 2.2 (2.6) | 2.3 (2.3) | 0.56 |
| Loop diuretics | 6 (11%) | 2.0 (2.3) | 3.8 (4.0) | 0.15 |
| Thiazides | 6 (11%) | 2.3 (2.7) | 2.0 (0.6) | 0.34 |
| Gastrointestinal | | | | |
| Proton pump inhibitors | 25 (44%) | 2.3 (2.9) | 2.0 (2.0) | 0.55 |
| Metabolic and endocrine | | | | |
| Metformin | 9 (16%) | 2.2 (2.7) | 2.3 (1.3) | 0.75 |
| Sex hormones | 9 (16%) | 2.3 (2.3) | 2.0 (2.8) | 0.74 |
| Thyroid hormones | 14 (25%) | 2.0 (2.3) | 3.2 (2.2) | 0.15 |
| Neurological and psychiatric | | | | |
| Anxiolytics | 7 (12%) | 2.2 (2.7) | 2.3 (1.7) | 0.90 |
| Antidepressants [a] | 13 (23%) | 2.3 (2.6) | 2.0 (1.3) | 0.27 |
| Antiepileptics | 7 (12%) | 2.3 (2.7) | 2.0 (2.7) | 0.80 |
| Hypnotics and sedatives | 11 (19%) | 2.3 (2.4) | 1.7 (1.7) | 0.15 |
| Other medications | | | | |
| Antihistamines | 14 (25%) | 2.0 (2.3) | 2.5 (2.4) | 0.38 |
| Antineoplastic drugs/immunomodulators | 10 (18%) | 2.0 (2.7) | 2.5 (3.1) | 0.45 |
| Opiates | 13 (23%) | 2.5 (2.3) | 1.7 (1.0) | 0.13 |
| Vitamins/minerals | 22 (39%) | 2.0 (2.0) | 2.5 (2.4) | 0.22 |

GSRS scores are given as median (IQR). Frequencies are given as *n* (%). Medications with frequencies ≤5 were excluded from statistical comparisons, including antiemetics (3; 5%), other antacids (4; 7%), NSAIDs (4; 7%) and anti-diabetic medications bar metformin. [a] All antidepressants were grouped together for statistical purposes, including SSRIs, SNRIs and TCAs. Abbreviations: GSRS = Gastrointestinal Symptom Rating Scale. ACEI = angiotensin-converting enzyme inhibitors. ARB = Angiotensin II receptor blockers. NSAID = Non-steroidal anti-inflammatory drugs. SSRI = Selective serotonin reuptake inhibitors. SNRI = Serotonin-norepinephrine reuptake inhibitor. TCA = Tricyclic antidepressants. IQR = Interquartile range.

Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS


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ISBN: 9788230852934 (print)
9788230860052 (PDF)