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Diagnosis & dietary intervention in patients with diabetic gastroparesis

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Gothenburg 2013

Abstract

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Background: Gastroparesis is a diabetic complication, which is often under-recognised. Existing treatment options are limited and diagnostic methods not easily accessible. **Aims of the thesis**: To compare two alternative diagnostic methods for gastroparesis in patients with insulin-treated diabetes (DM) and to compare gastrointestinal (GI) symptoms and metabolic control after intake of diet with a large (LP) and small particle size (SP) in patients with insulin-treated DM with gastroparesis.
Methods: In Paper I, gastric emptying of radiopaque markers (ROM) from the stomach using fluoroscopy was compared to gastric scintigraphy (current gold standard for diagnosing gastroparesis)) and the link to GI symptom severity was determined. In Paper II, the plasma glucose response after a test meal with a LP was compared to gastric scintigraphy in diabetic subjects with and without gastroparesis and the association with GI symptom severity was evaluated. In Papers III and IV, the effects of meals with a LP or SP were compared in randomised controlled trials (RCT). In Paper III, the effect of SP and LP diets on gastric emptying measured using scintigraphy and on the postprandial glucose response were studied in subjects with DM type 1 and gastroparesis and in healthy controls. In Paper IV, subjects with insulin-treated DM and gastroparesis were treated with a SP or LP diet for 20 weeks and the effects on GI symptoms and metabolic control were compared between the groups.
Results: *Paper I:* 115 patients with insulin-treated DM were included and 83 subjects had gastroparesis determined using scintigraphy. A moderately strong correlation was demonstrated between scintigraphic (% retained radioactivity at 120 min, T120) and ROM emptying (markers retained at 6 h) ($r = 0.47$; $p < 0.0001$).The sensitivity and specificity of the ROM test was 34% and 97% respectively. Only scintigraphic gastric emptying correlated significantly with GI symptom severity with the strongest associations for fullness/early satiety ($r = 0.34$; $p < 0.001$) and nausea/vomiting ($r = 0.30$; $p < 0.001$). *Paper II:* We included 83 patients with insulin-treated DM – 53 with gastroparesis and 30 with normal gastric emptying determined by gastric scintigraphy. The patients with gastroparesis had a blunted postprandial glucose response and demonstrated a lower maximum postprandial plasma glucose increase ($p < 0.05$) and a lower incremental area under the plasma glucose curve ($p < 0.05$). GI symptom severity had the best discriminative value to positively identify gastroparesis (sensitivity 87%, specificity 80%). By adding the plasma glucose response to GI symptom severity to identify patients with gastroparesis, the specificity increased (100%), but the sensitivity decreased (37%). *Paper III:* We studied seven patients with DM type 1 and gastroparesis and seven healthy controls. The lag phase in the stomach and the T120 was significantly shorter and the postprandial blood glucose dip in diabetic subjects was less and of shorter duration after a SP meal compared to a LP meal. Gastric emptying did not differ significantly between groups after a SP meal. *Paper IV:* We randomised 56 subjects with insulin-treated DM and gastroparesis to eating diet with a SP ('intervention diet'), compared to the recommended diet for DM ('control diet') for 20 weeks. A significantly greater reduction in the severity of the key gastroparetic symptoms – nausea/vomiting, postprandial fullness and bloating - were seen in patients on the intervention diet compared to the control diet.
Conclusions: The alternative diagnostic methods for gastroparesis tested in this thesis – gastric emptying of ROM, plasma glucose response after a standardized test meal and GI symptoms assessment – can add information in the clinical setting, but cannot replace the current gold standard, gastric scintigraphy. A meal with a small particle size increases the gastric emptying rate and reduces the postprandial blood glucose dip in DM Type 1 subjects with gastroparesis. Dietary treatment with a SP significantly improves the key symptoms of gastroparesis in patients with DM.

Key words: diabetic gastroparesis, gastrointestinal symptoms, scintigraphy, radiopaque markers, postprandial glucose, hypoglycaemia, gastric emptying, quality of life.
ISBN 978-91-628-8743-8

Till Björn, Cecilia och Per

Att våga är att förlora fotfästet en liten stund.

Att inte våga är att förlora sig själv.

(Sören Kirkegaard)

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ISBN: 978-91-628-8743-8

Published by:
Department of Internal Medicine and Clinical Nutrition
Institution of Medicine
Sahlgrenska Academy
University of Gothenburg
Gothenburg, Sweden

Printed by:
Ineko AB, Gothenburg

List of papers

1. Olausson EA, Brock C, Drewes AM, Grundin H, Isaksson M, Stotzer P, Abrahamsson H, Attvall S, Simrén M. Measurement of gastric emptying by radiopaque markers in patients with diabetes: correlation with scintigraphy and upper gastrointestinal symptoms. Neurogastroenterol Motil. 2013 Mar; 25(3):e224-32.

2. Olausson EA, Grundin H, Isaksson M, Brock C, Drewes AM, Attvall S, Simrén, M. Plasma glucose response after a test meal, and gastrointestinal symptom severity in patients with diabetic gastroparesis. Submitted.

3. Olausson EA, Alpsten M, Larsson A, Mattsson H, Andersson H, Attvall S. Small particle size of a solid meal increases gastric emptying and late postprandial glycaemic response in diabetic subjects with gastroparesis. Diabetes Res Clin Pract. 2008 May;80:231-7.

4. Olausson EA, Störsrud S, Attvall S, Simrén M. A small particle size diet reduces upper gastrointestinal symptoms in patients with diabetic gastroparesis: A randomized controlled trial. Submitted.

Contents

Abbreviations

BMI	Body Mass Index
DCCT	Diabetes Control and Complications Trial
DM	Diabetes Mellitus
GCSI	Gastroparesis Cardinal Symptom Index
GCSI-DD	Gastroparesis Cardinal Symptom Index Daily Diary
GERD	Gastroesophageal Reflux Disease
GFR	Glomular Filtration Rate
GI	Gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HbA1c	Glycosylated haemoglobin
IAUC	Incremental area under the curve
LADA	Latent Autoimmune Diabetes in the Adult
LP	Large Particle size
MODY	Maturity Onset Diabetes in Young diabetes
MMC	Migrating Motor Complex
PAGI-SYM	Patient Assessment of upper Gastrointestinal Symptom severity index
PN	Parenteral Nutrition
ROM	Radiopaque Markers
SF36	Short Form 36
PCS	Physical component score
MCS	Mental component score
SP	Small Particle size
^{99m}Tc	Technetium-99m
T_{50}	At the time, 50% of the isotope has passed through the stomach
T_{120}=R_{120}	The remaining isotope percentage in the stomach 120 minutes after ingested meal

Introduction

Over the past 25 years, my work has been focused on giving dietary advice to patients with diabetes mellitus (DM) at a specialized clinic at the Sahlgrenska University Hospital. The idea behind the research in this thesis stems from an incident some twenty years ago when I was privileged to participate in a one-day training programme for physicians on the subject of diabetic gastroparesis (i.e. delayed gastric emptying due to DM). One conclusion from the day was that the physicians had tried to help patients through dietary measures but always with the same disappointing results: “Dietary intervention for diabetic gastroparesis does not work”. This made me think: "Why does it not work – it must work." I had to try. I then recalled that, Inga Thorsdottir at the Department of Clinical Nutrition, a couple of years earlier had defended a thesis entitled: "Gastric emptying and postprandial glucose in healthy subjects and patients with diabetes mellitus type 2." In her thesis it was obvious that a diet with a small particle size (SP), such as mashed potatoes, passed through the stomach much more quickly than a diet with a large particle size (LP), such as pasta and rice, which ought to be valuable for patients with delayed gastric emptying. Based on this idea, I informed my patients with DM and gastroparesis- that the stomach needs to knead the diet into very small particles for it to pass through the pylorus as part of postprandial motility. I asked them to tell me what kind of food they thought suited them and told them about my dietary idea and asked them to try the SP diet in order to improve their symptoms.

I specifically remember one patient with DM and severe neuropathy. The patient had been in hospital for two months because of nausea, bloating, diarrhoea and faecal incontinence. Now, after a few weeks at home, she was back in the hospital. She was instructed to eat a SP diet and she did not need to be hospitalised again for gastrointestinal (GI) symptoms.

Another patient, who had a loss of appetite, nausea, abdominal fullness and bloating, as well as suicidal thoughts told me that it is acceptable to have poorer eyesight and to suffer from renal insufficiency but he could not handle being constantly nauseous. After eating diet with a SP, his appetite returned and he had no GI symptoms anymore. He looked forward to eating and no longer had suicidal thoughts.

I thereafter used these ideas about a SP diet to consecutive patients in my outpatient clinic and was heartened when I assessed the outcome in my first 65 patients who had clearly improved GI symptoms, fewer and milder episodes of postprandial hypoglycaemia and improved quality of life. I then realized that I had to perform proper studies to evaluate this diet in a scientifically sound way and the idea of starting a PhD project was born.

Historical background

The term 'gastroparesis' is a Greek word meaning 'a weakness of movement'. Gastroparesis is defined as delayed gastric emptying in the absence of an obstruction to outflow from the stomach and one of the most common causes is DM. The pathogenesis of this condition is still not understood very well although GI autonomic neuropathy is one plausible mechanism (1). Before the insulin era, diabetic gastroparesis was of little interest and the literature is devoid of any mention of that particular form of neuropathy. Gastric retention was first noted by Boas in 1925 (2). The radiological picture was described by Ferroir, who conducted the first thorough study of the stomach in diabetes subjects in Paris in 1937 (3). The focus was on hypochlorhydria, which was found in 60 per cent of 26 patients undergoing gastric analyses. Using the then relatively new barium meal study, he described the following abnormalities: "X-ray examination showed that in diabetics, the stomach is generally very chronic but the motor responses are weaker than normal. Contractions are slow, lack vigour and die out very quickly in 59% of the diabetics. Not infrequently, pyloric incompetence may be found with a hypotonic pyloric sphincter producing rapid evacuation in most cases." The first detailed description of gastric retention secondary to diabetic visceral neuropathy was by Rundles in 1945 (4). The term 'gastroparesis diabeticorum' was coined by Kassander in 1958, when he also indicated that this syndrome could be present in relatively asymptomatic diabetic subjects (5). To date, gastroparesis is still often under-recognised, inadequately investigated and poorly managed (6, 7), despite the fact that the condition has been known for more than fifty years.

Background

The incidence of DM is increasing worldwide. Population growth, ageing populations and urbanisation, with an associated lifestyle change, are likely to result in a 54% increase in worldwide numbers of people with DM between 2010 and 2030.

It is estimated that worldwide DM prevalence will be 6.4% and 7.7% for in 2010 and 2030 respectively (8). The total number among the adult population (aged 20-79 years) was about 285 million in 2010 and will be 439 million in 2030.

There is a difference between developed and developing countries. Between 2010 and 2030, there will be a 69% increase in the number of adults with DM in developing countries and a 20% increase in developed countries (8). The highest increase in prevalence will be in Africa with 98% in 2030 due to a growing population and increasing incidence.

After several years of DM, the patient could develop, micro- and macro-angiopathy complications. Retinopathy, nephropathy and neuropathy are micro-angiopathy complications and cardiovascular disease is a macro-angiopathy complication (9-13). These complications mean that the individual is suffering and is a financial burden on society as their care is expensive. The burden of DM complications is a growing problem.

Development of diabetes care

Knowledge of DM has increased and national and local diabetic care programmes have developed significantly over the past 20-30 years. Today, it is well known that good metabolic control, treatment of hypertension and hyperlipidaemia and absence of smoking are important in preventing complications (9, 10, 14-16).

Severe complications can be prevented by, for example, using fundus photography, where fundus changes can be detected at an early stage. Laser treatment can prevent blindness and foot care can prevent different foot problems and amputations.

The development of a method to examine metabolic control over the past 8-12 weeks, glycosylated haemoglobin (HbA1c), is a valuable tool for both patients and health care professionals (17, 18). Technical equipment that allows the patient to self-measure plasma glucose increases the options for achieving better metabolic control. Sophisticated technical equipment for continuous measuring of plasma glucose and insulin pumps with different technical solutions, e.g. different infusion rates at different times during the day, and delay of meal insulin doses, make it is easier to achieve good metabolic control. Other possible technical advantages with an insulin pump are that it can calculate the amount of insulin that is present in the body and how much insulin that is needed for a meal. All these developments increase the possibility of achieving good metabolic control, but despite this still many patients do not achieve good metabolic control and therefore develop complications.

Gastrointestinal autonomy neuropathy – delayed gastric emptying

Diabetic gastroparesis, i.e. delayed gastric emptying in the absence of an obstruction to outflow from the stomach, caused by gastrointestinal autonomic neuropathy (19) is another complication in DM (20, 21) and occurs in both DM type 1 (5, 22, 23) and DM type 2 (24, 25). The pathogenesis of this disabling condition is still not understood very well (21, 26). A common view is that it is only patients with long disease duration that may have diabetic gastroparesis and that gastroparesis occurs only after at least 10 years of DM (25, 27, 28). However, in individual cases, gastroparesis may occur after just a few years of diabetes (29). Usually, the patient not only has the micro-complications and GI autonomic neuropathy, but also other diabetic complications. Many patients with DM type 1 may have triopathy, i.e. neuropathy, retinopathy and nephropathy (28). Kockar et al. found a strong correlation between nephropathy, retinopathy and cardiac autonomic denervation and gastroparesis in subjects with DM type 1 and 2 (30). Hyett et al. demonstrated a correlation between gastroparesis and cardiovascular disease, hypertension and retinopathy (31). For the patient, each of these complications is a burden and together they lead to a considerable reduction in quality of life and a conspicuous increase in mortality (32). Gastroparesis is sometimes associated with GI symptoms

and/or poor metabolic control (25), dehydration, electrolytes disturbances and/or nutritional deficiencies (33).

Gastrointestinal symptoms

Some patients with delayed gastric emptying have GI symptoms (31, 34-37), while others are often asymptomatic, even with markedly delayed gastric emptying (5, 31, 38, 39). Conversely, Stanghellini et al. confirmed a high prevalence of delayed gastric emptying and gastroparesis in patients with upper GI symptoms (40). On the other hand, up to 50% of patients with markedly delayed gastric emptying had no GI symptoms whatsoever (39, 41). In addition, in a population-based study, DM was associated with increased prevalence of upper and lower GI symptoms. This was linked to poor glycaemic control (42) but not to duration of DM or type of treatment (43). GI symptoms that occur in patients with gastroparesis are upper GI symptoms such as loss of appetite, meal-related cough, early satiety, nausea, vomiting, abdominal fullness, bloating and regurgitation, but also lower GI symptoms such as constipation, diarrhoea with gas, particularly nocturnal, and faecal incontinence, which cannot be attributed to the delayed gastric emptying *per se*, but to a generalized visceral neuropathy (44). However, these GI symptoms are not specific for diabetic autonomic neuropathy, but also occur in other conditions, such as irritable bowel syndrome, functional dyspepsia and a multitude of organic GI diseases.

GI symptoms that correlate with gastroparesis are early satiety (25, 36), upper abdominal bloating/fullness (25, 34, 37), nausea/vomiting (25) and abdominal pain (45).However, it should be noted that the severity of GI symptoms does not always correlate with the rate of gastric emptying (34, 38).

Clinical manifestations are often underestimated and autonomic neuropathy should therefore be suspected in all diabetic patients with unexplained GI symptoms (7). Lack of GI symptoms does not exclude severe gastric emptying abnormalities (39). The lack of correlation between impaired gastric motility in the fasting state and dyspeptic symptoms shows that, on the basis of the clinical symptom analysis, the prevalence of such motor disorders could be underestimated (46). The early recognition of GI motility

alterations in autonomy neuropathy may be important for the better long-term management of patients with DM (46, 47).

Metabolic control

Both symptomatic and asymptomatic diabetic gastroparesis seem to be associated with poor glycaemic control by causing a mismatch between the onset of action of the exogenous insulin or oral hypoglycaemic drug, gastric emptying and the absorption of nutrients from the small intestine (48). Decreased postprandial glycaemia and late increased glycaemia, resulted in higher glucose fluctuations in subjects with abnormal gastric emptying than in those with normal gastric emptying (49). Clinical incidence of severe, emergency hypoglycaemic events occur sometimes in diabetic gastroparesis (50). Hypoglycaemic activation of counter-regulation (Somogyi phenomenon) in all subjects with insulin-treated DM is best defined as hyperglycaemia following hypoglycaemia and is caused by insulin resistance induced by hypoglycaemic activation of counter-regulation (51). This counter-regulation sometimes occurs for several hours, resulting in higher HbA1c (22, 39).

In addition, acute changes in blood glucose concentration affect gastric motor function; gastric emptying is slowed down during hyperglycaemia (52, 53) and is accelerated during hypoglycaemia (54). Hyperglycaemia should be taken into account in the treatment of the patient, as gastric emptying is slower than necessary. At a glucose level of 8 mmol/L, gastric emptying is already slower than at 4 mmol/L (53). It is therefore logical that DM patients have more severe postprandial fullness during hyperglycaemia than during euglycaemia (55).

Nutritional status

In patients with gastroparesis, the presence of GI symptoms is associated with eating problems, potentially resulting in food aversion. Patients with gastroparesis are thus at risk of weight loss and malnutrition.

In 2011, Parkman et al. published the first large study aimed at determining nutritional deficiencies in diabetic and idiopathic gastroparesis. In total, 194 patients (64%) reported caloric-deficient diets, defined as <60% of estimated daily total energy requirements. More severe symptoms (bloating and constipation) were characteristic of patients who reported an energy-deficient diet, and 82% of the subjects had protein intake <0.6 g/kg body weight. Some patients have protracted nausea, vomiting and diarrhoea, making it difficult to maintain hydration and electrolyte balance. Deficiencies in the intake of vitamins and minerals from diet ranged from 30% to 86% of patients (56). However, nutritional consultation took place infrequently (56).

The current dietary therapy for patients with diabetic gastroparesis is based on a few studies that changed one parameter at a time in normal volunteers and measured the effects on gastric emptying. Although the results from some of these interventions have reached statistical significance, they have not been shown to be *clinically* significant (57). Theoretically, a host of factors can slow gastric emptying but no clinical trials have been conducted in patients with gastroparesis to determine the success of any dietary interventions (57).

No randomised dietary study has been performed in patients with gastroparesis (58). For patients who fail to stabilise their weight loss or who cannot gain weight with oral feeding, enteral nutrition support may be indicated. Enteral nutrition not only allows the patient to stay hydrated and nourished but also provides ready access for consistent medication delivery (57). Occasionally, a jejunostomy may be helpful to maintain nutrition (59). Parenteral nutrition (PN) is associated with more infectious complications and is significantly more expensive (59). However, many patients with gastroparesis are drug refractory and invariably do not do well with enteral or parenteral access. Historically, these patients have been without effective therapeutic options. The development of gastric electrical stimulation has allowed patients with severe drug-refractory gastroparesis to be treated successfully and it may also improve survival rates (60). To summarize, nutritional but also psychological support is important for these patients, but unfortunately often neglected (61).

Physical and psychological well-being

Several studies have addressed the prevalence of GI symptoms in DM and their importance for physical and psychological well-being. GI symptoms in unselected DM subjects impact negatively on health-related quality of life in DM and this is similar in community and outpatient DM subjects. Increased levels of state anxiety, depression and neuroticism are associated with upper and lower GI symptoms in DM (62).

Parkman et al. arrived at the conclusion that quality of life in gastroparesis subjects, as assessed by SF 36, was below that of the US population. Gastroparetic subjects with DM type 1 had the lowest mental health summary score and in diabetes type 2 the lowest physical health summary scores were seen (63). Also the fact that GI symptoms in subjects with gastroparesis decrease quality of life has been confirmed in several studies (64, 65). Not surprisingly, nausea, vomiting (66) and bloating symptoms correlate with poorer quality of life in patients with DM and gastroparesis (67).

Also depressive symptoms have been demonstrated in diabetic gastroparesis, and by using the Beck Depression Index, 25% of the patients in the diabetic gastroparesis type 1 group were found to have severe depression and 17% of the patients in the diabetic gastroparesis type 2 group. Moreover, with the State-Trait Anxiety Inventory questionnaire, state and trait anxiety scores were found to be severe in a large proportion of these patients – around 45% and 30% in types 1 and 2 respectively (63).

To summarize, gastroparesis can be extremely troublesome, causing poor metabolic control and GI symptoms and result in poor quality of life (33, 68).

Care-intensive patients

Around 20% of hospitalised DM type 2 patients had delayed gastric emptying (36). A study in the USA found that gastroparesis-related hospitalisations from 1995-2004 had risen. Admission with gastroparesis as the primary diagnosis increased by 158% and 138% in those with the condition as a secondary diagnosis (69). The potential explanations for this

rise include the wider recognition of the disease, higher prevalence of DM and longer survival of DM patients (70).

Jung et al. (28) provided conclusive evidence that gastroparesis was associated with higher mortality but also with morbidity (31), increased hospitalisation and emergency department and doctor visits by DM types 1 and 2 patients with classic symptoms of gastroparesis. Patients with a documented delay in gastric emptying were more likely to have cardiovascular disease, hypertension and retinopathy, suggesting that the underlying complication might be related to micro-angiopathies or macro-angiopathies, which are known complications of poor metabolic control (28).

In a recent study, the healthcare consumption and the GI symptom severity in a small group of patients with gastroparesis and GI symptoms was determined, and it was confirmed that these patients form a high-risk group in terms of cost, quality of life, morbidity and mortality (71).

Normal gastric emptying

The stomach is composed of several regions with different yet complementary actions. The fundus is a storage area for food and the antrum and pylorus ensure grinding and move the stomach contents from the fundus to the antrum. The stomach is an innervated muscle and the motor function is co-ordinated with that of the pylorus to ensure fragmentation of the food bolus and ensure digestion regularity (50). Peristaltic activity is dependent on the pacemaker in the stomach, located on the greater curvature (Interstitial cells of Cajal). Peristaltic activity propagates down to the antrum and pylorus at a frequency controlled by a natural rhythm related to the gastric slow waves, and occurs at a maximum frequency of about three cycles per minute (50). The slow waves arrive continuously while the peristaltic contractions occur only after food intake. Solid nutrients usually empty in two phases over 3-4 hours. An initial lag phase (i.e. the retention phase) is followed by a propellant phase of relatively constant emptying. During the first phase, diet is churned while antral contractions propel particles towards the closed pylorus. Diet is emptied once it has been broken down into particles approximately 2 mm in diameter (72). Liquid diet is usually emptied faster, especially with large

volumes. If there is an increased number of calories in the liquid, emptying is relatively constant over time (72).

In the fasting state, gastric motility undergoes a cyclical pattern, termed the 'migrating motor complex' (MMC). This consists of phase I (motor quiescence, ~40 min), phase II (irregular contractions, ~50 min) and phase III (regular contractions of three per minute for ~5–10 min). Large, indigestible solid particles are usually emptied from the stomach into the small intestine during phase III (73).

Pathophysiology of diabetic gastroparesis

Gastroduodenal motor abnormalities in DM patients with delayed gastric emptying include parasympathetic nerve damage. However, changes in the secretion of hormones, such as motilin and ghrelin, are also involved in the pathophysiological process. These abnormalities lead to excessive relaxation in the corpus, less frequent antral contractions, antroduodenal incoordination (74, 75) and pyloric spasm (75). It should be noted that the latter rarely occurs in isolation and is typically associated with antral hypomotility (75). Abnormalities in small bowel motility might result in delayed gastric emptying of solids. Gastric motor dysfunction might be associated with small bowel dysmotility caused by a common mechanism (74). In addition, disturbances of proximal gastric compliance, either increased (76) or decreased (77), have been reported and could also contribute to symptoms.

In a fasting condition, the chronic influence of diabetic neuropathy on the stomach is decreased amplitude of the pressure waves in the antrum during MMC phase III, significantly fewer contractions and in half of the diabetic gastroparesis subjects a total loss of MMC phase III in the stomach (78).

Diagnosis

Gastroparesis is most often idiopathic, diabetic or postsurgical in nature, with other causes representing a minority of cases (79). Diabetic gastroparesis is found in about one-third of all gastroparesis patients (80).

Kassander coined the term 'gastroparesis diabeticorum' in asymptomatic patients with DM type 1 (5). However, other definitions were formulated later. Gastroparesis, literally defined as 'weakness' of the stomach, is characterised by an abnormal delay in gastric emptying in the absence of mechanical obstruction (81). There is a lack of a standard definition for gastroparesis, although it is frequently defined as a rate of emptying that is at least two standard deviations above the normal mean, usually determined using a scintigraphic technique (82). It has been suggested that a distinction should be made between gastroparesis and delayed gastric emptying. It has been suggested that gastroparesis, or gastropathy, be defined based on the presence of upper GI symptoms alone when other causes, including gastric outlet obstruction, have been excluded (83, 84). However, there is a lack of consensus as to its appropriateness. While many patients with gastroparesis have upper GI symptoms, there is a relatively poor relationship between symptoms and the rate of gastric emptying (82, 85). Gastroparesis can also have other important clinical manifestations, such as impaired glycaemic control in insulin-treated DM patients (85). It should be recognised that in many cases the delay in gastric emptying of solids or liquids is relatively modest and it can be argued that a distinction should be made between gastroparesis and delayed gastric emptying, i.e. that a diagnosis of gastroparesis should be restricted to those patients in whom emptying is grossly delayed (83).

Incidence

Few studies have addressed the incidence of gastroparesis. The cumulative proportions of patients who developed gastroparesis over a 10-year period were 5.2% for type 1 DM, 1.0% for type 2 DM, and 0.2% for non-diabetic controls (70). The age-adjusted incidence of definite gastroparesis per 100,000 person years for the period 1996-2006 was 2.4 (95% confidence interval, CI, 1.2-3.8) for men and 9.8 (95% CI, 7.5–12.1) for women (28). When comparing DM type 1 and type 2, patients with DM type 2 are 13 years older at onset of symptoms associated with gastroparesis than patients with DM type 1 (63).

Prevalence

The prevalence of gastroparesis in the community is difficult to estimate due to the relatively poor correlation of symptoms with gastric emptying rate and the need to apply a diagnostic test in a community setting. It is unclear whether the majority of patients with gastroparesis seek healthcare or how often they are referred to gastroenterologists. The true prevalence of gastroparesis is therefore unknown. In the DM population, the prevalence of gastroparesis is also difficult to estimate due to the apparently higher prevalence of the disorder in university centres than in smaller hospitals, in a primary care setting and in the community. A widely available diagnostic test that could be applied in a standard fashion is currently lacking in the primary care setting (86, 87).

Gastric scintigraphy is considered the gold standard worldwide. This method is expensive and requires specialised staff. One problem is that scintigraphy is not always performed according to the same standards. In gastric scintigraphy, measurement takes place either during two- or four hours and different test meals are used, hence consensus recommendations are not always followed (86, 88). In most centres different reference values are used for men and women (86), as women have slower gastric emptying than men. However, there are also differences between pre- and post-menopausal women depending on hormones (89). Moreover, in diabetic gastroparesis it is important to assess gastric emptying in a euglycaemic condition as hyperglycaemia delays gastric emptying (52, 53, 90). The study design is also important. Are the samples selected or unselected and which inclusion criteria are applied?

Most population-based DM studies in subsets of patients at risk of developing gastroparesis have focused on symptoms rather than gastric scintigraphy findings (81). In such investigations, 10–18% of individuals with DM report symptoms consistent with upper GI dysmotility, such as nausea and vomiting (43, 91, 92). Jung et al. made an attempt to study the prevalence of all kinds of gastroparesis in the general population. After studying the complete medical records in Olmsted County, Minnesota from 1996 to 2006, there were 3,604 potential cases of gastroparesis. After exclusion criteria were applied, 432 subjects remained. The inclusion criteria were: Definite, probable and possible gastroparesis and gastric emptying investigated using scintigraphy. The age-adjusted (compared to

the white population in the US in 2000) prevalence of definite gastroparesis per 100,000 persons was 24.2 (95% confidence interval [CI], 15.7– 32.6) for both genders, 9.6 (95% CI, 1.8 –17.4) for men and 37.8 (95% CI, 23.3–52.4) for women (28).

In another study, the prevalence of gastroparesis was 36% in symptomatic subjects with DM type 1 and 2 (93). Other studies have also confirmed that the prevalence in females is higher than in males (36, 70).

A study in the DM population assessed gastric emptying of a solid meal with scintigraphy under euglycaemic conditions (23), confirming the prevalence of gastroparesis in unselected patients with DM type 1 at 34%. In another study, the prevalence was 28% in DM type 1 (35). In two studies investigating selected groups of patients with long-standing type 1 DM, the prevalence was 40-44% (22, 48).

The prevalence of gastroparesis in subjects with DM type 2 is in the range 30-58% (94-96). However, these studies are limited by the small sample sizes, the presence of hyperglycaemia during testing and the variety of test meals and diagnostic methods used. In the study performed by Annese et al., 34% of patients had peripheral and autonomic neuropathy and 36% of the patients showed abnormal esophageal and gastric motor function (96).

Diagnostic methods

There are various means of assessing gastric emptying (97). The current gold standard is gastric scintigraphy, but other techniques have been evaluated and/or are under evaluation. Some of these will be reviewed below.

Scintigraphy. Using scintigraphy, the emptying time and intragastric distribution of solid and/or liquid meal components can be evaluated. Scintigraphy, which is non-invasive and reproducible, remains the most sensitive and accurate method and is considered to be the 'gold standard' technique. It measures the intragastric distribution and emptying of a solid or liquid meal labelled with Technetium- 99m, ^{99m}Tc. The isotope binds to meal protein and a gamma camera registers the ^{99m}Tc passage through the stomach. Gastric emptying is monitored for 3-4 hours after meal

consumption. The gastric emptying is evaluated as follows: Lag phase = the time from finished meal before the gastric emptying begins, T_{50} = at that time, 50% of the isotope has passed through the stomach and R_{120} or T_{120} = the remaining isotope percentage in the stomach 120 minutes after the ingested meal. This method is expensive and requires specialised staff (86), and is not easy accessible for many clinicians. Moreover, radiation exposure is another drawback with this technique. Alternative methods are therefore needed.

Breath tests. These tests assess gastric emptying using meals labelled with stable isotopes, such as ^{13}C-acetate or ^{13}C-octanoate and, in contrast to scintigraphy, does not involve exposure to ionising radiation. It has good reproducibility and the results have been reported to correlate well with scintigraphy, with a sensitivity and specificity of 86-89% and 80% respectively for the presence of delayed gastric emptying, including a DM population (98, 99). Furthermore, they are easy to administer and are inexpensive (100, 101). After ingestion, the labelled meal passes through the stomach to the small intestine, where the ^{13}C-acetate or ^{13}C-octanoate is absorbed, metabolised into $^{13}CO_2$ in the liver and exhaled via the breath. $^{13}CO_2$ in breath samples is analysed by means of mass spectrometry (45, 101). Although this technique has advantages over scintigraphy, information relating to the validity of breath tests in patients with markedly delayed gastric emptying is limited.

Ultrasonography. Two-dimensional ultrasonography is a convenient, valid, non-invasive method of measuring the emptying of liquids or semi-solids as well as antral contractions and transpyloric flow (102, 103). The more recently applied three-dimensional ultrasonography can provide comprehensive imaging of the stomach, including information about intragastric meal distribution, and has been validated against scintigraphy to measure gastric emptying in both healthy subjects and in patients with diabetic gastroparesis (104). Although ultrasonography is readily available and does not involve exposure to radiation, obesity, abdominal gas and the need for an experienced operator limit its widespread use.

SmartPill®. Swallowed capsule telemetry (SmartPill®) uses an ingestible capsule that measures intraluminal pH to determine the gastric emptying rate. Moreover, the capsule can also record pressure during the passage through the GI tract as a measure of contractions, as well as temperature.

This method has been reported to correlate well with scintigraphy with good sensitivity (82%) and specificity (83%) to diagnose delayed gastric emptying(61) but has only recently been approved for use in Europe. Emptying of the capsule presumably occurs after that of digestible meal components, and this technique has been criticised for measuring re-appearance of gastric fasting motility (MMC, phase III) rather than emptying of a meal.

The paracetamol (acetaminophen) absorption test. Another principle used to measure gastric emptying is the absorption of paracetamol assessed with serial blood samples after intake of paracetamol. The paracetamol (acetaminophen) absorption test is a simple bedside test, but its usefulness is limited to evaluation of the emptying of liquids and is generally not recommended as a diagnostic tool as its accuracy is moderate at best (105).

Radiopaque markers*.* Emptying of radiopaque markers (ROM) (indigestible solids) from the stomach using fluoroscopy is an easy and inexpensive method and is available at all hospitals. There is a significant correlation between gastric emptying of ROM with gastric scintigraphy in healthy subjects and in a small group of subjects with insulin-dependent DM (106). However, the correlation between gastric emptying of ROM and gastric scintigraphic emptying in larger groups of patients with gastroparesis has not been studied.

Magnetic resonance imaging. Magnetic resonance imaging has also been used to measure gastric emptying and wall motions of the stomach. Abdominal scans are generally obtained in the supine position every 15 min before and after a predominantly liquid meal. This method is still not widely spread and is under development. An advantage with this method is that it does not expose the subject to radiation, but it is limited by the use of specialized equipment, by being expensive and by using the supine position.

Limitations with existing diagnostic methods

Several of the existing diagnostic methods have limitations, such as radiation exposure, expenses etc., which has been described above. One

of the major limitations is availability, and there is a limited number of methods for investigating gastroparesis at small hospitals, which may be one reason why this condition has been investigated inadequately. In order to improve the diagnostic management of gastroparesis access to different diagnostic methods should be available in all hospitals. Fluoroscopy is available at all hospitals, and therefore we aimed to study the correlation between gastric scintigraphy and the ROM method in patients with gastroparesis, to evaluate if this widely available method could be used more in the diagnostic approach in patients with suspected delayed gastric emptying. Moreover, as patients with DM and delayed gastric emptying have an altered glucose response after meal intake (39, 107, 108) and some of them also report upper GI symptoms (25, 34, 36), we also hypothesized that measuring blood glucose after meal intake and to assess the symptom profile could be helpful in finding DM patients with suspected gastroparesis. Our research question was therefore if GI symptoms in recent weeks and/or glucose response after a test meal could be a screening method to strengthen the suspicion of gastroparesis?

Treatment options for patients with diabetic gastroparesis

The treatment for patients with diabetic gastroparesis is aimed at reducing GI symptoms, optimising glucose control and correcting fluid, electrolyte and nutritional deficiencies (109). The principles in the management of patients with diabetic gastroparesis is based on dietary/nutritional adjustments, optimisation of the glycaemic control, pharmacologic therapy with prokinetics or antiemetics, avoidance of opioids, and in very select cases specialized therapies such as surgery, botox injections or gastric electrical stimulation (110).

Dietary/nutritional treatment. To date, the recommendation for management of gastroparesis using dietary/nutritional measures is as follows:

1. The first line of management for gastroparesis patients should include restoration of fluids and electrolytes, nutritional support and, in DM patients, optimisation of glycaemic control. (Strong recommendation, moderate level of evidence.)

2. Oral intake is preferable for nutrition and hydration. Patients should receive counselling from a dietician regarding the consumption of frequent, small-volume nutrient meals that are low in fat and soluble fibre. If they are unable to tolerate solid food, then the use of homogenised or liquid nutrient meals is recommended. (Conditional recommendation, low level of evidence.)
3. Oral intake is the preferred route for nutrition and hydration. If oral intake is insufficient, then enteral alimentation by jejunostomy tube feeding should be pursued (after testing nasoenteric tube feeding). Indications for enteral nutrition include unintentional loss of 10% or more of the usual body weight during a period of 3-6 months and/or repeated hospitalisation for refractory symptoms. (Strong recommendation, moderate level of evidence.)
4. For enteral alimentation, postpyloric feeding is preferable to gastric feeding, as gastric delivery can be associated with erratic nutritional support. (Conditional recommendation, low level of evidence.)
5. Enteral feeding is preferable to parenteral nutrition. (Conditional recommendation, low level of evidence.) (109).
However, so far there is no randomised, controlled diet trial for gastroparesis. Dietary advice comprises suggestions that stem from the results of studies performed in subjects with normal gastric emptying. The major features in the dietary recommendations are to decrease fat (111-113) and fibre (114), as these slow gastric emptying. However, most studies added soluble fibre to liquid meals, which may have more impact of gastric emptying than soluble fibre added to a solid meal. In healthy subjects, a fat liquid test meal increased the lag period and decreased the slope of the emptying curve. During the lag period, there was initial filling of the distal stomach, followed by redistribution of the distal stomach contents back into the proximal stomach. At the onset of total gastric emptying, the proximal stomach also emptied (111). This redistribution must be taken account in patients with delayed gastric emptying.

In order to prevent formation of bezoars in the stomach of patients with delayed gastric emptying, advise to avoid foods that may lead to phytobezoar formation, such as oranges, persimmons, coconuts, berries, green beans, figs, apples, sauerkraut and Brussels sprouts, should be given (115). Moreover, small, frequent meals are suggested as large meals slow down gastric emptying in healthy subjects (116), and the lag phase

was prolonged in both solid and liquid large meals compared with smaller meals (117).

Pharmacologic therapy*.* The aim of the therapy is to improve the efficiency of the gastric pump and to relieve GI symptoms. Two classes are available to treat affected patients – prokinetic and antiemetic drugs. Of these, only prokinetics have been specifically studied in gastroparesis, whereas antiemetics, such as phenotiazines, antihistamine agents and serotonin 5HT3 receptor antagonists are used empirically based on their effect on nausea and vomiting. Only prokinetics will be described in some detail here**.** Prokinetics are the most commonly used medications for gastroparesis. These stimulate peristalsis and could specifically improve gastric pump function by influencing antral contractility and rhythm as well as antroduodenal co-ordination. Established prokinetic agents, including metoclopramide, domperidone and erythromycin, form the mainstay of the treatment. Metoclopramide has both prokinetic and antiemetic properties.

The long-term efficacy of metoclopramide, a dopamine D2 receptor antagonist, has not been established clearly and the prokinetic effects may potentially diminish over time (118). Metoclopramide is available in several formulations. It can be given orally, intravenously and subcutaneously. The use of metoclopramide is marked by a high prevalence of adverse effects on the central nervous system. Mild central neurological effects, including restlessness, agitation, dizziness and drowsiness, occur in up to 40% of patients, while dystonic reactions occur in approximately 1% (118). During more prolonged use, tardive dyskinesia may develop, which is potentially irreversible and may occur in 1-10% of patients who have been taking the drug for more than three months (119). These side effects greatly diminishes the clinical usefulness of metoclopramide.

Domperidone, another dopamine antagonist, appears to be effective in the management of symptomatic gastroparesis, including that associated with DM (120), with fewer side effects than metoclopramide (121). It is relatively impermeable to the blood-brain barrier and therefore causes fewer adverse central neurological effects (122). Acute administration of domperidone has been reported to accelerate gastric emptying of solids and liquids in both healthy subjects and in DM patients with autonomic neuropathy. The greatest effect is observed in patients with a marked delay in gastric

emptying (123). Domperidone has also been shown to improve quality of life in patients with DM through its alleviation of GI symptoms (120).

Erythromycin is a macrolide antibiotic that also has the ability to act as a motilin agonist through its interaction with motilin receptors. Erythromycin accelerates gastric emptying by increasing the frequency and amplitude of antral and duodenal contractions in the proximal stomach (85). The effect of erythromycin on GI symptoms is controversial, although there is evidence to suggest that it improves bloating in patients with functional dyspepsia and gastroparesis (82). However, long-term use of erythromycin for gastroparesis is less well substantiated and tachyphylaxis is thought to develop due to down-regulation of motilin receptors with chronic use. Furthermore, there is the potential risk of bacterial resistance (124). The major adverse effects of erythromycin are well recognised and include abdominal pain and cramping, nausea, diarrhoea, vomiting and skin rash. Erythromycin may also cause adverse cardiac effects (124).

Surgery and gastric electric stimulation

Some subjects with gastroparesis remain unsatisfactory despite dietary/nutritional adjustments, optimisation of the glycaemic control, and the use of prokinetic and/or antiemetic drugs. In these cases, gastric electrical stimulation is an option. Also surgical procedures, such as venting gastrostomy, gastrectomy or pyloroplasty, may be used in very select cases (110). Gastric electrical stimulation delivers high frequency, low energy electrical stimulation to the stomach and through an unknown mechanism many patients with diabetic gastroparesis demonstrate a substantial reduction of the key gastroparetic symptoms, especially nausea and vomiting (21). In the first multi-centre trial, thirty-eight highly symptomatic patients with drug-refractory gastroparesis with differing aetiology, including diabetic gastroparesis, received gastric electrical stimulation. In 97% of these patients more than 80% reduction in vomiting and nausea (including diabetic gastroparesis) was reported. (125). Several studies have followed and confirmed these initial positive results, especially in diabetic gastroparesis (21). However, access to a gastric pacing is limited to a few hospitals and few patients are in a position to benefit from this method. The cost is also rather high, limiting a widespread use of this treatment option.

General and specific aims of this thesis

Based on gaps in the existing literature and building on previous clinical and scientific experience with these patients our aims with the studies included in this thesis were:

1. To compare two alternative diagnostic methods for gastroparesis using gastric scintigraphy, the current golden standard, in patients with insulin-treated DM.
2. To compare GI symptoms and metabolic control after intake of diet with a LP and SP in patients with insulin-treated DM with gastroparesis.

Paper I

To evaluate the correlation between emptying of ROM from the stomach using fluoroscopy and gastric scintigraphy in a large group of patients with insulin-treated DM in order to define a potential role for ROM emptying in the management of patients with DM and clinical suspicion of delayed gastric emptying. We also wanted to assess the link between different GI symptoms, ROM emptying and scintigraphic gastric emptying of solids.

Paper II

To characterise thoroughly the postprandial glucose response after a test meal with LP in patients with DM and clinical suspicion of gastroparesis and to assess whether this, together with a questionnaire-based assessment of the severity of GI symptoms during the preceding two weeks, could help to predict delayed gastric emptying determined with gastric scintigraphy.

Paper III

To evaluate the effect of meal particle size on gastric emptying and postprandial blood glucose variations after a meal. To achieve this, we measured the gastric emptying time and postprandial blood glucose response in patients with DM Type 1 and gastroparesis and in healthy controls by comparing meal with a LP with the same meal with a SP.

Paper IV

To compare the effects of a dietary intervention that recommends diet with SP with the standard dietary recommendations given to patients with DM, in insulin-treated DM subjects with gastroparesis. Our primary aim was to improve GI symptoms associated with gastroparesis and the secondary aims were to assess the effects on body weight, nutritional intake, metabolic control, mental health and quality of life.

Methodological considerations

Subjects

The thesis summarises four studies incorporating insulin-treated DM subjects with and without gastroparesis and healthy control subjects; Papers I and II deal with validation of diagnostic and screening methods for gastroparesis. Papers III and IV deal with randomised trials studying the relationship between LP and SP in the diet and gastric emptying, postprandial plasma glucose and GI symptoms in subjects with insulin treated DM and gastroparesis.

The subjects included in Papers I, II and IV in this thesis were insulin treated DM patients recruited from DM outpatient clinics in eleven hospitals and four primary care teams in Region Västra Götaland of Sweden. The teams were informed about the study through personal visits to the clinics by EO and through e-mails. During the visits, the teams were informed about signs and symptoms associated with gastroparesis in order to find patients who had still not received a diagnosis. The recruitment process began in August 2007 and was completed in November 2011.

Paper I. 115 subjects with insulin treated DM and with a wide range of GI symptom severe were included.

Paper II. Insulin-treated DM patients with and without suspected gastroparesis were included.

Paper IV. Insulin treated DM patients with suspected gastroparesis were included. Only 14 DM subjects had normal gastric emptying and 2 subjects with gastroparesis were unwilling to participate in the study. Figure 1.

Paper III. These patients with gastroparesis were recuited from the Diabetes outpatient clinics, Sahlgrenska University Hospital and Kungälv Hospital in September 1996 and March 1998. The gender, age and body mass index matched healthy controls were recruited via an newspaper advertisement.

Exclusion criteria for all the studies were as follows: previous gastrointestinal surgery except appendectomy, severe psychiatric disease,

sequelae after cerebrovascular disease, untreated disease with a potential impact on gastric emptying, or GI symptoms.

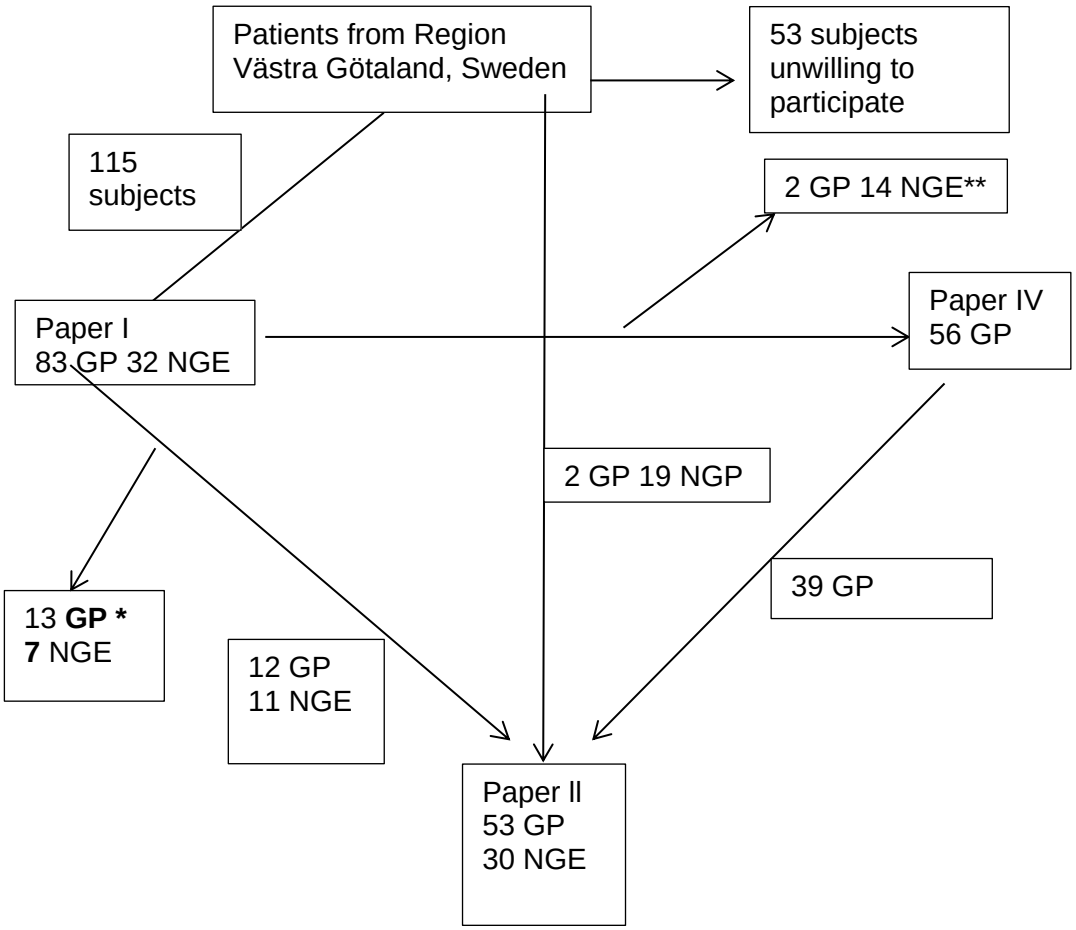


Figure 1. Study subjects in Papers I, II and IV.
GP = Subjects with gastroparesis. NGE = Subjects with normal gastric emptying.
*The subjects excluded after Paper I and could not participate in Paper II due to high plasma glucose at the start of the test.
** Subjects excluded before Paper IV: subjects with normal gastric emptying were not asked to participate in Study II. The two subjects with gastroparesis did not want to participate in Paper IV.

Approval by the Radiation Safety Committee and Ethical Review Board

The studies were approved by the Radiation Safety Committee at Sahlgrenska University Hospital, Sahlgrenska Academy, University of Gothenburg, and the Regional Ethical Review Board in Gothenburg, Sweden. Each participant received verbal and written information about the study and gave their written, informed consent before any study related procedure was performed.

Study design

Papers I and II. Before the test, the patients had completed the 'Patient Assessment of Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM)' and Gastroparesis Cardinal Symptom Index (GCSI). The subjects arrived at the hospital at 8 am in a fasting condition (10 hours). Alcoholic beverages were not permitted 24 hours before the test and drugs with an effect on GI motility were not permitted for 48 hours before the test. Smoking was not permitted during the test. The plasma glucose had to be ≤ 10.0 mmol/L at the beginning of the meal and the subjects had taken their ordinary dose of insulin for breakfast, adjusted to the carbohydrate content of the test meal (units insulin/g carbohydrates). Plasma glucose samples were taken before the meal and throughout the whole study period.

Paper I. On the same day, we measured solid gastric emptying using scintigraphy of a ^{99m}Tc labelled standard meal for three hours and followed emptying by fluoroscopy of ROM (non-digestible solids; 20 spherical radiopaque markers) added to the meal 4-6 h after meal intake. The fluoroscopy measurement of ROM was followed each hour for three hours or until all the ROM were emptied. The number of ROM in the stomach was counted each hour after meal intake. We focused on the time period 4–6 h after meal intake to test for delayed gastric emptying of ROM since indigestible solids or ROM are emptied with a time delay of 1.5–2 h relative to digestible solids (106).

Paper II. Before the study, gastric emptying was confirmed using a scintigraphic method. The ingestion time of the test meal of food in LP was

25 minutes. Plasma glucose was followed for three hours from the beginning of the meal.

Paper III. The subjects arrived at the hospital at 11.15 am after ingesting a standard breakfast at 07.30 am and a snack at 9 am. The study started at noon. Insulin-dependent DM patients with suspected gastroparesis took their ordinary dose of regular human insulin for lunch (units insulin/g carbohydrates) 30 minutes before the meal. Plasma glucose before the meal was ≤ 10.0 mmol/L. In random order, the subjects ingested solid meals with a LP and SP. Ingestion time was up to 25 minutes. Gastric emptying was followed by scintigraphy for three hours from the beginning of the meal. Plasma glucose and insulin were followed throughout the study period.

Paper IV*.* Insulin-treated DM subjects with confirmed gastroparesis were randomised to receive dietary advice, which differed regarding the particle size of the food (for more detailed information, see appendices). Otherwise the nutritional composition in the two dietary treatment groups was the same and in line with the recommendation for diabetic patients (126), with the exception of the recommendation that the fat content was reduced to 25-30% of total energy and the fibre content to 15 gram/1000 kcal according to Paper III, and in order to remain in line with the current recommendations for patients with gastroparesis (109). The study period was 20 weeks.

The subjects were also randomised to one of two dieticians, who provided the dietary advice, and they received dietary counselling on seven occasions. Both groups were advised to have the same meal schedule: breakfast, snack, lunch, snack, dinner and evening snack.

GI symptoms, quality of life, anxiety and depression were assessed at baseline and on completion of the study. The subjects completed the questionnaires: PAGI-SYM (127, 128), GCSI (129), Short-Form Health Survey (SF36) (130) and Hospital Anxiety and Depression Scale (HADS)(131). Nutritional intake was investigated at baseline and on completion of the study by keeping a four-day dietary record at home. One dietician provided the subjects with instructions regarding the questionnaires and dietary recording. Any ambiguities were resolved when the questionnaires and dietary records were returned. The same dietician

calculated the nutrient content in all dietary records from the Database Swedish National Food Composition Tables, 11th of April 2007 (National Food Agency, Uppsala, Sweden) using the computer program Dietist XP version 3.2, (Diet and Nutrition Data, Bromma, Sweden).The energy content (kcal), and the amount of protein, fat, carbohydrates and fibre (all in grams) were used.

Body mass index (BMI) was calculated at baseline and on completion of the study. Blood samples were taken at baseline and on completion of the study for analyses of glycosylated haemoglobin (HbA1c) were converted to the Diabetes Control and Complications Trial (DCCT), standard levels using the formula: HbA1c (DCCT) = (0.923 x HbA1c (MonoS) + 1.345; $R^2 = 0.998$) (132).

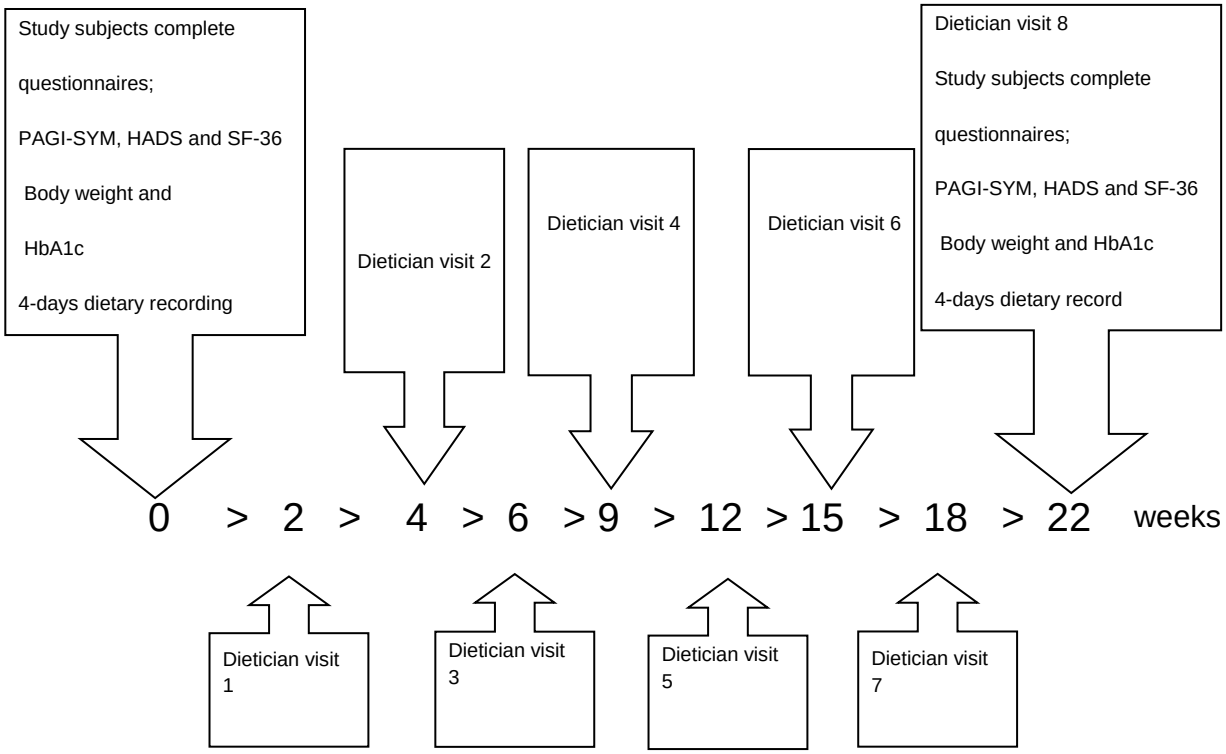


Figure 2. Flow chart for Paper IV.

Methods

Measurement of gastric emptying using a scintigraphic technique (Paper I).

Assessment of gastric emptying using gastric scintigraphy was registered for three hours in a fasting condition. A gamma camera registered one mean value every 5 minutes for 180 minutes. The gamma camera registered gamma radiation from ^{99m}Tc in anterior and posterior views of the stomach, mean value for three minutes followed by a pause for two minutes. The test meal was according to Swedish standard (133) and reference values were used (134). The nutrient content of the test meal, based on eggs, was 310 kcal, 19 g protein (25% of the total energy), 18 g fat (52 % of the total energy), and 17 g carbohydrates (23 % of the total energy) and 150 g water.

Comments. Because gastric emptying using scintigraphy is the worldwide 'gold standard', this method was also our choice. The energy percentage of fat was high in this meal, contrary to what is proposed to be used as the initial screening test for gastric emptying in the consensus of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine, U.S. (86). However, it is suggested that in some patients a low-fat, egg white meal may not prove to be an adequate functional challenge, especially for patients who report symptom exacerbations after eating lipid-rich diets. These subjects probably need a high-fat meal (86).

In our papers, separate reference values are presented for men and women before and after the menopause. Because gastric emptying in females is slower than in men and women before menopause have a lower gastric emptying rate, it is important to have different reference values for women (134). For the most part, certain time points have been used to evaluate gastric emptying: the time until gastric emptying begins after a finished meal (lag phase), the time point after a finished meal for emptying 50% of the isotope (T_{50}) and/or percentage isotope remaining in the stomach at time point 120 minutes from the finished meal (R_{120} or T_{120}). For diagnosis, T_{50} and/or R_{120} or T_{120} are most widely used. In this study, the measurement T_{50} could not be used because not all subjects had emptied 50% of the radioactivity from the ventricle during the study period (3 h). R_{120} has therefore been used to establish a diagnosis of gastric emptying. We

measured gastric emptying for three hours and not four hours as advocated in the literature (86). Abell et al. suggest measurements 1, 2, 3 and 4 hours after finishing the meal. The choice of three hours measurement only in our study was because the subjects were in a sitting position during the whole test, not just at four time points as recommended (86). It is very difficult to be in a sitting position for three hours and we considered four hours impossible.

Gastric emptying by radiopaque markers (Paper I).

To assess gastric emptying of ROM we used fluoroscopy and counted the number of ROM remaining in the stomach 3,4, 5 and 6 h after meal intake, which is a standard method used at our hospital (106).

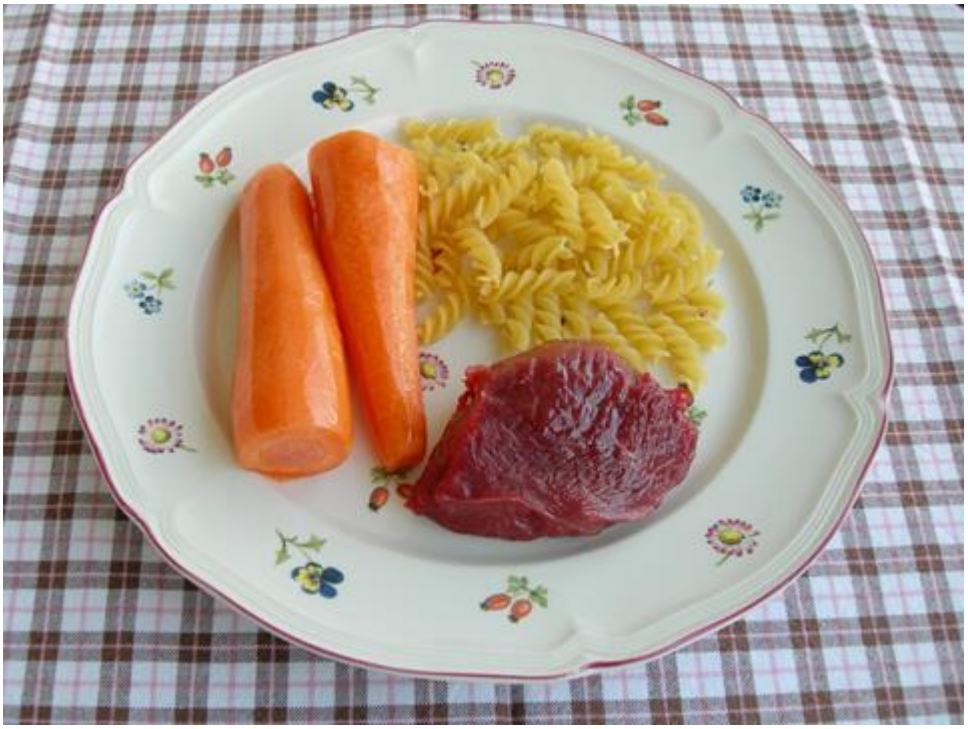
Comments. Measurement of gastric emptying with ROM using fluoroscopy has been compared to gastric scintigraphy in healthy individuals and in a small group of patients with DM. This validation revealed a significant correlation between the methods (106). One of several reasons that gastroparesis is under-recognised and inadequately investigated is poor access to scintigraphy. However, as fluoroscopy is available at all hospitals, emptying of ROM could serve as a screening method for delayed gastric emptying. This method has also been suggested as being a better means of detecting gastroparesis compared to scintigraphy (135). However, results with a lower correlation also exist (136). No comparison has been made between gastric emptying with ROM and scintigraphy in a large group of gastroparetic subjects. We therefore wanted to validate the method in gastroparetic patients.

Gastric emptying by scintigraphic technique (Paper III).

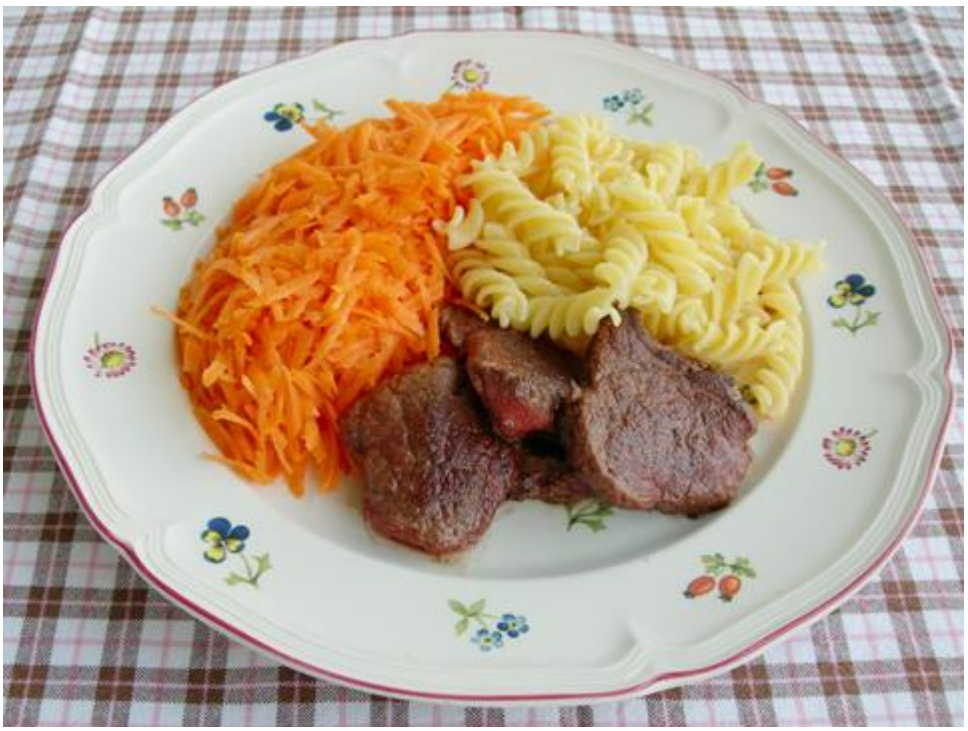
Gastric emptying was performed in a sitting position with the gamma camera positioned behind the subjects throughout the whole study period (0–180 minutes). The gamma camera registered the mean value every second minute throughout the 180 minutes. Gastric emptying was measured using two test meals. They consisted of 100 g of meat, 40 g of pasta, 150 g of carrot and 5 g of canola oil. The nutrient content was 375 kcal (1.57 MJ), 26 g protein, 13 g fat (31% of the total energy), 38 g carbohydrates and 4.8 g of fibre (3 g/MJ), calculated using the National Food Composition Tables (137). The only difference was the particle size. Pasta was chosen because it has a low glycaemic index, which is preferred

in a DM diet (138, 139). Five Mega Becquerel (MBq) of the tracer ^{99m}Tc were added to the uncooked pasta. Supplementary pictures 1-3.

Comments. Because the relationship between the different particle sizes and gastric emptying was being studied, it was not possible to use any standard test meal for the scintigraphic method (133), and reference values were therefore not available. Gender, age and BMI-matched healthy subjects were therefore included as references for normal gastric emptying rate.



Supplementary picture 1. Ingredients: carrot, meat and pasta



Supplementary picture 2. Test meal with large particle size

Supplementary picture 3. Test meal with small particle size

Plasma glucose response after a solid test meal (Papers I, II and III).

In Paper 1, plasma glucose was taken at the beginning of the meal (00), at the end of the meal (0), and after 15, 30, 45, 60, 90, 120, 150, 180, 210,

240, 270, 300, 330 and 360 minutes, or until all ROM had emptied from the stomach. In Paper II, blood samples were taken before the meal (0) and after 15, 30, 45, 60, 90, 120, 150, 180 minutes. In Paper III, the first blood sample was taken at the beginning of the LP and SP meal and then every 15 minutes throughout the whole study period of 180 minutes. Plasma glucose samples were analysed immediately in an automated plasma glucose analyser using a glucose oxidase method (Merck, Darmstadt, Germany) using HemoCue NAD-NADH (HemoCue AB, Ängelholm, Sweden).

Comments. If the postprandial glucose correlated with gastric emptying, this measurement should be a very cheap and widely available screening method for gastroparesis. Every diabetic team could take plasma glucose samples and thus have a cheap tool at their disposal.

During the testing in Paper II, the subjects were in a sitting position and were not allowed to walk around as it can affect both gastric emptying (140) and plasma glucose response. They only walked to the toilet close to the test room. In Paper III, the subjects were in a sitting position the whole time.

Metabolic control (Papers I, II, III and IV)

HbA1c was converted to the Diabetes Control and Complications Trial, standard levels using the formula: HbA1c (DCCT) = (0.923 x HbA1c (MonoS) + 1.345; R^2 = 0.998) (132).

Comment. To assess the metabolic control HbA1c was analysed in all studies as it reflects the metabolic control during 8-12 weeks (17, 141). The glycosylated haemoglobin (HbA1c) is presented according to the Diabetes Control and Complications Trial standard.

Measurement of insulin concentration (Paper III)

The insulin concentration was analysed every 15 minutes for 0 -180 minutes. The serum insulin samples were centrifuged and stored at -20ºC until analysis. The insulin levels were determined using a radio immunochemical RIA assay technique (Diagnostic Products Corporation, Los Angeles).

Comment. The insulin concentration has an impact on the postprandial glucose curve. To sort out the impact of gastric emptying on postprandial glucose, the impact of insulin concentration and gastric emptying needs to be differentiated.

Gastrointestinal symptoms (Papers I, II and IV)

The severity of GI symptoms were assessed using PAGI-SYM (Appendix 3) and GCSI. PAGI-SYM is developed to evaluate symptom severity during the preceding two weeks. The 20-item PAGI-SYM includes six subscales: heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain and lower abdominal pain, analysed on a 6-point Likert scale ranging from 0 (no symptoms) to 5 (very severe symptoms). PAGI-SYM has good reliability, responsiveness and evidence supporting construct validity in subjects with GERD, dyspepsia or gastroparesis (127). The Gastroparesis Cardinal Symptom Index-Daily Diary (GCSI-DD), which is a part of PAGI-SYM, consists of nine items with three subscales – fullness/early satiety, nausea/vomiting and bloating – has demonstrated excellent test-retest reliability and good validity and responsiveness to treatments for gastroparesis (142).

Comments. GI symptoms occur in some patients with gastroparesis, although there are gastroparetic patients without GI symptoms. To optimize treatment and management, it is important to detect how often patients are asymptomatic, and to find out which symptoms most often correlate with gastroparesis. PAGI-SYM is suitable for this as it has been validated and used in studies with gastroparetic patients (66, 143).

Anxiety and depression (Paper IV).

The severity of anxiety and depression were determined using the self-reporting questionnaire Hospital Anxiety and Depression Scale (HADS) (Appendix 4) (131, 144, 145). HADS contains 14 items, seven items on anxiety and seven items on depression. Patients score the extent to which they agree with each statement on a four-point scale, ranging from 0 to 3. Cut-off points for severity in each domain are the scores: 0–7 = normal, 8–10 = mild, 11–14 = moderate and 15–21 = severe. A score of 8 or above is considered abnormal. The HADS questionnaire has been reported to have good validity in DM subjects (145). Factor structure, discriminant validity and internal consistency were studied in a review paper and the authors

found that the sensitivity and specificity for detecting anxiety and depression were 0.80 (144).

Comment. HADS has previously been used in DM patients with gastroparesis and found to be useful in this patient group (67).

Quality of life (Paper IV)

The 36-item Short-Form Health Survey (SF-36) was used to evaluate quality of life(Appendix 5) (146, 147). SF-36 consists of eight different domains and these can be summarised in a physical component summary (PCS): physical functioning, role physical, bodily pain and general health; and a mental component summary (MCS): vitality, social functioning, role-emotional and mental health. The highest score possible is 100, where no limitations or disabilities are reported, and the lowest score possible is 0, where the greatest degree of limitation or disability is reported.

Comments. SF-36 is a general questionnaire and is not disease specific. It has been used in many studies in different diseases and in health surveys in the general population. This makes it possible to compare the quality of life in different groups of patients.

Dietary intake (Paper IV)

The subjects kept four-day dietary diaries at home. Three weekdays and one weekend day were chosen. The amounts of all food and beverages were recorded in weight and household measures. The nutrient content was calculated in all dietary records using the Database Swedish National Food Composition Tables, April 11, 2007 (148) and the computer program Dietist XP version 3.2, (Diet and Nutrition Data, Bromma, Sweden). For this paper, the caloric content (kcal), and the amount of protein, fat, carbohydrates and fibre (all in grams) were calculated.

Comments. Methodological error was minimised by the same dietician providing instructions on how the dietary diary should be kept. This dietician interviewed each subject and any ambiguities were resolved when the dietary records were returned. The same dietician thereafter calculated the nutrient content in all dietary records to reduce variability in the assessment.

Nutrition status (Paper IV)

Body weight was recorded with the person in their underwear and without shoes to the nearest 0.1 kg. Calibrated, electronic scales were used (Serial no 11087, system 31, Advanced Weighing Co Ltd, New Haven, East Sussex, BN9 0DU, UK). Height was measured in a standing position to the nearest 0.5 cm. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2) (kg/m^2).

Comment. In the literature, it is suggested that gastroparetic DM subjects have nutritional deficiencies (56). Therefore we considered BMI to reflect energy intake.

Statistical analysis

Statistical evaluations were performed using the statistical software package IBM SPSS/ PC statistics 19 (Chicago, IL, US).

Results are generally presented as median and range, unless otherwise noted. Correlations were calculated using Spearman's correlation coefficients. Nominal data were compared by using the Pearson’s Chi-squared test. Comparisons between groups were made with the Mann-Whitney U-test.

In Papers I and II, the sensitivity, specificity and positive and negative predictive value were estimated in order to diagnose gastroparesis with gastric scintigraphy being the gold standard. In Paper I, these were analysed using ROM emptying at different time points. In Paper II, a receiver operating characteristics (ROC) curve was used to determine sensitivity and specificity of upper GI symptom severity (GCSI) and postprandial glucose parameters to make a diagnosis of gastroparesis, again with scintigraphy being the gold standard. An area under the ROC curve (AUROC) of >0.7 is considered to be fair, >0.8 is considered to be good and >0.9 is considered to reflect excellent discriminating ability. The best cut-off values for discriminating between patients with and without gastroparesis were determined.

In Paper II a mixed between-within subjects analysis of variance (ANOVA) was conducted to assess the effect of delayed gastric emptying, i.e. gastroparesis, on postprandial glucose response across the three-hour

period after intake of the test meal. Postprandial plasma glucose response is also presented as the maximum increase in plasma glucose after meal intake (peak glucose response) and the time to reach the peak glucose value after meal intake, and these parameters were compared between patients with and without gastroparesis.

In both Papers II and III the incremental area under the curve (IAUC) of the postprandial glucose values was calculated using the trapezium rule (149).

In Paper IV, the demographic characteristics of the patients and the outcome variables at baseline and after the treatment period in the two groups are shown as mean ± SD and median (range). For comparisons within the groups, the Wilcoxon Signed Rank test was used and comparisons between the groups for outcome variables were made using Analysis of Covariance (ANCOVA), adjusting for baseline values, and the between-group differences in changes in the outcome variables are shown as a mean and 95% CI. In all papers statistical significance was accepted at $p < 0.05$.

Results

Paper I

We included 115 subjects with insulin-treated DM (56 men, 59 women, median age 53, range 21-69 years) and all patients completed the investigation. Of these, 72 were referred to our unit for evaluation of suspected gastroparesis and 43 were recruited from a trial aimed at assessing GI symptoms in patients with insulin-treated diabetes. On clinical grounds, the principal investigator (EO) suspected that 99 of the patients suffered from delayed gastric emptying. The subjects were grouped into two main DM groups. In the type 1 DM group, we included 78 subjects with type 1 DM, three patients with Latent Autoimmune Diabetes in the Adult (LADA) and one subject with secondary diabetes (caused by pancreatitis). Included in the type 2 DM group were 31 subjects with type 2 DM, one with Maturity Onset Diabetes in Young (MODY) and one with secondary diabetes caused by corticosteroid medication. The characteristics of the subjects are shown in Table 1.

The plasma glucose level was median 8.3, range 4.0–10.0 mmol/L at the beginning of the test meal. During the test meal, the lowest plasma glucose value was 3.0 mmol/L and the highest value was 17.2 mmol/L. The plasma glucose level during the first three hours of the test was 8.5, 4.7–13.1 (median, range) mmol/L and 8.3, 4.7–13.1 mmol/L during the entire test (six hours). Ten subjects needed glucose supplementation during the study because of a plasma glucose level below 4 mmol/L.

The correlation between gastric emptying using a scintigraphic method at 1, 2 and 3 hours and ROM by fluoroscopy at 3, 4, 5 and 6 hours was 0.41 to 0.54, ($p < 0.0001$). (Figure 3 and Table 2).

Eighty-three (72%) patients had a delayed gastric emptying rate using the scintigraphic technique (delayed emptying at 2 hours), whilst 29 (25%) patients had delayed emptying of ROM at 6 hours. Of the 29 patients with delayed gastric emptying of ROM, 28 also had delayed scintigraphic emptying, whereas 55 of the patients with a normal ROM test (total 86 patients) had delayed gastric emptying with scintigraphy, indicating poor sensitivity (34%) and negative predictive value (36%) of ROM emptying and

Table 1. Characteristics of the subjects with type 1$^{\alpha}$ and type 2$^{\gamma}$ diabetes.

	Type 1 diabetes, n=82		Type 2 diabetes, n=33	
	Median	Range	Median	Range
Age, year	50***	21-69	63***	27-69
Weight, kg	77.1***	48.7–124.5	92.4***	56.5–114.5
BMI, Kg/m^2	26.0****	18.4 –38.0	31.0****	18.6–40.9
Duration of diabetes, year	30****	2-63	17****	2-40
Insulin treated, year	30****	2-63	8****	1-24
U insulin/kg body weight	0.5**	0.1–1.3	0.8**	0.1–3.1
Number of injections, n	4*	1 - 8	4*	1-6
HbA1c, %	7.9 ns	4.2–10.1	7.8 ns	5.7–12.1
HbA1c 5 years ago, %	8.1 ns	5.7–12.0	8.2 ns	5.8–11.7
Creatinine, µmol/L	72 ns	51 - 140	81 ns	47 - 174
GFR, mL/min/1.73 m2	88.5 ns	40 - 141	86 ns	34 - 144

α Type 1 diabetes: type 1 diabetes, LADA= Latent Autoimmune Diabetes in the Adult and secondary (pancreatitis) diabetes
γType 2 diabetes: type 2 diabetes, MODY=Maturity Onset Diabetes in Young diabetes and secondary (cortisone) diabetes
GFR=glomular filtration rate, HbA1c=glycosylated haemoglobin
*p=0.034, ** p=0.006, *** p=0.001, **** p<0.0001

high specificity and a positive predictive value of 97% for both in diagnosing gastroparesis. An alternative definition of abnormal ROM emptying retention (5 hours and/or 6 hours) resulted in higher sensitivity (40%) but at the expense of reduced specificity (94%). Other alternative definitions of abnormal gastric emptying of ROM yielded lower sensitivity, specificity and positive and negative predictive value.

Both upper and lower GI symptoms were reported frequently by the patients. The median (range) subscale scores of PAGI-SYM were: nausea/vomiting 0.67 (0-5), fullness/early satiety 2.0 (0–5), bloating 2.5 (0–5), upper abdominal pain 2.0 (0–5), lower abdominal pain 1.0 (0–5), and heartburn/regurgitation 1.3 (0–4.9) (Figure 4). The strongest correlations

Table 2. Correlation coefficients between gastric scintigraphy and emptying of radiopaque markers (ROM)

	Scintigraphy Retention 1 hour	Scintigraphy Retention 2 hours	Scintigraphy Retention 3 hours
ROM Retention 3 hours	0.42	0.45	0.41
ROM Retention 4 hours	0.54	0.49	0.48
ROM Retention 5 hours	0.44	0.45	0.48
ROM Retention 6 hours	0.41	0.47	0.52
ROM Retention 4-6 hours	0.53	0.52	0.52

between gastric emptying and upper gastrointestinal symptoms were noted for scintigraphic emptying and nausea/vomiting ($r = 0.30$; $p < 0.001$) and postprandial fullness/early satiety ($r = 0.34$; $p < 0.0001$). No sum score was significantly associated with emptying of ROM.

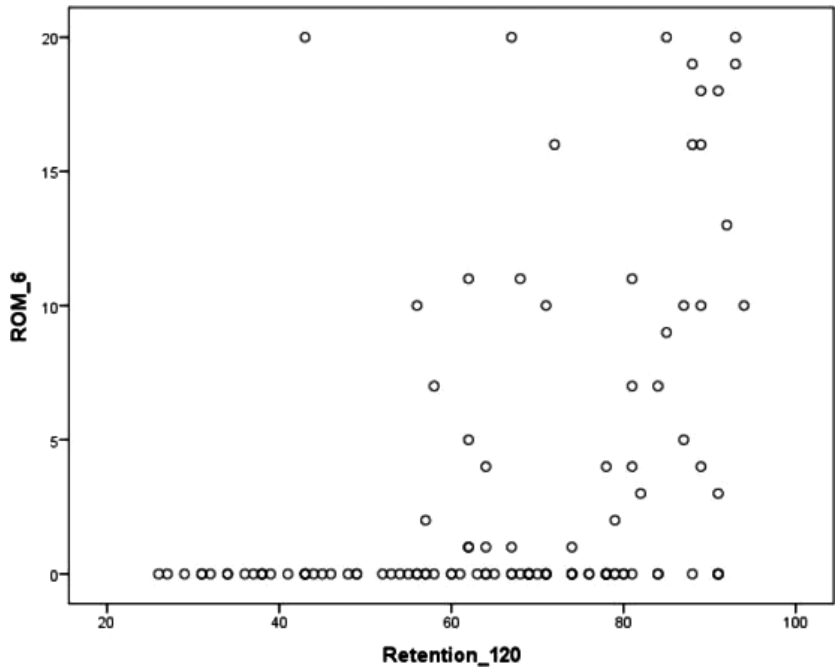


Figure 3. Association between retention of the radioactivity in the stomach at 120 min (R_120) and number of radiopaque markers (ROM) at 6 h (ROM_6) after meal intake in 115 diabetic subjects ($r = 0.47$; $P < 0.0001$).

Comments. Plasma glucose ≤ 10.0 mmol/L was chosen as hyperglycaemia could decrease gastric emptying. The subjects arrived at the hospital in the morning in a fasting condition. This means that the subjects had not taken any insulin in the morning. During the morning, plasma glucose increases because of stress hormones, making it difficult to achieve plasma glucose

of 4-6 mmol/L (150). Moreover, several of the subjects had travelled to the hospital for 2-3 hours during the morning before the test. When the subjects finished registration using a gamma camera, they were transported immediately in a wheelchair to the fluoroscopy equipment. This was done as walking has been shown to increase gastric emptying (140). The time between final registration by scintigraphy and the first fluoroscopy measurement was no more than five minutes. This means that we tried our best to remove potential confounders, but despite this the ROM test were only found to be moderately helpful in the clinical setting. However, a positive ROM test seems to be reliable, whereas a negative test is less reliable.

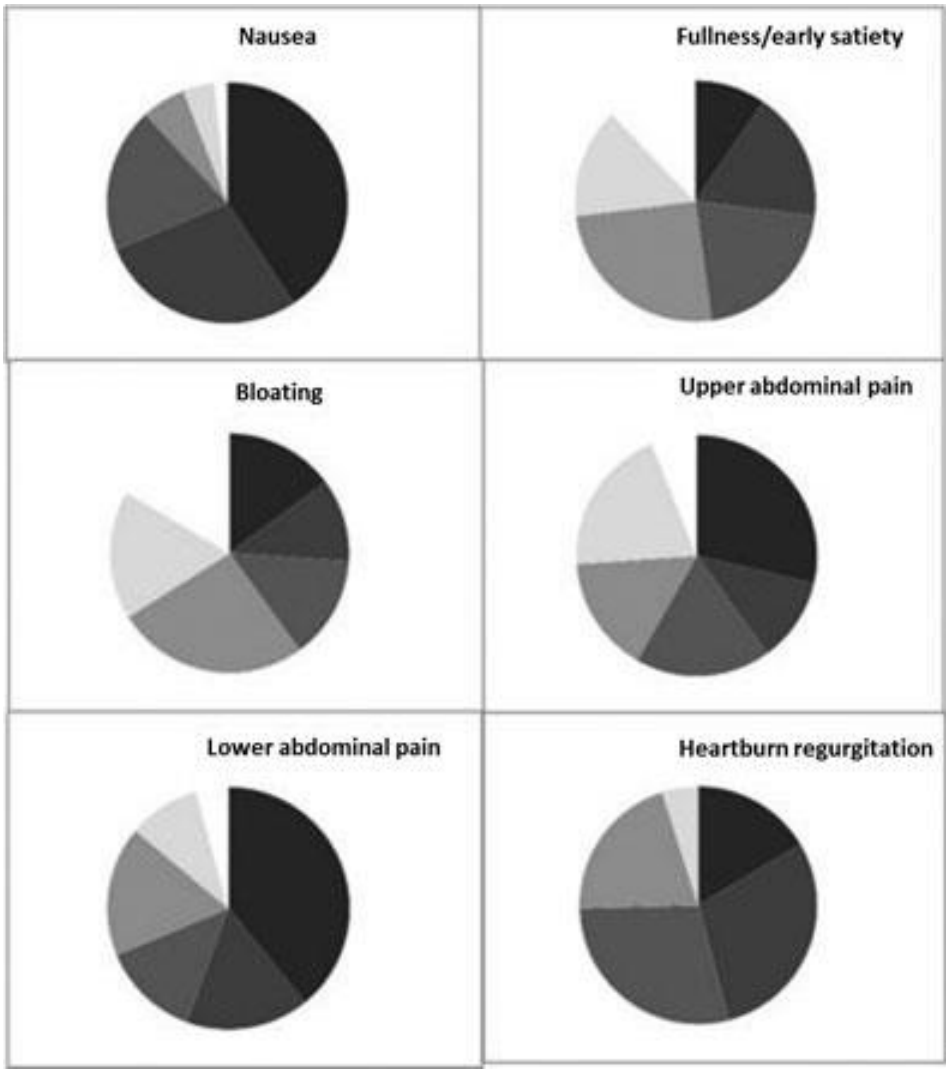


Figure 4. Severity of GI symptoms in subjects with insulin-treated diabetes with and without gastroparesis. Distribution of PAGI-SYM summary scores (0–5); white represents the highest score (very severe symptoms), and with increasing darkness of the gray colour the severity of the symptoms decreases
(darkest gray colour = no symptoms).

Paper II

Forty-eight men and 35 women with insulin-treated DM were included in this study. They were recruited due to clinical suspicion of gastroparesis, such as GI symptoms and/or poor metabolic control. Of the subjects included, 55 had type 1 DM, 23 had type 2, three had LADA and two had secondary DM secondary to cortisone medication. The subjects with DM type 1, LADA and secondary DM were treated with short-acting insulin, either lispro or aspart, and long-acting insulin, either glargin or detemir. The subjects with DM type 2 were treated with lispro, human insulin or aspart and human isophan, glargin, detemir insulin or mixed insulin. Gastroparesis was confirmed in 53 (64%) subjects, 29 (55%) of them were women and 38 of them were in the DM type 1 group. Clinical characteristics of the patients obtained from a chart review are shown in Table 3, divided into groups with (n = 53) and without (n = 30) gastroparesis.

The subjects tolerated the test meal well (Supplementary picture 2).The median ingestion time was 25.0 minutes (range 19-35). Median plasma glucose at the beginning of the meal was 7.5 mmol/L (range 4.3-10.0) in subjects with gastroparesis and 8.4 mmol/ L (4.9-10.0) in subjects without gastroparesis, which was not significantly different ($p = 0.23$). During the 3-hour study period, 12 subjects with gastroparesis and one subject with normal gastric emptying needed glucose supplementation due to plasma glucose <4.0 mmol/L (range 6-36 g of glucose). No clinical hormonal counter regulation was detected in these subjects as their highest measured plasma glucose at 180 minutes was lower (8.7 mmol/L) than in all subjects (17.5 mmol/L). The plasma glucose value before glucose supplementation was used for the subsequent analyses (most recent data carried forward).

The postprandial plasma glucose is illustrated in Figure 5, differentiated into subjects with and without gastroparesis. There was a significant difference between the groups in glucose response, $p <0.0005$. The incremental area under the curve (IAUC) and the peak level were lower in the gastroparetic group than in the group with normal gastric emptying. Peak time was the same for both groups (Table 4). A weak but significant correlation between the peak glucose response and gastric scintigraphic retention at two hours was seen ($r = -0.23$ ($p = 0.04$).

Table 3. Demographic charactaristics of diabetic subjects with and without gastroparesis.

	Subjects with gastroparesis, n=53		Subjects with normal gastric emptying, n=30	
	Median	Range	Median	Range
Age, year	54*	27-69	62	29-69
Weight, kg	84.3	48.7-124.5	83.8	68.0-119.5
BMI, Kg/m^2	27.0	19.00-40.9	27.0	21.9-37.0
Duration of diabetes, years	25	2-55	16	2-48
Insulin treated, years	23	1-55	15	2-48
U insulin/kg body weight/day	0.6	0.2-2.2	0.6	0.2-1.7
Number of insulin injections/day, n	4	1-8	5	2-7
HbA1c, % ∫	7.4	5.7-12.0	7.5	5.4-10.1
Gastric scintigraphic retention at 120 minutes, %	74	55-91	38	17-62
Creatinine, µmol/L	73	55-142	76	47-162
GFR, mL/min/, 1.73 m^2	85	43-128	88	37-141

BMI = body mass index, GFR = glomerular filtration rate, HbA1c = glycosylated haemoglobin. * $p<0.05$.
∫= HbA1c the Diabetes Control and Complications Trial, standard

The GI symptoms are presented in Table 4. GI symptoms were significantly more severe ($p = 0.0001$) in the gastroparetic group in comparison with the non-gastroparetic group. The correlation between severity of GI symptoms and retention at 2 hours using the scintigraphic method was also significant for all PAGI-SYM subscale scores ($p = 0.001$) (Table 5). Between the postprandial glucose variables (IAUC and peak glucose levels) and PAGI-SYM subscale scores weaker correlations were noted (Table 5).

GI symptom severity (GCSI total score) had the best discriminative validity in identifying patients with gastroparesis (AUROC = 0.85) with the optimal cut-off point being a GCSI total score of ≥0.8, yielding a sensitivity of 87% and a specificity of 80%. The positive and negative predictive values were 88% and 77% respectively. The optimal cut-off point for the peak glucose

response increase in order to identify patients with gastroparesis was ≤1.8 mmol/L, yielding a sensitivity of 60% and a specificity of 70%.

Table 4. Postprandial glucose response after test meal and GI symptoms during 2 weeks according to PAGI-SYM in diabetic patients with and without gastroparesis.

	Diabetes with gastroparesis, n=53		Diabetes without gastroparesis, n=30		p value
	Median	Range	Median	Range	
IAUC	58	0–722	196	0.6-1101	0.018
Time to peak glucose level (min)	45	15–180	60	15-180	0.30
Peak glucose response (mmol/L)	1.3	-2.1–5.8	2.4	-0.3–8.8	0.011
PAGI-SYM: Nausea/vomiting #	1.00	0.0-4.33	0.0	0.0-2.33	0.0001
PAGI-SYM: Fullness/early satiety #	2.25	0.0-5.00	0.25	0.0-4.25	0.0001
PAGI-SYM: Bloating #	3.00	0.0-5.00	0.0	0.0-4.50	0.0001
PAGI-SYM: Upper abdominal pain	2.00	0.0-5.00	0.0	0.0-3.50	0.0001
PAGI-SYM: Lower abdominal pain	1.50	0.0-5.00	0.0	0.0-4.0	0.0001
PAGI-SYM: Heartburn/regurgitation	1.00	0.0-3.14	0.0	0.0-4.14	0.0001

PAGI-SYM = Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index.
IAUC=Incremental Area Under the glucose Curve.
# Makes up the Gastroparesis Cardinal Symptom Index (GCSI)

A combination of GCSI total score ≥0.8 and a peak glucose increase ≤1.8 mmol/L resulted in a sensitivity of 37% but a specificity and a positive predictive value of 100%. All 20 patients who had this combination had gastroparesis. However, the negative predictive value was only 47%. If patients were allowed to have a GCSI total score of ≥0.8 and/or a peak glucose increase of ≤1.8 mmol/L, the sensitivity and specificity in identifying gastroparesis would be 87% and 67% respectively.

Table 5. Correlation between retention of the isotope in the stomach at 120 minutes after finished meal, incremental area under the glucose curve, respectively and GI symptom severity (PAGI-SYM scores).

Diabetic Subjects n =83	PAGI-SYM nausea/ vomiting	PAGI-SYM fullness/ early satiety	PAGI-SYM bloating	PAGI-SYM upper abdominal pain	PAGI-SYM lower abdominal pain	PAGI-SYM heartburn/ regurgitation
R_{120}	r=0.60 p< 0.0001	r=0.62 p<0.0001	r=0.63 p<0.0001	r=0.55 p<0.0001	r=0.49 p<0.0001	r=0.64 p<0.0001
IAUC	r= - 0.32 p=0.003	r=-0.27 p=0.02	r=0.36 p=0.01	r=0.27 p=0.05	r=0.42 p=0.000	r=-0.22 p=0.048
Peak glucose level	r=-0.30 p=0.006	r=-0.19 p=0.088	r=-0.26 p=0.019	r=-0.20 p=0.071	r=-0.30 p=0.007	r=-0.12 p=0.26

$R_{120=}$ retention of the isotope in the stomach at 120 minutes after finished meal.
IAUC = incremental area under the plasma glucose curve.
PAGI-SYM= Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index.

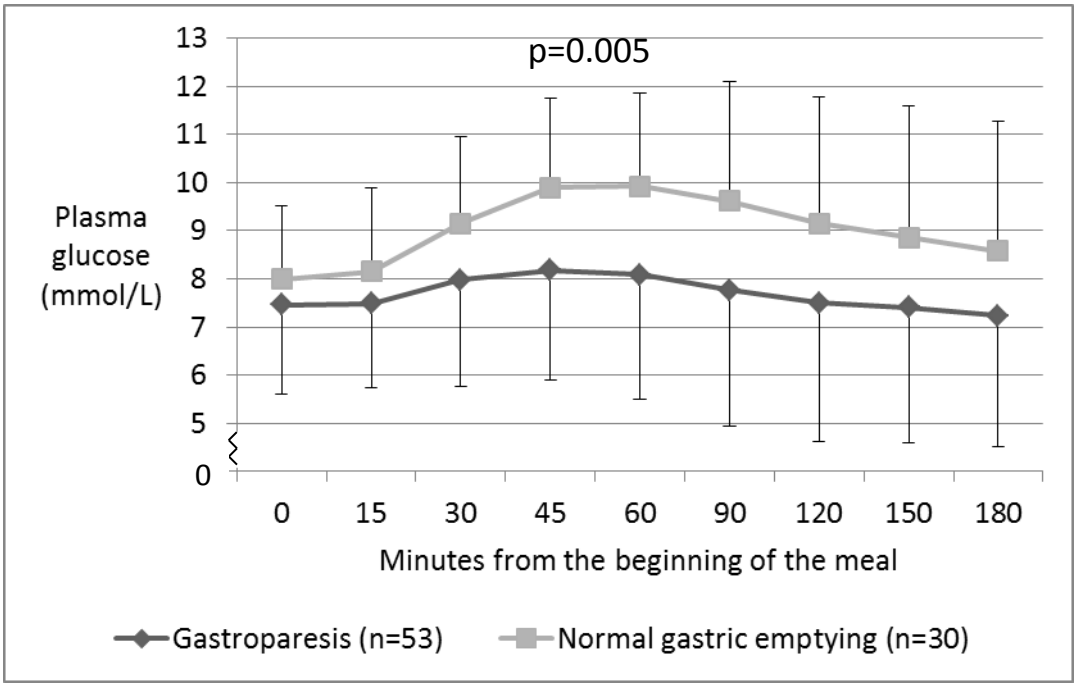


Figure 5. Plasma glucose response after a test meal (0-180 min) in diabetes patients presented with and without gastroparesis. A mixed between-within subjects ANOVA demonstrated a significant main effect of the diagnostic group, i.e. the plasma glucose response differed between patients with and without gastroparesis, with a blunted plasma glucose response in the gastroparetic group (p=0.005).

Comments. The gastroparetic patients demonstrated a blunted postprandial glucose response and this in combination with the presence of GI symptoms seem to be of potential usefulness in the clinical setting raising a suspicion of delayed gastric emptying in diabetic patients.

Paper III

Seven subjects with insulin dependent DM and gastroparesis were included in the study. The characteristics of the seven subjects are shown in Table 6. Gastroparesis was determined by gastric scintigraphy in according to the criteria set by Stotzer et al. (106) in one subject before the study. They had no insulin pump and had not undergone surgery for gastrointestinal disease. Women of fertile age, and smokers were excluded. Seven healthy subjects were recruited from an advertisement in a newspaper. They were matched with the diabetic subjects for gender, age and BMI. All subjects tolerated the test meals well.

Tracer added to the test meal

Before each meal was served, the pasta was incubated with ^{99m}Tc for three hours and shaken at + 37ºC in artificial gastric juice. As a result, 87.0 ± 2.0% of the pasta in the SP meal and 87.4 ± 1.8% of the pasta in the LP meal were tagged.

Gastric emptying

In the DM subjects, the gastric lag phase was 15.1 ± 3.7 minutes for the LP meal and 1.4 ± 0.8 minutes for the SP meal (p = 0.028). In the control group, the gastric lag phases were 7.1 ± 3.9 minutes and 0.9 ± 0.6 minutes respectively, which did not differ significantly (Figure 6).

After an SP and LP meal, T_{120} in the DM subjects was 31.6 ± 4.3% and 72.3 ± 4.9% respectively (p = 0.018). This statistical difference was the same at T_{180} (R_{180}). In the control group after an SP and LP meal, T_{120} (R_{120}) was 17.9 ± 6.7% and 47.8 ± 3.5% respectively. Between the groups of subjects, T_{120} (R_{120}) was significantly slower after an LP meal in the DM subjects (p = 0.018) but not after an SP meal (p = 0.09).

Blood glucose and serum insulin response

Blood glucose was 7.2 ± 1.1 mmol/L before the SP meals and 8.1 ± 0.5 mmol/L before the LP meals (p = 0.44) in the DM subjects. A significantly greater (p = 0.018) IAUC for blood glucose was found in DM subjects after the SP meal compared to after the LP meal (Figure 7). In the DM subjects, the correlation coefficient between the retention of the SP meal in the stomach and the glucose response at 180 minutes was r = 0.82.

There were no significant differences between the plasma insulin concentrations in DM subjects at 0 minutes before the SP meal and LP meal.

Comments. The stomach grinds the diet into small particles 2 mm in size and gastric emptying begins. The study design was therefore performed with two equal meals with only one difference, the particle size. The hypothesis was that small particles would leave the stomach easier. Pasta

Table 6. Demographic charactaristics of diabetic subjects with gastroparesis and healthy control subjects.

	Diabetic subjects	Healthy subjects
Male/female (n)	3/4	3/4
Age, year	59.3±9.3	59.3± 9.1
BMI, kg/m^2	23.4±2.2	23.5±1.9
HbA1c, %	8.2±0.8	5.7±0.3
Duration of disease, year	37±14	
Average daily insulin dose, U/d	35.9±5.6	
Serum Creatinine, mmol/L[a]	110.7±32.5	
Urinary protein, mg/min	44.9±72.2	
Retinopathy, n	7	
Orthostatic hypotension,n[b]	4	

Data are presented as means ± S.D.
a Serum creatinine, reference value 60–120 mmol/L.
b Orthostatic hypotension, decrease of systolic blood pressure, BP, was ≥30 mmHg.

was chosen because of its low glycaemic index, which is recommended in a diabetic diet (126).
The study was performed at noon as it is very difficult to achieve an euglycaemic glucose level in the morning in insulin-sensitive subjects, such as type 1 DM (150). It is confirmed that MMC phase III is often absent/infrequent in gastroparetic subjects (78, 151). This means that the stomach is not always empty in the morning. The subjects were therefore instructed to have a standard breakfast and snack before the test. At the

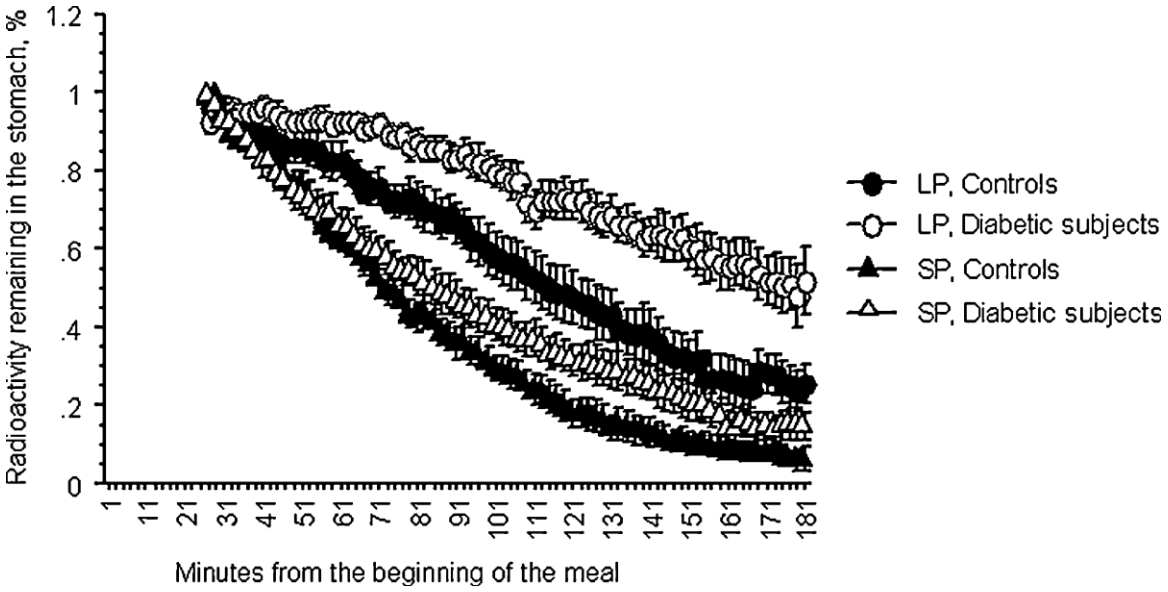


Figure 6. Gastric emptying (mean W S.E.M.) of meals of small particle size (SP, triangle symbols) and large particle size (LP, round symbols) in diabetic subjects with gastroparesis (open symbols) and healthy subjects (solid symbols) after correction for ingestion time. Gastric emptying was significantly slower (p=0.018) after LP meal in diabetic group than in control group, but no significant difference after SP meal between the groups.

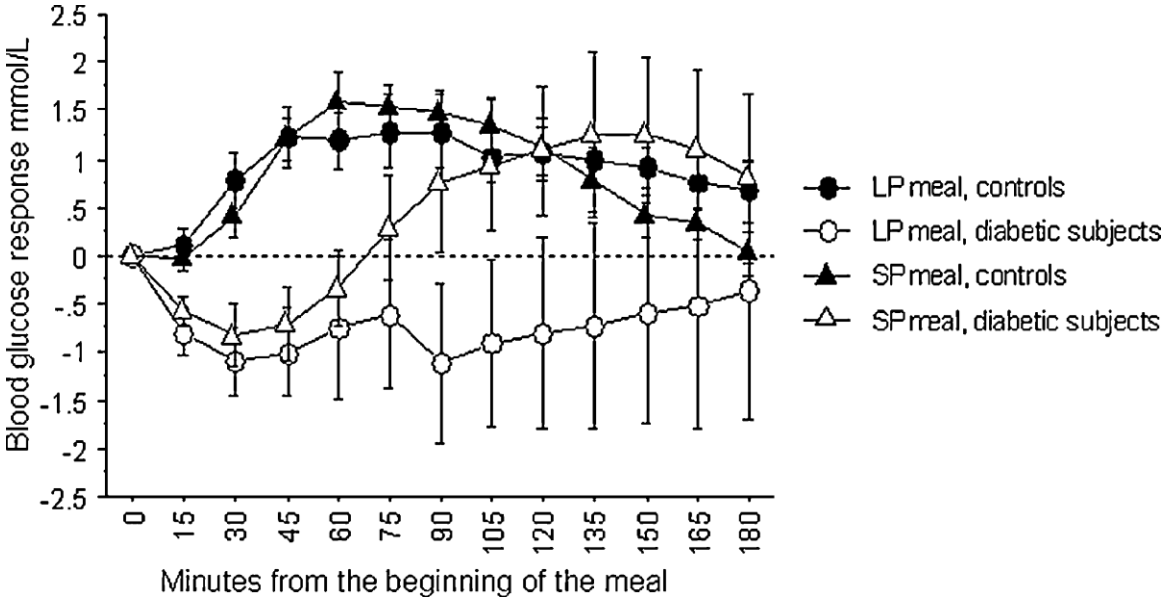


Figure 7. Blood glucose response mmol/L (mean±S.E.M.) after meals with small particle size (SP, triangle symbols) and large particle size (LP, round symbols) in diabetic subjects with gastroparesis (open symbols) and healthy subjects (solid symbols). Incremental area under the curve for blood glucose (IAUC) was significantly greater (p=0.018) after SP meal than LP meal in diabetic subjects.

same time, the subjects could adjust the glucose level, with a dose of insulin for breakfast, achieving a blood glucose level of ≤10 mmol/L at noon. In this study, the test meal was not supplemented with any beverage as it has been found that water with a meal increases the gastric emptying of the meal (152).

Paper IV

Of 83 diabetic subjects with insulin-treated DM and suspected gastroparesis who were invited to participate in the study, 72 chose to participate. Following investigation using gastric scintigraphy, gastroparesis was found in 58 subjects although two of these did not want to participate in the study. The remaining 56 subjects (36 women) were randomised to the treatment groups and to one of two dieticians (Figure 8). In the intervention group, 22 subjects had type 1 DM, five subjects had type 2 DM and one subject had Latent Autoimmune Diabetes in the Adult (LADA) diabetes. The control group consisted of 14 subjects with type 1 DM, 13 with type 2 DM and one subject with Maturity Onset Diabetes in Young (MODY) diabetes. The demographic and clinical characteristics of the randomised patients are presented in Table 7.

During the treatment phase, one patient in the intervention group died and five patients left the control group prematurely because of a worsening of existing upper GI symptoms (n = 3), occurrence of new GI symptoms (n = 1 after a visit to Africa) or without any specific reason mentioned (n = 1). These missing data were imputed from the previous assessment (baseline), using the most recent observation carried forward technique, and were included in the analysis.

All GI symptoms, except for upper abdominal pain, improved significantly (lower PAGI-SYM scores) after the intervention diet (Figure 9A), whereas none of the GI symptoms improved after the control diet (Figure 9B). All the primary outcome variables improved significantly more after the intervention diet compared to the control diet; nausea/vomiting (-0.56 (-1.01- -0.11) (mean change difference (95% CI); p = 0.01), fullness/early satiety (-0.61 (-1.14- -0.08); p = 0.02) and bloating (-0.86 (-1.48- -0.25); p = 0.006). Regurgitation/heartburn also improved after the intervention diet compared to the control diet (-0.51 (--0.94- -0.07); p = 0.02).

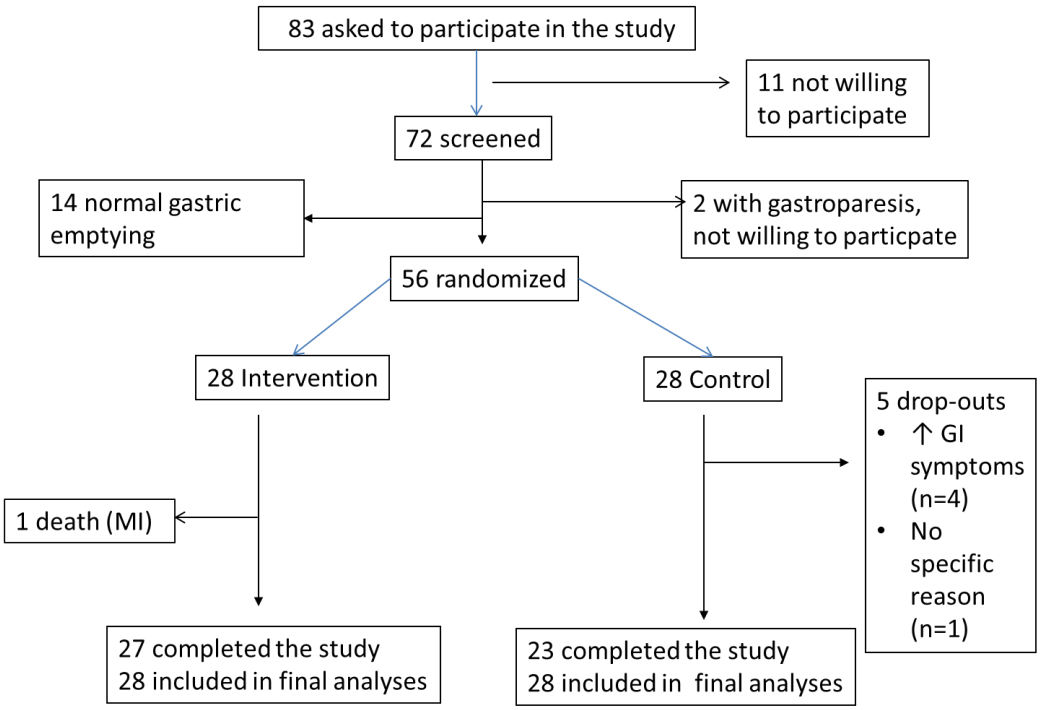


Figure 8. Flow chart demonstrating the number of patients in the different phases of the study.

After the treatment period, the severity of anxiety (HADS) was reduced in the intervention diet group but not in the control diet group. However, the between-group comparison of change in the anxiety score was not significant (Table 8).

Depression (HADS) and quality of life (mental and physical component summary of SF-36) remained unchanged in both groups (Table 8). The fat intake increased significantly in the intervention diet group but not in the control diet group, whereas within-group comparisons for total intake of calories, fibre, carbohydrates and protein remained unchanged in both groups without any between-group differences. No differences were seen between or within the groups regarding body weight or metabolic control (HbA1c). Supplementary pictures 4-11 show examples with meals in SP.

Table 7. Demographic and clinical characteristics of subjects with insulin treated diabetes and gastroparesis presented as mean ± SD and median (range).

	Age, years	Duration of diabetes, years	Insulin treated, years	Insulin/kg body weight, U	Body weight, kg	BMI, kg/m^2	S-Creatinine, µmol/L	GFR, mL/min/ 1.73 m^2	R^{120}, %	R^{180}, %
Intervention diet, n=28	51.5 ± 11.7 51 (31-69)	28.25 ± 14.8 28.0 (2.0-65.0)	23.7 ± 15.8 28 (4- 46)	0.6 ± 0.3 0.5 (0.3-1.7)	77.9 ± 16.0 74.65 (52.3 – 110.3)	25.6 ± 4.7 25.0 (20.1-40.9)	82.2 ± 20.5 76.5 (55-138)	80.0± 18.8 82.5 (40-126)	77.1 ± 9.8 79.5 (53 – 91)	57.8 ± 16.4 61 (18 – 81)
Diabetes diet, n=28	55.0 ± 11.4 54.5 (27-69)	23.6 ± 15.6 18.0 (2.0-64.0)	21.6 ± 17.4 16 (1-63)	0.7 ± 0.5 0.5 (0.2-2.2)	78.4 ± 15.8 80.8 (54.6 – 114.4)	27.7 ± 4.9 28.4 (18.4-36.0)	72.2 ± 12.3 74.0 (54-100)	82.7 ± 19.2 86 (48-128)	74.7 ± 12.9 72.5 (55 – 94)	59.9 ± 19.7 55.5 (31 – 91)

R^{120}=Retention of the radioactivity in the stomach 120 minutes after meal intake (gastric scintigraphy)
R^{180}=Retention of the radioactivity in the stomach 180 minutes after meal intake (gastric scintigraphy)
GFR = glomerular filtration rate

Table 8. Variable at baseline and at finished 20 weeks study period grouped in intervention and control group, mean ± SD, median (range). The variables change within the group and between the groups, mean, 95% Confidence interval. P < 0.05.

	Intervention diet, n=28				Diabetes diet, n=28				P value I/D diet	Diff change mean, 95CI
	Base line mean±SD median(range)	Finished study mean±SD median(range)	Change mean±SD median(range)	p value	Base line mean±SD median(range)	Finished study mean±SD median(range)	Change mean±SD median(range)	p value		
Body weight, kg	78.4 ± 16.3 75.5 (54-112.4)	77.9 ± 16.0 74.7 (52.3-110.3)	-0.5 ± 3.6 0.6 (-13.9-3.9)	ns	79.0 ± 15.6 82.0 (54.5-111.0)	78.5 ± 15.8 80.8 (54.6-114.4)	-0.5 ± 2.2 -0.7 (-5.0-3.8)	ns	0.99	-0.012(-1.6-1.6)
Kcal	1505 ± 462 1480 (840-2893)	1585 ± 483.1 1507 (771-3058)	80 ± 385.0 108 (-555-921)	ns	1551 ± 423.1 1574 (897-2893)	1454 ± 319 1469 (708-2153)	-97 ± 417.9 0 (-1392-488)	ns	0.096	154 (28-336)
Protein, g	65 ± 21.7 61 (33-127)	67 ± 17.9 65 (41-118)	1 ± 23.6 0 (-63-55)	ns	69 ± 19.6 66 (39-127)	65 ± 14.0 65 (39-92)	-5 ± 20.9 4 (-83-25)	ns	0.38	5 (-6 -15)
Fat, g	60 ± 25.8 55 (31-142)	67 ± 27.6 62 (28-162)	7 ± 21.9 4 (-58-49)	ns	62 ± 23.9 58 (29-142)	57 ± 13.1 55 (27-82)	-5 ± 22.6 0 (-70-24)	ns	0.034	11 (1-20)
Carbohydrate, g	163 ± 48.9 160 (78-269)	166 ± 51.0 166 (79-268)	3 ± 48.3 3 (-86-113)	ns	162 ± 44.8 153 (83-278)	149 ± 47.7 141 (64-253)	-13 ± 50.0 2 (-134-69)	ns	0.17	16 (-7-40)
Fibre, g	17 ± 6.3 15 (7-34)	16 ± 5.5 15 (9-33)	-1 ± 6.7 -1 (-21-11)	ns	17 ± 6.2 18 (7-33)	17 ± 7.5 16 (7-38)	0 ± 6.0 0 (-13-12)	ns	0.53	-1 (-4 -2)
HbA1c, %	7.4 ± 0.8 7.3 (5.6-9.2)	7.4 ± 0.8 7.3 (5.2-9.01)	-0.0 ± 0.5 0.0 (-1.2-0.9)	ns	7.9 ± 1.2 8.1 (5.4- 9.8)	7.8 ± 1.1 7.9 (5.7-10.5)	-0.2 ± 0.6 0.0 (-1.3-0.7)	ns	0.98	-0.0 (-0.3-0.3)
HADS, anxiety	7.8 ± 4.3 8.0 (0-18)	6.5 ± 4.7 6.0 (0-21)	-1.3 ± 2.7 -2.0 (-5.0-4.0)	0.024	7.2 ± 4.6 7.0 (1-17)	6.4 ± 4.4 6.5 (1-21)	-0.8 ± 3.4 0.0 (-10.0-5.0)	ns	0.63	-0.4 (-2.0-2.0)
HADS, depression	6.3 ± 4.9 4.5 (0-17)	5.6 ± 5.4 3.5 (0-21)	-0.6 ± 2.5 -0.5 (-8.0-4.0)	ns	6.6 ± 4.6 5.0 (1-19)	5.9 ± 4.8 5.0 (0-21)	-0.7 ± 4.2 0.0 (-12.0-8.0)	ns	0.99	-0.0 (-1.8-1.8)
SF-36: PCS	39.0 ± 11.4 39.2 (7.4-55.3)	40.2 ± 10.9 39.4 (19.4-59.5)	1.2 ± 8.0 0.9 (-18.3-20.3)	ns	37.6 ± 12.0 37.4 (13.1-55.3)	35.5 ± 12.8 32.9 (8.7-55.5)	-2.1 ± 9.2 -1.2 (-21.9-16.7)	ns	0.11	3.6 (-0.8-8.0)
SF-36: MCS	41.5 ± 15.9 39.9 (10.5-71.0)	43.8 ± 15.2 47.3 (9.7-62.2)	2.3 ± 15.0 2.8 (-50.4-26.6)	ns	42.1 ± 13.3 46.8 (7.5-56.6)	41.5 ± 14.8 42.0 (8.9-66.1)	-0.5 ± 10.9 0.6 (-32.0-20.4	ns	0.48	2.6(-3.8-9.0)

BMI=Body Mass Index, HbA1c = glycosylated haemoglobin, DCCT standard, HADS= Hospital Anxiety and Depression Scale,
PAGI-SYM=Patient assessment of upper gastrointestinal symptom severity index, SF36=The Short Form (SF36) Health Status Survey,
SF-36: PCS=Physical health, SF36:MCS=Mental health
R^{120}=Retention of the radioactivity in the stomach 120 minutes after meal intake (gastric scintigraphy)
R^{180}=Retention of the radioactivity in the stomach 180 minutes after meal intake (gastric scintigraphy)
GFR = glomerular filtration rate

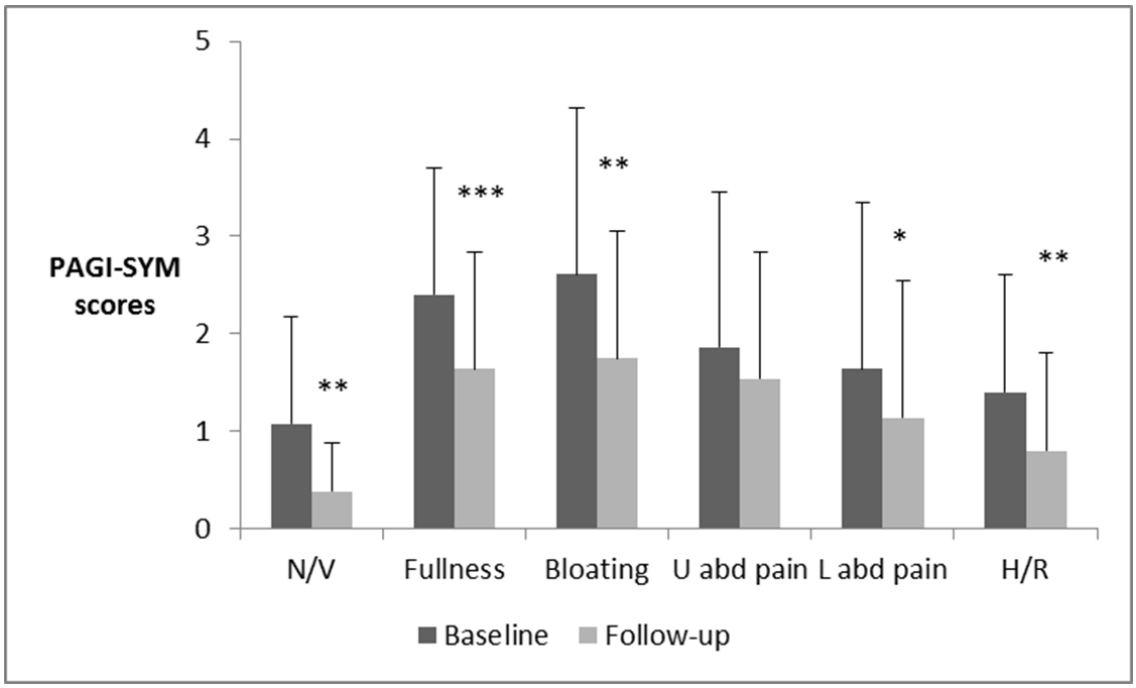


Figure 9A. GI symptom severity, as measured with PAGI-SYM, at baseline and after the dietary treatment period (20 weeks) in the group who received advice to eat the intervention diet (small particle size).
PAGI-SYM domains: N/V = nausea/vomiting; Fullness = fullness/early satiety;
U / L abd pain = Upper / Lower Abdominal Pain; H/R = Heartburn/regurgitation.
* p<0.05, ** p<0.01, *** p<0.001 vs. baseline.

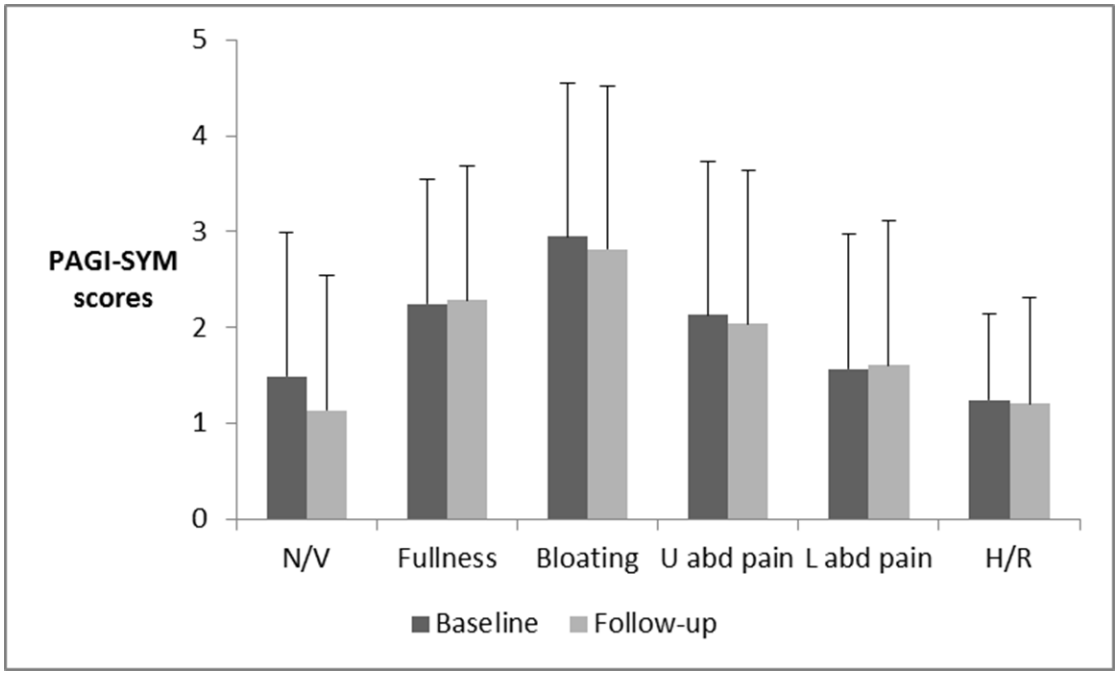
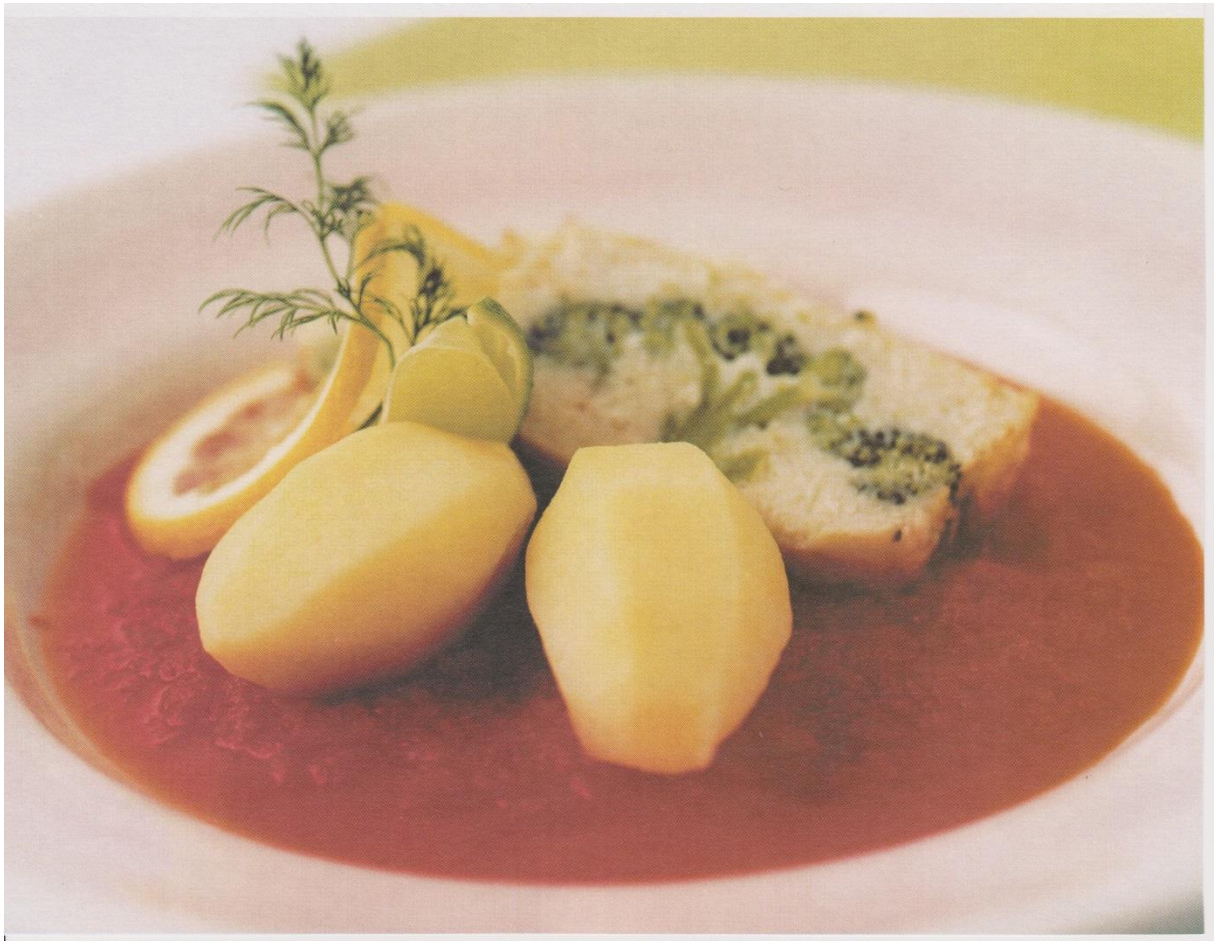


Figure 9B. Figure 2. GI symptom severity, as measured with PAGI-SYM, at baseline and after the dietary treatment period (20 weeks) in the group who were instructed to follow the control diet (B).
PAGI-SYM domains: N/V = nausea/vomiting; Fullness = fullness/early satiety;
U / L abd pain = Upper / Lower Abdominal Pain; H/R = Heartburn/regurgitation.
* p<0.05, ** p<0.01, *** p<0.001 vs. baseline.

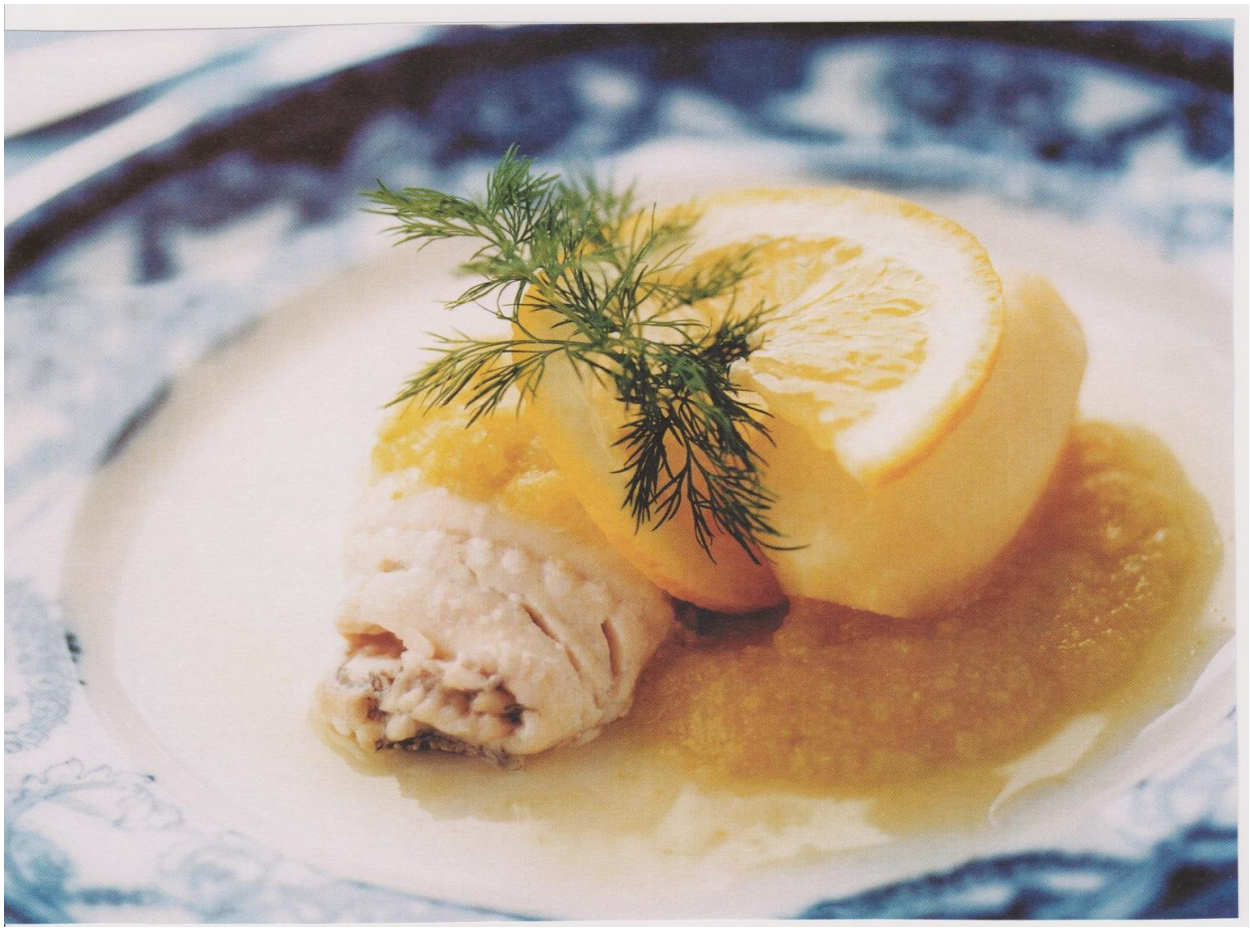


Supplementary picture 4. Fish pâté, boiled potatoes and pepper sauce.

Supplementary picture 5. Meatloaf and mango sauce.

Supplementary picture 6. Vegetable pâté

Supplementary picture 7. Yellow chicken soup.



Supplementary picture 8. Steamed plaice, boiled potatoes, lemon- and squash sauce.

Supplementary picture 9. Mixed peach and strawberry.

Supplementary picture 10. Fruit salad

Supplementary picture 11. Ice cream and raspberry sorbet

General discussion

In the present thesis, I have demonstrated that gastric emptying of ROM and plasma glucose response after a standardized test meal can add information in the clinical management of DM patients, but cannot replace the current gold standard to diagnose gastroparesis, gastric scintigraphy. Moreover, a meal with SP increases the gastric emptying rate and reduces the postprandial blood glucose dip in Type 1 DM subjects with gastroparesis. In line with this, dietary treatment with SP significantly improves the key symptoms of gastroparesis in patients with DM.

In **Paper I**, we noted a moderate association between gastric emptying of digestible solids, measured using gastric scintigraphy, and gastric emptying of indigestible solids, measured using ROM. The difference in results between the methods could be due in part to the fact that the methods do not measure exactly the same variables. However, based on our results it seems as if gastric emptying with ROM, using fluoroscopy could be used as a screening method for gastroparesis. If the measurement shows delayed emptying at 6 h, this is probably true. If the gastric emptying is normal but there is still a clinical suspicion question of gastroparesis, further investigation is required. The specificity and positive predictive value of the method were 97%, if ROM emptying at 6 h was used, but both the sensitivity and negative predictive value were clearly lower. In another study, emptying of ROM seemed to be very potent in predicting gastroparesis (135). The discrepancy between our study and Feldman et al. may be partly be due to different patient populations and potentially also different size of the markers.
The correlation between GI symptoms and the gastric emptying rate was strongest for nausea/vomiting and postprandial fullness/early satiety when using a scintigraphic method, but there was no significant correlation with the fluoroscopy method in **Paper I**.

Many factors are involved in gastric emptying, such as blood glucose level and a number of dietary factors. It is now well known that hyperglycaemia decreases gastric emptying. It is therefore important to have as normal plasma glucose as possible before and during the investigation. Chang et al. suggest a plasma glucose level of 4-10 mmol/L at the beginning of the test (85), which we used in our studies. It seems to be of great importance that departments measuring gastric scintigraphic emptying should have

equipment to measure plasma glucose, and as far as possible normalize the glucose levels before commencing and during the test. A blood glucose level of 8 mmol/L decreases gastric emptying compared to 4 mmol/L (53) although there is an increase in the gastric emptying at 2 mmol/L (54). Hyperglycaemia is also known to inhibit the antral component of MMC phase III (90). Moreover, Jones et al. found that hyperglycaemia masks the medical effect of prokinetics (153). Based on these results we followed glucose levels carefully in our studies, and when needed normalized the levels in order to avoid the confounding effect of glucose levels on gastric emptying as far as possible.

In **Paper II** the plasma glucose response was blunted in subjects with gastroparesis compared with subjects without gastroparesis. However, the GI symptom severity during the preceding two weeks was an even stronger predictor for gastroparesis than the plasma glucose response.

In the literature, different correlations are presented between GI symptoms and gastric emptying and/or a diagnosis of gastroparesis (34, 36, 38, 55, 68, 154). In **Papers I and II**, the correlation between these parameters was different. This could probably be caused by the inclusion criteria, since all subjects in **Paper I** had significant upper GI symptoms, but in **Paper II** also subjects with milder GI symptoms were included. Moreover, the proportion of subjects with normal gastric emptying was higher in **Paper II than in Paper I,** which could have an impact on the association between gastric emptying rate and GI symptom severity. Plasma glucose level before the test investigation the diagnosis was the same in both studies. Therefore the effect on gastric emptying and the diagnosis by the plasma glucose level was most likely the same in both studies. Moreover, Byzter et al. found in DM subjects in general that they had more severe GI symptoms when there was poor metabolic control (43). In **Paper I and II** HbA1c was not significantly different between the groups , ruling out differences in metabolic control as an explanation behind the discrepancy.

In **Paper III,** the gastric emptying after SP meal was not significantly different in DM type 1 subjects with gastroparesis than in healthy subjects. However, after LP meal the gastric emptying rate was slower in subjects with gastroparesis than in healthy subjects. The IAUC of the plasma glucose response after SP meal in gastroparetic subjects was also significantly larger than after LP meal. These findings strengthened my

hypothesis that a meal with SP is beneficial for DM patients with gastroparesis, and this diet was then further tested in Paper IV.

Up to now there has been no randomised trial of dietary interventions in gastroparesis and consequently there are no evidence-based recommendations (58). It has been advocated that the diet in diabetic gastroparesis should be low in fat and fibre (109). The test meals used in **Papers II and III** have a fat content of 31 energy per cent and 3 gram/MJ. The recommendation was 25-30 energy per cent fat and 27-30 gram fibre at the time **Paper III** was planned (155). Despite the fact that gastric emptying was more rapid after a test meal with SP in both gastroparetic subjects and in healthy controls, there was no significant difference in terms of gastric emptying rate between the groups after a meal with SP. However, gastric emptying after the LP meal was significantly slower in the patient group than in the healthy group. Both test meals were identical – only the particle size differed. The impact of different diet particle sizes ceased earlier, resulting in a significantly different gastric emptying rate (156). This means that fat and fibre content play a lesser role than particle size in gastric emptying; knowledge that we used in our controlled dietary intervention in **Paper IV**.

Fat has a different impact on gastric emptying depending on whether the fat is in a liquid or a solid meal and when the fat was ingested. When fat was ingested in a liquid meal 30 minutes before a carbohydrate-containing solid meal, the lag phase was prolonged – the gastric emptying slope did not change in healthy subjects or in subjects with DM type 2. If fat was added to a solid meal and ingested immediately, the lag phase was short and the slope was reduced (112, 113). Often it has been suggested that a liquid meal should leave the stomach easier. However, Houghton et al. found that in young, healthy subjects a fat liquid meal caused the contents to move into the distal stomach, followed by redistribution of the contents in the distal stomach and then back into the proximal stomach in healthy subjects. When gastric emptying started, the contents moved down into the distal stomach again (111). In addition, the lag phase was prolonged and the slope decreased after a fat liquid meal. Based on these observations, other factors than merely the fat content *per se* should be considered when giving dietary advice to patients with delayed gastric emptying.

It can be noted that soluble fibre in a liquid and a solid meal may also not affect the gastric emptying rate in the same way. Bianci et al. studied gastric emptying after solid meals with 5 g of added soluble fibre. There were no significant changes in gastric emptying between the meals with and without added fibre in healthy subjects (157). Leiper et al. found that osmolality had a greater impact on gastric emptying than the viscosity of the meal (158). Insoluble fibre sometimes contributes to bezoars (115). It is therefore logical to decrease the fibre content in the diet for DM patients with gastroparesis. If the fibre is SP it may not form bezoars as diet with SP leaves the stomach more easily. On the other hand, there are many gastroparetic patients who suffer from constipation and a diet low in fibre could worsen the constipation (25).

Other factors that have an impact on gastric emptying are the temperature, drinks with the meal and the volume of the meal. A meal with a temperature of <4ºC and >50ºC slows down gastric emptying (159). When a DM subject needs glucose due to hypoglycaemia, the usual advice is to take water with the glucose tablets. It is important that the drink is not too cold. The drink must then be warmed by the stomach before moving from the stomach into the duodenum. This will delay glucose absorption into the blood. The test meals in **Papers II and III** were served without a drink due to the fact that Thorsdottir et al. confirmed increased gastric emptying when 300 ml water was added to a meal compared to without (152). It has also been confirmed that a large meal volume delays gastric emptying in healthy subjects (160). Moreover, the meal size may be a problem specifically for patients with DM and neuropathy, as these patients have impaired relaxation of the proximal stomach after an ingested meal and this correlates with bloating (77). Therefore, taking the meal size into consideration when giving dietary advice to DM patients seems to be of importance.

When assessing gastric emptying by means of scintigraphy, the lag phase and T_{50} and T_{120} (R_{120}) are commonly used measures. When assessing insulin-treated gastroparetic patients, the duration of the insulin profile must be taken into account. Otherwise, reading the slope will be incorrect and the lag phase needs to be taken into account. The dietary intake also needs to match gastric emptying and plasma glucose with the specific profile of the insulin duration.

The aim behind dietary treatment of gastroparesis is to optimise metabolic control, decrease GI symptoms, improve nutritional intake and quality of life. In our study in **Paper IV**, a diet with SP improved GI symptoms, but no clear effects on metabolic control or quality of life were noted.

In **Paper IV** HbA1c were not changed in any group. This could probably depend on 20 weeks being a too short study period, as HbA1c is a mirror of metabolic control for up to 12 weeks (141). On the other hand, the change is a process that takes place over time – and the patient needs time to learn the new diet. Studies with longer duration are needed in order to evaluate if diet with SP can affect the metabolic control in the long run.

All upper GI symptoms except upper abdominal pain were improved in the intervention group, but not in the control group. There was a small increase in fat intake, but this did not result in gain in body weight, probably because of the short study period. It is interesting to note that in the intervention group, the GI symptoms improved, but not in the control group, even though they had not increased their fat intake. No other nutritional intake changes were noted in any of the groups. It may again depend on the short study period. GI symptoms in DM subjects generally is associated with psychological distress (161) and decreased quality of life (62). The GI symptoms, such as nausea, vomiting, bloating, abdominal pain, fullness, early satiety, diarrhoea and faecal incontinence, are disabling for the patient. The patient cannot eat all types of food and do not take part in any social life. The patients never know when hypoglycaemia could occur, thus further contributing to anxiety and depression. Impaired quality of life is also associated with GI symptoms (66). In our study in **Paper IV**, a decrease in severity of anxiety was only seen in the intervention group from baseline to the end of study. This result is in line with the results in earlier studies (162). However, the severity of depression did not was no change, neither within nor between the groups. Probably a longer study period than 20 weeks is needed, since the subjects need time to learn to change to SP diet and time to affect the depression. The quality of life assessed by SF-36 (mental and physical component) was not changed in any group. This may also depend on the short study period, as the effect on quality of life probably comes after the full effect of the dietary intervention. However, it also depends on other diabetic complications. The subjects in Paper IV had

several other severe diabetic complications, which has an impact on quality of life, as well as on psychological symptoms. To summarize, further studies with larger samples and longer study periods needs to evaluate the full dietary effect of SP diet on metabolic control, nutritional intake, body weight, psychological well-being and quality of life.

The main cornerstone in our dietary treatment of insulin-treated DM gastroparesis was the particle size. In **Paper III**, it was shown that a diet with SP produces a more rapid gastric emptying rate. An indicator showing that the treatment works, is when the patient's hunger and appetite has returned (163). The MMC phase III in the stomach is of importance for gastric emptying of food with LP (164). Samsom et al confirmed in a small sample that MMC phase III was reduced in gastroparetic patients and in 50% of the subjects this motility phase did not occur at all (78). In a recent review it was concluded that the absence of MMC phase III has been associated with gastroparesis (151) and consequently it is important that the patient does not eat a diet with LP. To be successful with the treatment it is important to follow the intervention diet for every meal since a meal with LP could remain in the stomach for a long time depending on the degree of impairment of the patient's gastric emptying. It is also important to consider the motor function of the entire GI tract when giving dietary advice to patients with DM and gastroparesis, as many of these patients not only have upper GI symptoms, but also constipation, diarrhoea and faecal incontinence.

Moreover, the carbohydrate content and the glycaemic index of the meal should be taken into account when giving dietary advice to patients with DM and gastroparesis. A solid meal with a high glycaemic index does not result in a high plasma glucose response because of delayed gastric emptying in the DM gastroparetic subject. However, if gastric emptying of a liquid meal or drinks are normal, the carbohydrates have shorter gastric emptying time than solid meals and therefore yields a high glucose response, which is negative, as hyperglycaemia further delays gastric emptying (53). This is important considerations when dietary advice is given to this patient group.

General conclusions

1. A gastric emptying test with ROM is a widely available screening method to detect delayed gastric emptying in patients with diabetes, where a positive result seems reliable. However, a normal ROM test does not exclude delayed gastric emptying, and if the clinical suspicion of gastroparesis remains, scintigraphy should be performed.

2. Patients with diabetic gastroparesis have a blunted postprandial plasma glucose response. Combining this information with the presence of GI symptoms can help clinicians identify diabetic patients with gastroparesis.

3. A SP diet increases gastric emptying and the late postprandial glycaemic response in DM type 1 subjects with gastroparesis.

4. Dietary treatment with a SP diet reduces the GI symptoms in insulin treated DM subjects with gastroparesis.

Summary in Swedish

Gastropares (=långsam magsäckstömning) är en ofta förbisedd diabeteskomplikation. Prevalensen är osäker, men det har bedömts att 30-40% av alla patienter med diabetes mellitus (DM) typ 1 har gastropares. Liknande prevalens har setts vid DM typ 2. Gastropares utgör för den enskilde patienten ett stort lidande, i form av bristande metabol kontroll, mag-tarm (GI) symtom och med näringsbrister som följd. Den tillförlitligaste undersökningen för att påvisa gastropares är scintigrafi, men tillgängligheten är dålig. Behandlingen av gastropares syftar till att förbättra metabola kontrollen, minska GI symtom och minska eller förebygga näringsbrister. Idag finns ingen randomiserad studie för hur kostbehandlingen vid gastropares ska vara utformad.
Denna avhandling omfattar utvärdering av diagnosmetoder och kostbehandling vid gastropares.

Arbete I. En alternativ utredningsmetod är att via röntgen följa röntgentäta markörers (ROM) tömning från magsäcken. Röntgen finns vid alla sjukhus Magsäckstömningen mätt med tömning av ROM med hjälp av röntgen jämfördes med magsäckstömningen av en isotopmärkt måltid via scintigrafi samma dag hos 115 patienter med DM Jämförelsen visade att om ROM testet visade långsam magsäckstömning, så var det gastropares, men om undersökningen visade normal tömning, så kunde gastropares inte uteslutas. Vid kvarstående misstanke om gastropares måste patienten utredas vidare. De GI symtom patienterna rapporterade var associerade med magsäckstömningen mätt med scintigrafi, men inte med ROM testet.

Arbete II. En alternativ screeningmetod för gastropares studerades. Svårigheten av GI symtom kartlades under 2 veckor, därefter fick patienten äta en testmåltid. En ur diabetes synpunkt optimal måltid utgjorde testmåltiden. Plasmaglukos mättes vid ätstart av testmåltiden och sedan med jämna intervall under 3 timmar. Svårighetsgraden av GI symtomen korrelerade väl med patientens tidigare påvisade magsäckstömning, medan blodsockersvaret efter testmåltiden var en något svagare prediktor för förekomsten av gastropares.

Arbete III. Om matens partikelstorlek har ett samband med magsäckstömningen och blodsockersvaret studerades hos diabetespatienter med gastropares och en frisk kontrollgrupp. Samma

livsmedel och i samma mängder tillagades till två måltider med liten respektive stor partikelstorlek. Magsäckstömningen mättes med scintigrafi. Blodsocker togs inför undersökningen och under 3 timmar. Magsäckstömningen av måltid med stor partikelstorlek var mycket långsammare än måltiden med liten partikelstorlek hos bägge grupperna. Magsäckstömningen av måltiden med liten partikelstorlek tömdes lika fort hos patienterna som hos den friska kontrollgruppen. Blodsockerfallet var mindre och gick fortare över efter måltid i liten partikelstorlek i patientgruppen.

Arbete IV. Vi randomiserade 56 patienter med insulinbehandlad DM och gastropares till kostbehandling med diabeteskost (kontrollgrupp) eller en försökskost med mat i liten partikelstorlek (försöksgrupp). Studien pågick under 20 veckor. Vid 7 besök instruerades patienterna om den kost som patienten blivit randomiserad till. Vid studiens inkludering och vid avslut av studien studerades: GI symtom, näringsintag och blodsockerinställning (HbA1c). I gruppen som åt kost med liten partikelstorlek hade GI symtomen förbättrats signifikant, vilket inte var fallet i kontrollgruppen. Fettintaget hade ökat marginellt, men statistiskt säkerhetsställt i försöksgruppen, men inte i kontrollgruppen. Metabola kontrollen hade inte ändrats i någon grupp.

Denna avhandling vill förbättra utredningen, så att fler DM patienter med gastropers kan bli tidigare diagnostiserade genom att använda alternativa och mer tillgängliga diagnosmetoder som komplement till scintigrafi. Studierna visar också att aktiv kostbehandling med mat med liten partikelstorlek vid DM och gastropares minskar intensiteten av GI symtom och ger mindre blodsockersvängning efter måltid.

Future perspective

Even though the studies in this thesis have expanded the knowledge about patients with DM and gastroparesis, they also reveal a need for more studies regarding treatment options and diagnostic methods for patients with DM and gastroparesis:

Regarding diagnostic methods, a larger study assessing the clinical value of measuring gastric emptying with the ROM method in an unselected DM population would be useful.

Moreover, a study measuring the correlation between gastric emptying assessed by scintigraphy and postprandial glucose response after a test meal at noon after a standard breakfast and a snack in the morning is another study that might yield clinically useful results.

Also, further evaluation of the usefulness of GI symptom assessment in combination with assessment of the postprandial glucose response in defining gastroparetic patients in clinical practice in large, unselected patient groups is needed.

Further investigations are also required to study the impact on the outcome of gastric emptying assessment depending on the composition of the most recent meals before the fasting measurement of gastric emptying.

Our very promising treatment results in Paper IV need to be confirmed in randomised studies with larger number of subjects, but also with a longer study period, in order to see if the small particle diet in the long run may affect glycaemic control, metabolic factors and quality of life, and not only GI symptoms, as in our study.

Furthermore, in order to spread the knowledge from this thesis regarding the importance of the particle size of the meal into clinical practice, it is imperative to train dieticians in dietary advice using SP meals and thereafter evaluate its usefulness in everyday clinical practice.

Also, as patients with DM not only complain of upper GI symptoms, but also of constipation, diarrhoea, faecal incontinence and other lower GI symptoms, dietary advice that takes all GI symptoms into account needs to be developed and tested .

The impact of treatment with an insulin pump in a randomised study with delayed bolus insulin infusion matching the gastric emptying rate is another clinical problem that needs to be studied. The same holds true for the use of the continuous glucose monitoring (CGM) technique in patients

with severe gastroparesis and recurrent, frequent hypoglycaemia and insulin coma despite dietary advice.
To summarize, even though our studies have expanded the knowledge regarding DM and gastroparesis, substantial unmet needs for these patients are still present.

Acknowledgements

I would like to thank all the patients who participated in these studies. Circumstances have sometimes been difficult, involving long, early-morning journeys to the hospital for examination. It is during these morning hours that you feel the worst! It has been a heroic effort and without your participation these studies would not have been possible. Thank you!

Magnus Simrén, my main supervisor. Thank you for believing in me and making it possible for me to complete this thesis. My sincere thanks for devoting so much time to my thesis and so much you have taught me.

Stig Attvall, my co-supervisor. Thank you for you always having faith in me. You were the first person to encourage me to prove scientifically that my intervention diet hypothesis works. Thank you for devoting so much time to my thesis and for your involvement, resulting in solutions to the various practical difficulties in these studies. You made it much easier for me to determine patient requirements. Thank you!

Hasse Abrahamsson, my co-author. Thank you for your trust in me and my hypothesis and for introducing me to Magnus Simrén. Thank you also for all the discussions we have had over the years and for sharing your enormous knowledge in GI motility.

Håkan Grundin, my co-author. Thank you for your good co-operation and pleasant company during in all the studies we made together and for all the coffee and snacks you kindly offered me.

Mats Isaksson, my co-author. Thank you for your fruitful co-operation.

Stine Störsrud, my co-author. Thank you for your involvement in the study and your excellent co-operation during the study.

Christina Brock, Asbjörn M Drewes, Per-Ove Stotzer, Henrik Andersson, Håkan Mattsson, Magne Alpsten and Anhild Larsson. Thank you for your good co-operation.

I would like to express my gratitude to Ulf Smith for having confidence in me and convincing me that my skills were sufficient for a thesis.

Marianne Hagman, head nurse at the internal medicine outpatient clinic. Thank you for all your support during this work.

My colleagues and friends in the diabetes team: Veronica Broström, Ingegerd Olofson, Linda Schiller, Agneta Lantz, Lennart Sternemalm, Ingela Kristensson, Karin Granhage, Gun Näslund, Madeleine Berntsson, Jeanette Eriksson-Ljungström, Thord Thierfelt, Marie Mattsson, Lars-Olof Ohlsson, Christian Wesslau, Katarina Eeg-Olofsson, Björn Eliasson, Soffia Gudbjörnsdottir, Gerhard Brohall, Tom William-Olsson, Madeleine Sandquist, Maria Svensson, Christel Hero, Peter Jacobsson, Per-Anders Jansson, and Anne-Marie Hansen. Thank you for your good co-operation, for believing in me and for always supporting me.

The staff at the GI Laboratory, Anette Lind, Gisela Ringström, Pernilla Jerlstad, Jenny Lövdahl, Gunilla Nässlin, Len Jaremo and Christina Pihlquist. Thank you for our excellent team work during the surveys.

Thanks to Lena Hulthén, Ewa Silander, Christina Hellerud, Lena Gripeteg, Janet Leksell, Mette Axelsen and Maria Magnusson, for sharing your knowledge, for encouraging me to do research and for being my friends.

Sincere thanks to my friends Ingrid Jacobsson, Karin Bachelard, Mimmi Rhodin, Kerstin Terning, Lena Abrahamsson, Ulla Mauritzson, Ingrid Torehov and Eva Hessel for supporting me during this thesis.

Ingrid Larsson and Helen Forslund-Bertéus. Thank you for our close and enjoyable discussions about work and research.

Mattias Molin and Nils-Gunnar Persson, Statistical Consulting Group – thank you for your excellent statistical support.

Most of all my family – Björn, my beloved daughter Cecilia and Per. I am so proud of you and I love you so much. You make my life worth living and you are a reminder of what is important in life!

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Appendix 1. INTERVENTION DIET

Poorly digestible food	**Medium digestible food**	**Easily digestible food**
Vegetables and Roots		
Raw: Carrots, Turnip, Parsnips	Cooked: Carrots, Turnip, Parsnips	Mashed Turnips, Mixed Beetroot Pickled Beet
Cooked Cauliflower and Broccoli Stem,	Cooked Cauliflower Flower, Broccoli Flower	
Asparagus Stalk		Asparagus Tip
Green Pea		Green Pea Purée
Boiled Corn		(Cooked and mixed) Corn paté
Cooked Beans		(Cooked and mixed) Beans paté
Cooked Brussels Sprouts		(Cooked and mixed) Brussels sprout paté
Raw and Cooked Cabbage		
Raw, Boiled and Fried Mushrooms	Mixed Mushrooms	Mushroom Paste
Boiled and Fried Onion		Fine Mixed Onion, Dried Powdered Onion
Cooked Leeks		Mixed Leeks
Rhubarb		
Salad, Cucumber, Tomatoes,		Canned Crushed Tomatoes, Tomato Paste
Pepper	Pepper without Skin	Mixed Pepper
Avocado		Mashed Avocado

Poorly digestible food	Medium digestible food	Easily digestible food
Fruit and Berry		
Fresh Fruit	**Cooked and Canned Fruit or Berry**	**Puree of Fruit or Berry**
Skin and membrane of Citrus:		
Orange, Clementine, Grapefruit, Pineapple	Ripe Pears without Skin	Ripe Pears without Skin, Canned Peach
	Raspberries, Strawberries	Gooseberries
Blueberries, Currant, and Lingo Berries		Mixed: Blueberries, Currant and Lingo Berries
Blackberry, Cloudberries		
Green and Green-Yellow Banana	Yellow Banana	Yellow-Brown Banana
Netted Melon	Kiwi, Soft Gala Melon	Mixed Kiwi, Water Melon
	Mango, Papaya	
Nuts and Almonds		Flour of Nuts and Almonds
Potato		
Fried Potatoes, French Potatoes	Boiled Potatoes, Baked Potatoes	Mashed Potatoes, Pressed Potatoes, Creamed Potatoes
Pasta and Rice		
Pasta		
Parboiled Rice and Brown Rice, Non-Parboiled Rice Bulgur, Couscous Porridge		

Poorly digestible food	Medium digestible food	Easily digestible food
Bread		
White Fresh Bread	Wholegrain Cereal Flour Bread	Brown crisp
Bread with Seeds and Whole Grains	Bread Baked on Coarse Flour	Bread Baked on Whole Meal Flour, Rye Crisp, Rusks
Cheese		
Fat Cheese, Ripened Cheese	Cottage Cheese	Processed Cheese, Spreadable cheese, Quark
Eggs		
Hard-Boiled Eggs, Soft Boiled Eggs		Mashed Boiled Eggs, French Omelet
Pancakes		
Scrambled Eggs Made in Frying Pan	Scrambled Eggs Made in Pot	Baked Omelet Swedish Style, Baked Egg
Butter Pudding		
Meat		
Whole Meat	Minced Meat Dishes	Mixed Minced Dishes, Sausage
	Jellied Veal	
	Extra-thin Slices of Ham	
Fish and Seafood		
Cured Salmon, Smoked Salmon	Baked Salmon	Baked Flatfish, Boiled Fish Loaf Dishes, Fish Pudding

Poorly digestible food	Medium digestible food	Easily digestible food
Raw Spiced Salmon	Baked Mackerel Baked Cod Fish	Fish Soufflé, Fish Balls, Fish Pate, Fish gratin Herring terrine,
Shrimp, Crab, Clams, Tails		Mixed Shrimp, Crab, Clams, Tails

Cooking Methods		
Raw, Wok	Cooked, Canned	Puree, Mixed, Pate, Timbale, Sauces
Fried in a Pan, Deep-Fried, Wok	Roasted, Baked	Cooked
Coating with Egg and Breadcrumbs,		
Coating with Breadcrumbs		
Fat Cooking Methods		Lean Cooking Methods

Appendix 2. CONTROL DIET

Dietary treatment

Beverages

Free intake of beverages containing < 0.5 g carbohydrates/ 100 ml ready to drink beverages

Preparations to choose

Raw or lightly cooked vegetables
Fresh fruit and berries

Foods providing good metabolic control:

Bread made of whole grain and whole grain flour.
Rice and pasta rather than potatoes

Potatoes are allowed only in combination with raw or light cooked vegetables

Pasta and rice with long cooking rather than with short cooking time

Combination of food items to improve glycemic index
Legumes

Food items to avoid

Mashed potatoes and mashed turnips
Other mashed or mixed foods

Breads made of flour without grains and/or sourdough

Fruit or berry compote or cream

Canned vegetables

Porridge, corn flakes and gruel

Smooth soup

Sweet drinks

Appendix 3

PAGI-SYM

(Swedish version)

Detta frågeformulär handlar om hur svåra de symtom är som du eventuellt har i samband med dina mag-tarmproblem. Det finns inga riktiga eller felaktiga svar. Var snäll och svara på varje fråga så noggrant som möjligt.

Vill du för varje symtom *ringa in den siffra* som bäst beskriver hur *svårt* symtomet var under de senaste 2 veckorna. Om du inte haft symtomet, ringa in siffran 0. Om symtomet var mycket milt, ringa in siffran 1. Om symtomet varit milt, ringa in siffran 2. Om det var måttligt, ringa in siffran 3. Om det var svårt, ringa in siffran 4. Om det var mycket svårt, ringa in siffran 5. Se till att du besvarar alla frågor.

Ange hur svåra följande symtom har varit under de senaste 2 veckorna.

		Ej haft	Mycket mild	Mild	Måttlig	Svår	Mycket svår
1.	Illamående (kväljningskänslor som om du skulle kräkas)	0	1	2	3	4	5
2.	Ulkningar (kväljningar som om du skulle kräkas men inget kommer upp)	0	1	2	3	4	5
3.	Kräkningar	0	1	2	3	4	5
4.	Mättnadskänsla	0	1	2	3	4	5
5.	Oförmåga att äta upp ett normalt mål mat	0	1	2	3	4	5
6.	En känsla av att vara övermätt efter måltider	0	1	2	3	4	5
7.	Brist på aptit	0	1	2	3	4	5
8.	En känsla av uppkördhet (att du behövde lossa på dina kläder)	0	1	2	3	4	5
9.	Magen eller buken är synbart större	0	1	2	3	4	5
10.	Smärta i övre delen av buken (ovanför naveln)	0	1	2	3	4	5

Ange hur svåra följande symtom har varit under de senaste 2 veckorna.

		Ej haft	Mycket mild	Mild	Måttlig	Svår	Mycket svår
11.	Obehagskänsla i övre delen av buken (ovanför naveln)	0	1	2	3	4	5
12.	Smärta i nedre delen av buken (nedanför naveln)	0	1	2	3	4	5
13.	Obehagskänsla i nedre delen av buken (under naveln)	0	1	2	3	4	5
14.	Halsbränna (brännande smärta i bröstet eller halsen) under dagen	0	1	2	3	4	5
15.	Halsbränna (brännande känsla i bröstet eller halsen) när du ligger ner	0	1	2	3	4	5
16.	En känsla av obehag i bröstet under dagen	0	1	2	3	4	5
17.	En känsla av obehag i bröstet under natten (under sömnen)	0	1	2	3	4	5
18.	Uppstötningar eller reflux (vätska från magen som kommer upp i halsen) under dagen	0	1	2	3	4	5
19.	Uppstötningar eller reflux (vätska från magen som kommer upp i halsen) när du ligger ner	0	1	2	3	4	5
20.	Bitter, syrlig eller sur smak i munnen	0	1	2	3	4	5

Appendix 4

Markera det alternativ som stämmer bäst för Dig.

Tänk inte för mycket, utan markera det alternativ som spontant känns rätt!

- Jag känner mig spänd eller uppgiven:
  - Ja, nästan hela tiden
  - En stor del av tiden
  - Av och till, tillfälligt
  - Inte alls

- Jag finner nöje i saker som jag brukat ha glädje av:
  - Ja, absolut
  - Inte så mycket
  - Bara lite
  - Inte alls

- Jag får en känsla som om något skrämmande är på väg att hända:
  - Ja, absolut och att det är något förfärligt som ska hända
  - Ja, men det som ska hända är inte lika hemskt
  - Lite, men känslan skrämmer mig inte
  - Har inte alls någon sådan känsla

- Jag kan skratta och se det roliga i situationer:
  - Så mycket som jag alltid gjort
  - Inte lika mycket nu
  - Inte alls så mycket nu
  - Inte alls

- Skrämmande tankar kommer över mig:
  - En stor del av tiden
  - Ganska ofta
  - Tillfälligt av och till
  - Bara i undantagsfall

- Jag känner mig glad:
  - Inte alls
  - Inte ofta
  - Ibland
  - Mest hela tiden

- Jag kan sitta rofylld och känna avslappning:
  - Alltid
  - Vanligen
  - Sällan
  - Inte alls

- Jag känns som om jag slagit ner på takten:
  - Nästan hela tiden
  - Mycket ofta
  - Ibland
  - Inte alls

- Jag får en känsla av fjärilar i magen:
  - Aldrig
  - Tillfälligt
  - Inte ofta
  - Mycket ofta

- Jag har tappat intresset för mitt utseende:
  - Ja, absolut
  - Jag tänker sällan på mitt utseende
  - Jag tänker ganska ofta på mitt utseende
  - Jag tänker lika mycket på mitt utseende nu som jag gjort tidigare

- Jag känner mig rastlös, som om jag skulle behöva gå iväg:
  - Alltid
  - Ganska ofta
  - Inte ofta
  - Inte alls

- Jag ser på framtiden med tillförsikt
  - Lika mycket som jag gjorde förr
  - Mindre än vad jag gjorde tidigare
  - Absolut mindre än vad jag brukat göra
  - Inte alls

- Jag får plötsliga panikkänslor:
  - Ja, mycket ofta
  - Ganska ofta
  - Inte särskilt ofta
  - Inte alls

- Jag kan njuta av att läsa en bra bok, lyssna på radio eller se på TV
  - Ofta
  - Ibland
  - Inte ofta
  - Sällan

Kontrollera att du svarat på alla frågor

Appendix 5

HÄLSOENKÄT

INSTRUKTION: Detta formulär innehåller frågor om hur Du ser på Din hälsa. Informationen skall hjälpa till att följa hur Du mår och fungerar i Ditt dagliga liv.

Besvara frågorna genom att sätta en ring runt den siffra Du tycker stammer bast in på Dig. Om Du ar osäker, ringa ändå in den siffra som känns riktigast.

1. I allmänhet, skulle Du vilja saga att Din hälsa ar:

(Satt en ring runt en siffra)

Utmärkt 1

Mycket god 2

God 3

Någorlunda 4

Dålig ..... S

2. Jämfört med för ett år sedan, hur skulle Du vilja bedöma Ditt allmänna hälsotillstånd nu?

(Satt en ring runt en siffra)

Mycket bättre nu an för ett år sedan 1

Något bättre nu an för ett år sedan 2

Ungefar detsamma 3

Något sämre nu an för ett år sedan 4

Mycket sämre nu an för ett år sedan 5

3. De följande frågorna handlar om aktiviteter som Du kan tänkas utföra under en vanlig dag. Är Du på grund av Ditt hälsotillstånd begränsad i dessa aktiviteter nu? Om så är fallet, hur mycket?

(Sätt en ring runt en siffra på varje rad)

	Ja, mycket begränsad	Ja, lite begränsad	Nej, inte alls begränsad
a. Ansträngande aktiviteter, som att springa, lyfta tunga saker, delta i ansträngande sporter	1	2	3
b. Måttligt ansträngande aktiviteter, som att flytta ett bord, dammsuga, skogspromenader eller trädgårdsarbete	1	2	3
c. Lyfta eller bära matkassar	1	2	3
d. Gå uppför flera trappor	1	2	3
e. Gå uppför en trappa	1	2	3
f. Böja Dig eller gå ner på knä	1	2	3
g. Gå mer än två kilometer	1	2	3
h. Gå några hundra meter	1	2	3
i. Gå hundra meter	1	2	3
j. Bada eller klä på Dig	1	2	3

4. Under de senaste fyra veckorna, har Du haft något av följande problem i Ditt arbete eller med andra regelbundna dagliga aktiviteter som en följd av Ditt kroppsliga hälsotillstånd?

(Sätt en ring runt en siffra på varje rad)

	JA	NEJ
a. Skurit ned den tid Du normalt ägnat åt arbete eller andra aktiviteter	1	2
b. Uträttat mindre än du skulle önskat	1	2
c. Varit hindrad att utföra vissa arbetsuppgifter eller andra aktiv eter	1	2
d. Haft svårigheter att utföra Ditt arbete eller andra aktiviteter (t.ex. aenom att det krävde extra anstränaninal	1	2

5. Under de senaste fyra veckorna. har Du haft något av följande problem i Ditt arbete eller med andra regelbundna dagliga aktiviteter som en följd av känslomässiga problem (som t.ex. nedstämdhet eller ängslan)?

(Sätt en ring runt en siffra på varje rad)

	JA	NEJ
a. Skurit ned den **tid** Du normalt ägnat åt arbete eller andra aktiviteter	1	2
b. **Uträttat mindre** an Du skulle önskat	1	2
c. Inte utfört arbete eller andra aktiviteter så **noggrant** som vanligt	1	2

6. Under de senaste fyra veckorna, i vilken utstrackning har Ditt kroppsliga halsatillstånd eller Dina känslomässiga problem stort Ditt vanliga umgänge med anhönga, vänner, gramar eller andra?

(Sätt en ring runt en siffra)

Inte alls 1

Lite 2

Måttligt 3

Mycket 4

Väldigtmycket 5

7. Hur mycket värk eller smärta har Du haft under de senaste fyra veckorna?

(Sätt en ring runt en siffra)

Ingen 1

Mycket lätt 2

Lått 3

Måttlig 4

Svår 5

Mycket svår 6

8. Under de senaste fyra veckorna. hur mycket har varken eller smärtan stört Ditt normala arbete (innefattar både arbete utanför hemmet och hushållssysslor)?

(Sätt en ring runt en siffra)

Inte alls 1

Lite 2

Måttligt 3

Mycket 4

Väldigt mycket 5

9. Frågorna här handlar om hur Du känner Dig och hur Du haft det under de senaste fyra veckorna. Ange för varje fråga det svarsalternativ som bast beskriver hur Du känt Dig. Hur stor delav tidenunder de senaste fyra veckorna.

(Sätt en ring runt en siffra på varje rad)

	Hela Tiden	Största delen av tiden	En hel delav tiden	En del av tiden	Lite av tiden	Inget av tiden
a. Har Du känt Dig riktigt pigg och stark?	1	2	3	4	5	6
b. Har Du känt Dig mycket nervös?	1	2	3	4	5	6
c. Har Du känt Dig så nedstämd att ingenting kunnat muntra upp Dig?	1	2	3	4	5	6
d. Har Du känt Dig lugn och harmonisk?	1	2	3	4	5	6
e. Har Du varit full av energi?	1	2	3	4	5	6
f. Har Du känt Dig dyster och ledsen?	1	2	3	4	5	6
g. Har Du känt Dig utsliten?	1	2	3	4	5	6
h. Har Du känt Dig glad och lycklig?	1	2	3	4	5	6
i. Har Du känt Dig trött?	1	2	3	4	5	6

10. Under de senaste fyra veckorna, hur stor del av tiden har Ditt kroppsliga hälsotillstånd eller Dina känslomässiga problem stört Dina möjligheter att umgås (t ex hälsa på släkt, vänner, etc.)?

(Sätt en ring runt en siffra)

Hela tiden 1

Slörsta delen av tiden 2

En delav tiden..... 3

Lite av tiden 4

Inget av liden..... 5

11. Välj det svarsalternativ som bäst beskriver hur mycket vart och ett av följande påståenden STÅMMER eller INTE STÅMMER in på Dig.

(Sätt en ring runt en siffra på varje rad)

	Stämmer precis	stämmer ganska bra	Osäker	Stämmer Inte särskilt bra	Stämmer inte alls
a. Jag verkar ha lite lättare att blisjuk än andra människor	1	2	3	4	5
b. Jag ar lika frisk som vem som helst av dem Jag känner	1	2	3	4	5
c. Jag tror min hälsa kommer att bli sämre	1	2	3	4	5
d. Min halsa ar utmärkt	1	2	3	4	5