University of Groningen

Dumping syndrome after bariatric surgery

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DOI:
[10.33612/diss.106406421](https://doi.org/10.33612/diss.106406421)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Emous, M. (2019). *Dumping syndrome after bariatric surgery*. [Thesis fully internal (DIV), University of Groningen]. Rijksuniversiteit Groningen. <https://doi.org/10.33612/diss.106406421>

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Dumping syndrome after bariatric surgery

MARLOES EMOUS

rijksuniversiteit
 groningen

Dumping syndrome after bariatric surgery

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. C. Wijmenga
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 18 december 2019 om 16.15 uur

door

Marloes Emous

geboren op 26 juli 1975
te De Bilt

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A close-up photograph of a dark, circular opening in a blue, textured surface, possibly a metal plate. A bright orange-red light or flame emanates from the opening, creating a vertical streak of light that extends downwards. The background is a deep blue with a rough, pebbled texture.

Chapter 1

Introduction and aims of thesis

OBESITY TREATMENT BY SURGERY.

Worldwide the prevalence of obesity has more than doubled since 1980 and currently 12% of adults in The Netherlands are considered to be obese ($\text{BMI} > 30 \text{ kg/m}^2$), as illustrated in figure 1.¹ The World Health Organization has defined obesity as a chronic disease because of its impact on health with related diseases and the increased risk of mortality.² Weight reduction remains the single most effective way to treat these related diseases, increase survival and improve quality of life. Of all the therapeutic options, bariatric surgery provides the best opportunity for sustainable weight loss.³ Bariatric surgery comprises several surgical procedures aimed at reducing weight. Nowadays it is primarily done by the reducing gastric volume (sleeve gastrectomy) and/or bypassing the duodenal and upper jejunal part of the small bowel by various methods, but the most popular operation is the Roux-en-Y gastric bypass.

Obesitas

% van bevolking van 20 jaar of ouder

Figure 1: Increasing prevalence of obesity in the Netherlands

Source: Central Bureau of Statistics, the Netherlands

The history of bariatric surgery has been reviewed by Faria and Dexter in two excellent recent publications.^{4,5}

The first description of bariatric surgery comes from the 10th century, where King Leon of Spain lost his throne because of his obesity, which prevented him from being able to walk, ride horseback or pick up his sword. The legendary doctor Hasdai Ibn Shraput treated his king by suturing his lips, leaving him unable to consume anything but liquids. The king lost half of his weight and regained his abilities and thereby his throne.⁶

Figure 2: Jejunio-ileal bypass

Figure 3: horizontal bypass with loop ileostomy by Mason⁵

In 1977 Rodgers treated 17 patients with jaw wiring. The first results were as good as the results of gastric bypass, but patients quickly regained weight after removal of the wires.⁷

The first documented metabolic surgery was in 1953 by Varco at the University of Minnesota (USA). It began as an observation of weight loss after extensive resection of the small bowel due to various diseases. After that a jejunio-ileal bypass (JIB) was successfully applied for the treatment of dyslipidemia and weight loss (Figure 2). Many others made adjustments but finally the JIB was not widely adopted because of complications such as severe diarrhea, bacterial overgrowth, liver failure and death.⁸ In 1966 Mason noted that patients who underwent a subtotal gastrectomy for cancer lost a considerable amount of weight and he proposed the first bariatric operation: the gastric bypass (Figure 3).⁹ The first gastric bypasses were performed with horizontal gastric transection and loop ileostomy, but because of bile reflux the operation was optimized by making a smaller pouch and a reconstruction with a Roux-en-Y loop (Figure 4).¹⁰ For decades this Roux-en-Y gastric bypass was the golden standard of bariatric surgery (Figure 4).

One of the first bariatric surgeons in the United States of America was Rutledge, who was also a trauma surgeon.¹¹ In 1997 he treated a seriously injured gunshot patient. Part of the small bowel, distal stomach, spleen and pancreas had to be removed and Rutledge secured the continuity of the gastrointestinal tract with a known Billroth II anastomosis. The day after this operation he planned to perform a Roux-en-Y gastric bypass for obesity, but he found it too demanding. To simplify the procedure, he decided to perform the same reconstruction as he had the day before, thereby developing the mini gastric bypass (Figure 5). This was a bypass with only one anastomosis and both a smaller and a longer pouch to prevent bile reflux.

Figure 4: Roux-en-Y gastric bypass⁴²

Figure 5: Mini gastric bypass⁴³

Restrictive procedures started with a Nissen-like wrap.¹² This technique first evolved to the vertical banded gastroplasty, developed in 1982 by Mason with a vertical stapler creating a pouch and a banded outlet (Figure 6).¹³ The years following saw the search for an easier technique without stapling or dissecting, and a specialized band was developed that could be placed around a little pouch of the upper stomach (Figure 8).¹⁴ With the start of laparoscopic procedures in 1992, gastric banding became extremely popular because of the short operative time, fewer perioperative complications and good short-term weight loss.

At that time most surgeons believed that malabsorptive procedures were a more efficient way to lose weight, and several modifications were made to the RYGB to achieve a more efficient malabsorptive procedure. In 1976 Scopinaro developed a gastric bypass with a horizontal partial gastrectomy and a very long alimentary limb, (Figure 8) and a common channel (where the alimentary limb, bile acids and pancreatic fluids from the biliopancreatic limb come together) of only 50 cm. However, this procedure resulted in higher mortality rates due to liver failure. Consequently the common channel was enlarged to 100 cm which was considered to be safer.¹⁵ This technique underwent further modifications because of complications such as steatorrhea, malabsorption and protein loss. The most well-known modification was the duodenal switch in which a vertical gastrectomy was performed, followed by a common channel of 100 cm (Figure 9).¹⁶

Because of the complexity of this procedure, it was proposed to split the operation into two parts: the vertical sleeve gastrectomy (Figure 10) followed, a few months later, by the second procedure: the duodenoileal bypass.¹⁷ However, after the first procedure it was observed that patients lost enough weight (i.e. excess weight loss of 60%). Both patients

Figure 6: Vertical Banded Gastroplasty by Mason¹³

and doctors refused to take the more risky second step of this procedure, and the vertical sleeve gastrectomy became a stand alone (restrictive) procedure.¹⁸

In the early years of bariatric surgery, it was believed that operations could be divided into restrictive (jaw wiring, banding, sleeve gastrectomy) and malabsorptive procedures (RYGB, Scopinaro, duodenal switch), as stated above. But in the last few years, more and more has become known about the (patho-)physiology of these procedures. It is now known that the weight loss resulting from all these procedures is due to the changed intestinal anatomy, with the diversion of nutrient flow exposing more distal parts of the intestines to undigested nutrients, while at the same time excluding the more proximal intestinal parts. Consequently, a change in the concentrations of gut hormones like Glucagon Like Peptide 1 (GLP-1), Ghrelin and PYY occurs. However, the mechanism by which bariatric surgery works is complex. After surgery, patients often experience marked changes in their behaviour. Most patients experience a reduction in appetite and feel full directly after eating. Patients often state that they enjoy healthy foods and lose many of their food cravings. Rarely do people feel deprived of food. These complex behavioural changes are partially due to alterations in several hormones (ghrelin, GIP, GLP, PYY) and neural signals produced in the GI tract that communicate with the hunger centres in the brain.¹⁹⁻²¹ In fact, some of these changes can also be imitated by GLP-1 analogues, causing weight loss, and a change in food preferences.^{22,23}

NOT ALWAYS A SUCCESS STORY: THE HISTORY OF DUMPING SYNDROME

The first papers on dumping syndrome were written at the beginning of the 20th century. Dumping syndrome was seen as a condition caused by gastric surgery²⁴ and described as a very rare syndrome which caused a series of vasomotor symptoms, together with a sense of fullness and diarrhea which diminished over time.^{19,24,25} In 1940, Glaessner described the first nine cases of patients with hypoglycemia after gastric surgery.²⁶ In 1946, Custer et al was the first to provide an overview of the historical data and to make a thorough description of early dumping.²⁷ He attributed the following symptoms to early dumping: nausea and weakness, generalized and unpleasant warmth throughout the body; a cold diaphoresis of the face, especially the forehead; cardiac palpitations, and in extreme cases explosive diarrhea. Custer describes an incidence of 5.6 % of early dumping, but made no indication he was aware that hypoglycemia could occur as a complication.

Figure 7: Gastric banding⁴²

Figure 8: Biliopancreatic diversion ("Scopinaro-bypass")⁴²

Figure 9: Duodenal switch⁴²

Figure 10: Sleeve gastrectomy⁴²

That followed in 1955 when Conn and Seltzer wrote a paper about spontaneous hypoglycemia, in which the classification and treatment of "spontaneous" hypoglycemia are discussed.²⁸ Post-operative hypoglycemia was then classified in the organic group, as a consequence of an anatomic lesion. Treatment advice consisted of a low carbohydrate and high protein diet.

In the years following these first publications more and more was written about dumping syndrome, which at that time occurred mainly after gastrectomy.²⁹⁻³³ The main focus of these papers however, was on early dumping, but most of the described tests on post-gastrectomy patients had a duration of only 120 minutes, which may have been too short to document hypoglycemia. In fact, the observations in these studies were mainly focused on volume changes, and (paradoxically), the rise in blood sugar.^{31,32} With the introduction of bariatric surgery and the decreasing numbers of patients undergoing gastrectomy for ulcer treatment, interest in early dumping was fading. Remarkably, early dumping after bariatric surgery was initially seen as a way of losing extra weight, because it was found that patients became unable to eat foods containing high fat or sugar contents without suffering discomfort associated with this condition.^{34,35}

In addition, at that time, it was thought that hypoglycemia was a result of normal insulin peak after hyperglycemia.³⁶ But some early authors had already shown that hypoglycemia only occurred after oral induced hyperglycemia, and not after intravenous induced hyperglycemia.³⁷⁻³⁹ With the discovery of gut hormones, especially incretins (intestinal hormones that promote the secretion of insulin), a new research domain was established in the late 1970s.¹⁹ For example, the role of Glucagon-Like Peptide 1 was studied revealing its role as an incretin, a satiety hormone and, most recently, as a neuroprotective peptide. Since 2000, an enormous increase in bariatric procedures has occurred with a concomitant rise in the prevalence of hypoglycemia. This has attracted worldwide research interest. A simple search in PubMed for “bariatric surgery” and “hypoglycemia”, gives 200 hits from just the last 6 years.

PERSONAL EXPERIENCE AND GENERAL CONSIDERATIONS FOR THIS THESIS

I started my bariatric surgery training in September 2011. As part of this surgical specialisation I started a research project. My attention was drawn to late dumping because we had just had a case with severe hypoglycaemia which we studied by functional imaging.⁴⁰ In the literature, the prevalence of severe hypoglycaemia after gastric bypass was reported to be very low. In fact, in 2010 the SOS study reported that less than one percent of patients needed hospitalisation for hypoglycaemia.⁴¹ However, we felt that the incidence of hypoglycaemia in our outpatient clinic was much higher, and that some patients had a severely reduced quality of life as a consequence. To explore this in more detail, we started to collect data on patients operated on between 2008 and 2011. Initially, we used this database to explore whether a single step conversion to a RYGB after failed banding was a safe procedure. We then explored the prevalence of both early and late dumping. All the patients from the 2008-2011 cohort were contacted and asked to fill in a questionnaire regarding complaints relating to early and late dumping. In addition, we also started to perform dynamic tests

to see if we could provoke hypoglycaemia after a controlled stimulus. For this we initially used the 75 g glucose challenge (a modified glucose tolerance test), but became increasingly worried when the clinical chemists at our hospital expressed their concern that almost all the patients needed to lie down and were unwell after the test. We wondered whether the mixed meal tolerance test, which is based on a more natural stimulus of carbohydrates, fat and protein would be a better test. We studied and reviewed the literature on this subject to look for accurate tools for diagnosing hyperinsulinemic hypoglycaemia.

It seemed that historically, most of the tests were done on a highly selective patient group, usually with severe complaints, which we felt was not appropriate to generate proper prevalence estimates. Therefore, we decided to perform a mixed meal tolerance test on an unselected (random) sample. We were not only able to gain more insight into prevalence estimates, but the dynamic tests were also very helpful for studying its pathophysiology. We found out that not all patients in the outpatient clinic responded well to carbohydrate restriction or acarbose. Some patients had such a severe reaction that they needed a continuous infusion with glucose to counteract the hypoglycemia. We searched the literature for all known treatments for late dumping to see which strategies could be used, and this was followed by a review of all the possible therapeutic options.

These issues of early and late dumping regarding prevalence, consequences, treatment and pathophysiology, were the main drivers for my research and formed the basis for this thesis.

THE AIM AND OUTLINE OF THIS THESIS

The general aim of this thesis is to summarize what is currently known about early and especially late dumping syndrome, and to improve our understanding of this disease, with the ultimate goal of providing additional practical information for both surgeon and patient regarding their prevalence, consequence and pathophysiology .

This thesis is divided into three parts.

Part I Tools and treatment for dumping syndrome – current state of affairs.

Chapter 2 gives an overview of the literature of the diagnostic tools used to study or to establish the presence of late dumping.

Chapter 3 describes the current knowledge of the pathophysiology of early and late dumping, and provides practical treatment advice.

Part II Improving our understanding of dumping syndrome.

Chapter 4 describes the short- to mid-term symptom prevalence of dumping syndrome after primary gastric-bypass surgery, and its impact on (health-related) quality of life when studied by means of patient questionnaires.

Chapter 5 reports on the prevalence and pathophysiology of early dumping in a random selection of patients after undergoing a mixed meal tolerance test.

Chapter 6 describes the results from chapter 5, focusing on late dumping.

Part III solving old problems, creating new ones.

Chapter 7 describes the results of conversion of failed laparoscopic adjustable gastric banding to Roux-en-Y gastric bypass, and provides information about its safety as a single-step procedure.

Chapter 8 reveals that the conversion to Roux-en-Y gastric bypass after gastric banding has consequences with regard to late dumping. In this chapter results on self-reported symptom prevalence of dumping are given on patients after sleeve gastrectomy, primary, and revisional gastric bypass surgery.

Chapter 9 provides a general discussion on the main findings in this thesis and addresses future perspectives.

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Part I

Tools and treatment for dumping syndrome –
current state of affairs

Chapter 2

Diagnostic tools for post-gastric bypass hypoglycaemia.

Emous M, Ubels F, van Beek AP.

Obes Rev. 2015 Oct;16(10):843-56.

ABSTRACT

In spite of its evident success, several late complications can occur after gastric bypass surgery. One of these is post-gastric bypass hypoglycaemia. No evidence-based guidelines exist in literature on how to confirm the presence of this syndrome.

This study aims to describe and compare the tests aimed at making a diagnosis of post-gastric bypass hypoglycaemia and to provide a diagnostic approach based on the available evidence. A search was conducted in Pubmed, Cochrane and Embase. A few questionnaires have been developed to measure the severity of symptoms in post-gastric bypass hypoglycaemia but none has been validated. The gold standard for provocation of a hypoglycaemic event is the oral glucose tolerance test or the liquid mixed meal tolerance test. Both show a high prevalence of hypoglycaemia in post-gastric bypass patients with and without hypoglycaemic complaints as well as in healthy volunteers. No uniformly established cut-off values for glucose concentrations are defined in literature for the diagnosis of post-gastric bypass hypoglycaemia. For establishing an accurate diagnosis of post-gastric bypass hypoglycaemia, a validated questionnaire, in connection with the diagnostic performance of provocation tests, is the most important thing missing. Given these shortcomings, we provide recommendations based on current literature.

INTRODUCTION

Morbid obesity is a growing healthcare problem in the world. Obesity prevalence has been estimated to be between 12% and 26% in a recent study across seven European countries, conforming that obesity has become an epidemic.¹

Weight-loss surgery is the best way to reduce weight permanently, resolve comorbidity and improve survival rates for morbidly obese people.² Roux-en-Y gastric bypass and sleeve gastrectomy are currently the most frequently performed weight-loss operations.³⁻⁶ Despite their success, certain long-term effects can develop, such as dumping.

Dumping can be subdivided into early dumping and late dumping.⁷ Early dumping occurs within the first hour after a meal and is the result of rapid emptying of food into the small bowel. Due to the hyperosmolality of the food, rapid fluid shifts occur from the plasma compartment into the bowel, resulting in hypotension and a sympathetic nervous system response (7). Early dumping develops mostly directly after bariatric operation. Late dumping is a result of (incretin-driven) hyperinsulinaemic response after carbohydrate ingestion, which usually occurs one to three hours after a meal.⁸ It normally develops months to years after the operation. Previously, gastrectomy for ulcers or cancer was a notorious cause of early and late dumping.⁹ Nowadays, the procedure most frequently known to induce this is gastric bypass as a primary or secondary operation.

Hypoglycaemia is defined by the American Diabetes Association as all episodes of an abnormally low plasma glucose concentration that expose an individual to potential harm.¹⁰ With regard to the issue of harm, it is not only the nadir glucose concentration that is inherently dangerous but also the frequency and the duration of hypoglycaemic events. Frequent hypoglycaemic events interfere with daily living and lead to defective glucose counter-regulation and hypoglycaemia unawareness.^{10,11} In contrast to Type 1 diabetes patients who have non-severe hypoglycaemic events one to two times per week^{12,13}, the frequency of hypoglycaemia after gastric-bypass surgery in affected patients can be much higher, with episodes often occurring several times a day.¹⁴ The prevalence of hypoglycaemia after gastric-bypass surgery as assessed by an oral glucose tolerance test (oGTT) or a mixed meal tolerance test (MMTT) is estimated at between 17% and 68%, depending on the biochemical criteria, the hypoglycaemia-inducing stimulus and the population studied.¹⁵⁻¹⁸ The estimated prevalence of severe hypoglycaemic episodes leading to hospital admission is 1%.¹⁹

In this review, we will focus on the diagnosis of hypoglycaemia after gastric bypass surgery. For the purpose of this review, we use the term 'late dumping' only in a historical context and prefer to use 'post-gastric bypass hypoglycaemia' because it better describes this disease entity. It must be noted that other types of upper gastrointestinal surgery involving altered nutrient delivery or leading to vagus nerve dysfunction, such as gastric banding, gastrectomy and esophageal resection, can also induce these complaints.²⁰⁻²³ However, these patients are less well characterized and the prevalence of late dumping after sleeve gastrectomy

and gastric banding is estimated to be 5 and 10 times lower, respectively, than after gastric-bypass surgery.²⁴

A diagnosis of post-gastric bypass hypoglycaemia can be established using different diagnostic modalities such as questionnaires, blood sampling, glucose sensing, provocation tests and, potentially, functional imaging. In this paper, we will review the different diagnostic tools to diagnose post-gastric bypass hypoglycaemia and make recommendations based on current literature.

METHODS

Search strategy

Published studies were identified from a literature search on three online databases (Pubmed, Cochrane, and Embase). The search of this non-systematic review was restricted to full papers published in English. Case reports were excluded.

Search terms included (1) (gastric bypass OR Roux-en-Y gastric bypass OR RYGB OR Gastrojejunostom* OR bariatric surgery) AND (hypoglycaemia/hypoglycaemia OR dumping OR questionnaire OR oral glucose tolerance test OR oGTT OR mixed meal tolerance test OR hyperinsulin* OR imaging); (2) (diabetes AND hypoglycaemia AND questionnaire).

In addition, relevant articles identified by the papers found in this search strategy were also selected.

RESULTS

Search

The search was carried out on 5 February 2015. The total number of papers identified was 461. After reading the titles 115 papers were left. After reading the abstracts, an initial selection was made of 45 papers. These were read in full, and finally 24 papers were included in this review.

Afterwards, the references of these papers were reviewed for missing papers on the subject and four additional papers were identified. Papers describing oGTT or MMTT without describing the prevalence of hypoglycaemia were disregarded, with the exception of a few historical papers. Papers only focussing on early dumping were also disregarded. No randomised controlled trials were found comparing different questionnaires or oGTT and MMTT. Most studies are retrospective or prospective cohort studies.

Questionnaires and symptom scales

In 1970, Sigstad proposed the clinical diagnostic index (later named the Sigstad Dumping Score) to assess the presence of dumping (Table 1).²⁵ The test was used on patients after partial gastrectomy in cases of peptic ulcer disease. Patients underwent an oGTT and clinicians used the Sigstad Score to score symptoms. The primary focus, however, was on early dumping, by diagnosing signs and symptoms such as a high pulse rate or increased haematocrit indicative of hypovolemia. The test was validated against the plasma volume that was measured with Evans blue. The test was aborted after 75 minutes, at which time a rise in plasma glucose was observed. Due to the short duration of the test, hypoglycaemia was not documented. Later, both Svennevig and Paik exchanged the Sigstad Dumping Score for a self-administered questionnaire.^{17,26} The population in both studies consisted of patients after partial gastrectomy in case of gastric ulcer. This application of the Sigstad Dumping Score changed over time in various studies to patients after gastric bypass surgery with hypoglycaemia after glucose loading.²⁷⁻³⁰ It should be kept in mind that the Sigstad Dumping Score was developed and validated for complaints of early dumping and not of postprandial hypoglycaemia.

Arts *et al.* developed a dumping severity score in which the symptoms of early and late dumping (eight and six symptoms, respectively) were scored on a 4-point Likert scale.³¹ This questionnaire was tested on patients with early and late dumping but was never formally validated. It was used to measure treatment response to octreotide. A borderline significant correlation was found between the nadir plasma glucose and symptoms of drowsiness or the total dumping severity score, suggesting potential usefulness.

Mine *et al.* used a questionnaire in patients after different gastric operations for ulcers and cancer.³² It consisted of six questions (cold sweat, dizziness, faintness, tremor, loss of consciousness, and hunger). A positive score was defined as a visual analogue score (VAS) above 10 mm for one of the symptoms. The prevalence of late dumping in this study after gastrectomy was 38%. The questionnaire was not validated.

Relevant questionnaires with respect to post-gastric bypass hypoglycaemia can be derived from the field of diabetes that investigates symptoms of hypoglycaemia or the fear of hypoglycaemia. Hepburn and Deary developed the Edinburgh Hypoglycemia Scale in which 11 items were tested.³³⁻³⁵ The Edinburgh Hypoglycemia Scale was tested in diabetic patients on different treatment strategies. No studies were found that tested the Edinburgh Hypoglycemia Scale in relation to plasma glucose concentrations. McAuley and co-workers validated a 19-point scale for symptoms of hypoglycaemia in patients with diabetes mellitus.³⁶ This revision of the Edinburgh Hypoglycemia Scale comes from the same group of investigators. They proposed using a VAS or 7-point Likert scale to grade each symptom of hypoglycaemia. Neither hypoglycaemia symptom score developed for use in diabetes patients has ever been used for the study of post-gastric bypass hypoglycaemia.

Table 1: Questionnaires for dumping and hypoglycemia assessment.

Study (author, year)	Name of questionnaire	Type of patients (number) and validation	Questionnaire specifications	Conclusion	Remarks
Sigstad,1970 (25)	Clinical Diagnostic Index (Sigstad Dumping Score)	Patients after partial gastrectomy for peptic ulcer (n=49). Validation against a fall in plasma volume measured with Evans Blue. A clinical diagnostic index ≥7 after an ingestion of a glucose solution (175 mL, 50 %) is suggestive of dumping.	16 items score of variable weighting per item. Scored by clinician during oGTT. Later (modified) versions were self-administered (17,26, 28-30,48)	First dumping questionnaire. The Sigstad score can be used to identify hypovolemic (early) dumping, but not hypoglycemic (late) dumping.	Mainly focusing on hypovolemic (early) dumping. Duration of test (75 minutes) too short to measure post-gastric bypass hypoglycemia. Of note: An early rapid rise and higher plasma glucose index was found in dumpers.
Arts <i>et al.</i> , 2009 (31)	Dumping Severity Score	Patients after upper GI surgery (bariatric, gastric cancer and Nissen fundoplication) before and on treatment with octreotide (n=30). Validation: Questionnaire developed based on symptom patterns reported in literature. Not formally validated. Used to measure treatment response.	8 items related to hypovolemic dumping symptoms and 6 items related to hypoglycemic symptoms. Scores are rated on a 4-point Likert Scale (0, absent; 1, mild; 2, relevant; 3, severe and interfering with daily activities)	Treatment response was significant after octreotide with marked reduction in early and late dumping	Easy to perform questionnaire; At baseline a relation between blood glucose nadir (after a 75 g oGTT) and the late dumping symptom 'drowsiness' and the total late dumping score was observed. Potential usefulness for screening for hypoglycemic dumping after gastric bypass surgery.
Mine <i>et al.</i> , 2010 (32)	No name.	Patients after various types of gastrectomy and reconstruction for gastric cancer (n=1153). Not formally validated. Reproducibility was assessed in the first 90 patients. A median kappa of 0.56 for all symptoms was found indicating a substantial reproducibility.	6-item questionnaire on late dumping symptoms occurring within 2-3 h after a meal (cold sweat, dizziness, faintness, tremor, loss of consciousness and hunger) scored on a VAS.	Incidences of late dumping syndrome in all patients was 38%.	A very low cut-off for dumping complaints was used (VAS score > 10 mm). A single item on the questionnaire was sufficient to label patients as symptomatic for late dumping.

Table 1: Questionnaires for dumping and hypoglycemia assessment. (continued)

Study (author, year)	Name of questionnaire	Type of patients (number) and validation	Questionnaire specifications	Conclusion	Remarks
Deary <i>et al.</i> , 1993 (33,34)	Edinburgh Hypoglycemia Scale	Patients with diabetes mellitus (n=295) Validated on a separate group of insulin-treated diabetic out-patients (n=303)	11 key items of hypoglycemic symptoms segregated into three clear factors: autonomic, neuroglycopenic and malaise (nausea and headache). Self-rating questionnaire. Using a 7-points scale to grade symptoms	This questionnaire can be used for research and clinical practice in diabetes patients.	Scale not tested in patients who underwent bariatric procedures.
McAuley <i>et al.</i> , 2001 (36)	'Revised' Edinburgh Hypoglycemia Scale	Patients with diabetes mellitus. 'Validated' but without detailed description in review article.	19-item list, divided in autonomic, neuroglycopenic and non-specific (malaise) symptoms. Self-rating. Using a VAS-score or 7-points scale to grade symptoms	Symptoms of hypoglycemia are age-specific and change over time. Some patients are unaware of having hypoglycemia.	Scale not tested in patients who underwent bariatric procedures.

GI, gastrointestinal; oGTT, oral glucose tolerance test; VAS, visual analogue score.

Discussion on the use of different questionnaires

None of the questionnaires is validated for assessment of post-bariatric hypoglycaemia. The Sigstad Dumping Score is developed for early dumping provoked after gastrectomy and is often inappropriately used in literature for the diagnosis of late dumping, for which it is not validated. The hypoglycaemia scores for diabetes are not tested on patients with post-bariatric hypoglycaemia. The questionnaires used by Mine and Arts are somewhat alike. Arts used the test for treatment response and not for diagnosis per se. Mine used his questionnaire for this latter purpose and by using a very low cut-off score was likely to find an overestimation of the prevalence of late dumping. It must be emphasized that none of the symptom questionnaires for post-gastric bypass hypoglycaemia was validated against objective glucose measurements.

Therefore, we propose to use a symptom score only in a research setting for post-gastric bypass hypoglycaemia until a validated questionnaire is available. For the clinical setting, we propose that the clinician take a profound history, including abdominal, vegetative and neuroglycaemic symptoms and that the patient keep a diary to link symptoms and food intake.

Laboratory testing

Single glucose measurements

In a historic publication, Whipple put forward that the mere presence of complaints cannot be ascribed with confidence to hypoglycaemia unless the plasma glucose concentration is low at the same time and the symptoms are relieved when it is raised.³⁷ Therefore, at least two reliably measured glucose values should be available: one during hypoglycaemia and one during euglycaemia.

Glucose measurements, whether scheduled or random, can be performed on patients visiting a hospital. The diagnostic yield is most likely low but increases during the presence of symptoms. No definitive cut-off values are defined for random glucose concentrations.

Capillary glucose measurements (finger-prick tests)

The use of capillary blood glucose (finger-prick) measurements is not advocated to reliably document hypoglycaemia. Current self-monitoring blood glucose devices have large deviations compared with the laboratory-obtained glucose values, resulting in inaccurate glucose measurements and often leading to false conclusions.³⁸

Provocative testing, the oral glucose tolerance test

Originally, the 2-hour oGTT (Table 2a) was used as a diagnostic tool to assess hyperglycaemia, with clear definitions over which glucose concentration diabetes mellitus was diagnosed. This test has been widely accepted in various forms since the 1960s.³⁹ The recognition that it might serve as a dynamic (provocation) test for the detection of meal-induced hypoglycaemia was first published in 1981 by Lev-Ran *et al.*⁴⁰ They performed a standardized 100g oGTT test in patients with suspected meal-induced hypoglycaemia and in a control group without complaints of hypoglycaemia after provocation or regular meals.

Table 2a: Studies of the oral Glucose Tolerance Test as hypoglycemic stimulus in patients after upper gastrointestinal surgery and in control populations.

Study (Author, year)	Patients (number)	Controls (number)	oGTT composition and definition of hypoglycemia	outcome	remarks
Lev-Ran and Anderson., 1981 (40)	Patients with complaints of hypoglycemia (n=118), without prior bariatric procedures or upper gastrointestinal surgery and without diabetes mellitus or glucose impairment.	Patients analyzed for glucose tolerance without complaints of hypoglycemia (n=650).	Caffeine-free cola with 100 g of sugar, duration 300 minutes. Glycemic nadir distribution described in healthy population: 25% had a glucose < 3.0 mmol/l; 5% < 2.4 mmol/l; 2.5% < 2.2 mmol/l.	16 of 118 (14%) of the patients had symptoms typical of hypoglycemia at oGTT coinciding with glucose nadirs < 2.7 mmol/l. The nadirs of hypoglycemic patients and controls overlap.	The authors conclude that true hypoglycemia in patients referred for analysis is relatively rare. The accurate diagnosis of postprandial hypoglycemia requires that symptoms develop concurrently with low blood sugar and are absent at other times.
Halverson <i>et al.</i> , 1982 (41)	Patients after gastric bypass surgery (n=14)	Morbidly obese patients prior to gastric bypass surgery (n=11) and non-obese healthy subjects (n=10)	Glucose 75 g, volume not specified, duration 300 minutes. Hypoglycemia defined as glucose ≤ 2.7 mmol/l.	Hypoglycemia prevalence was approximately 50% in patients after gastric bypass surgery reached on average after 150 minutes. No hypoglycemia in the control groups was described.	This study was designed to describe the altered glucose and insulin response as well as change in insulin sensitivity after gastric bypass surgery without particular interest in hypoglycemia.
Van der Kleij <i>et al.</i> , 1996 (18)	Patients with previous partial or total gastrectomy or vagotomy with typical complaints of late dumping (n=11).	Patients with previous gastric surgery (similar to the patient group) but without complaints of late dumping (n=18).	Glucose 50 g in 300 ml water; duration 360 minutes Hypoglycemia defined as glucose ≤ 2.7 mmol/l.	In patients with complaints of late dumping 64% had a nadir glucose ≤ 2.7 mmol/l. Lowest glucose in control group was 2.7 mmol/l.	All patients with late dumping had complaints of dumping during the test; none of the controls had complaints of late dumping.
Kim <i>et al.</i> , 2009 (15)	Patients with symptomatic hypoglycemia after gastric bypass surgery (n=9)	Asymptomatic patients after gastric bypass surgery (n=9) and matched controls matched for BMI and divided in tertiles based on insulin sensitivity (n=30).	Glucose 75 g, water volume not specified, duration 180 minutes. Hypoglycemia defined as glucose < 2.8 mmol/l.	Minimally different glucose and insulin responses in symptomatic and asymptomatic patients, but both gastric bypass groups demonstrate an exaggerated hyperinsulinemic response compared to controls. Prevalence of hypoglycemia in patients was 33%, whereas in controls with better insulin sensitivity, this was 10% and with poorer insulin-sensitivity, this was 0%.	Almost the same results in patients with or without symptoms of late dumping. No data on contra-regulatory hormones.

Table 2a: Studies of the oral Glucose Tolerance Test as hypoglycemic stimulus in patients after upper gastrointestinal surgery and in control populations. (continued)

Study (Author, year)	Patients (number)	Controls (number)	oGTT composition and definition of hypoglycemia	outcome	remarks
Arts <i>et al.</i> , 2009 (31)	Patients after upper GI surgery (bariatric, gastric cancer, Nissen fundoplication) with postoperative dumping (n=30).	Same patients after treatment with octreotide (n=30).	75 g glucose, volume not specified, duration 180 minutes. Hypoglycemia defined as glucose < 3.3 mmol/l.	In patients with symptoms of early and late dumping the prevalence of hypoglycemia at baseline was 80%.	Prevalence of hypoglycemia improved on octreotide treatment.
Roslin <i>et al.</i> , 2011 (42)	Patients who were at least 6 months postoperative from gastric bypass surgery (n=36)	No controls	100 g glucose, volume not specified, duration 240 minutes. Hypoglycemia was defined as an absolute serum glucose level < 3.3 mmol/l or a drop of 5.6 mmol/l in serum glucose level in 1 hour.	26 of 36 (72%) patients developed hypoglycemia.	No information about symptoms of late dumping.
Paik <i>et al.</i> , 2011 (17)	Patients after gastrectomy for early gastric cancer with small intestinal bacterial overgrowth (n=59)	Patients after gastrectomy for early gastric cancer without small intestinal bacterial overgrowth (n=17)	75 g glucose, water volume not specified, duration 180 minutes. Hypoglycemia was defined as glucose < 3.3 mmol/l.	Hypoglycemia occurred in 17% with small intestinal bacterial overgrowth and in 24% without this disorder (not significantly different).	Not tested in patients after bariatric procedures. Although the prevalence of hypoglycemia did not differ between groups, the plasma glucose was significantly lower in patients with than without small intestinal bacterial overgrowth at 120 and 150 minutes after oral glucose load (P < 0.05).
Jacobsen <i>et al.</i> , 2012 (52)	Patients within 2 weeks after gastric bypass operation (n=8)	Same patients undergoing same tests preoperatively.	Two oGTT's were used: 25 g/ 200 ml and 50 g/200 ml. Hypoglycemia definition not specified.	Two patients reported postprandial dumping in response to 50 g of glucose after the operation, scoring the symptoms nausea and palpitations at 40 mm (of 100 mm) on the VAS questionnaire. Prevalence of hypoglycemia in patients not stated.	Study aims to describe early post-gastric bypass hormonal changes. The oral test meals were designed to cause little side effects (such as dumping). Patients were tested very early in the postoperative state.

Table 2a: Studies of the oral Glucose Tolerance Test as hypoglycemic stimulus in patients after upper gastrointestinal surgery and in control populations. (continued)

Study (Author, year)	Patients (number)	Controls (number)	oGTT composition and definition of hypoglycemia	outcome	remarks
Roslin <i>et al.</i> , 2013 (16)	Patients at least 6 months after gastric bypass (<i>n</i> =63).	No controls	Glucose 100 g, water volume not specified, duration 240 minutes. Hypoglycemia defined as glucose < 3.3 mmol/l.	Hypoglycemia was observed in 68% of patients 1-3 hours after ingestion of the glucose load.	No information about symptoms of late dumping
Itariu <i>et al.</i> , 2014 (43)	Non-diabetic patients who underwent elective bariatric surgery (<i>n</i> =36) (predominantly gastric bypass, <i>n</i> =30)	Same patients preoperative.	Glucose 75 g, water volume not specified, duration 120 minutes. Hypoglycemia defined as glucose < 3.3 mmol/l in the 2nd hour of the OGTT.	Hypoglycemia was detected in 16 of 30 patients who underwent prior gastric bypass surgery. Most patients who experienced hypoglycemia reported no complaints at all.	The investigators used a fixed time period to define hypoglycemia and the duration of the test was relatively short. No formal measurements of hypoglycemic symptoms described.

BMI, body mass index; GI, gastrointestinal; *n*, number, OGTT: oral glucose tolerance test; VAS, visual analogue scale.

Table 2b: Studies of the Mixed Meal Tolerance Test (MMTT) as hypoglycemic stimulus in patients after upper gastrointestinal surgery and in control populations.

Study Author, year	Patients (number)	Controls (number)	Definition of hypoglycemia	outcome	remarks
Goldfine <i>et al.</i> , 2007 (45)	Patients with symptomatic hypoglycemia after gastric bypass (n=12)	Patients after gastric bypass without symptoms of hypoglycemia (n=9); further healthy morbidly obese patients without prior gastric bypass matched for preoperative weight (n=5), and healthy patients matched for post operative weight of the gastric bypass group (n=10)	<3.3 mmol/l.	3 out of 9 (33%) asymptomatic patients after gastric bypass developed hypoglycemia within 2 hours after start of the test. Patients with symptomatic hypoglycemia after gastric bypass demonstrated only marginally lower glucose values over the entire 2 hours than asymptomatic patients.	Insulin, C-peptide and GLP-1 after the liquid mixed meal were all higher relative to the glucose level achieved in persons with symptomatic hypoglycemia after gastric bypass compared with asymptomatic individuals.
Halperin <i>et al.</i> , 2011 (55)	10 patients on medical treatment for symptomatic hypoglycemia after gastric bypass.	6 patients after gastric bypass without symptoms of hypoglycemia.	< 3.9 mmol/l.	3/9 (33%) patients with symptomatic hypoglycemia developed hypoglycemia after a mixed meal tolerance test. However, in asymptomatic patients this was 3/5 (60%).	Test compared MMTT with CGM. The authors conclude that asymptomatic hypoglycemia after gastric bypass surgery is more frequent than commonly recognized. For clinicians evaluating patients for post-gastric bypass neuroglycopenia, CGM may be a valuable diagnostic tool.
Salehi <i>et al.</i> , 2011 (30)	Patients with recurrent hypoglycemia after gastric bypass surgery (n=12)	Asymptomatic individuals with previous gastric bypass surgery (n=12) and matched healthy non-operated control subjects (n=10).	Hypoglycemic symptoms associated with blood glucose < 2.8 mmol/l. It must be noted that studies were terminated if subjects developed symptomatic hypoglycemia.	Following ingestion of the test meal, blood glucose fell to <2.8 mmol/l (with complaints) in 9 of 11 hypoglycemic subjects and in 2 of the 12 asymptomatic (without complaints) subjects.	The exaggerated effect of GLP-1 on postprandial insulin secretion in surgical subjects is not significantly different in those with and without recurrent hypoglycemia.
Jacobsen <i>et al.</i> , 2012 (52)	Patients within 2 weeks after gastric bypass operation (n=8)	Same patients undergoing same tests preoperatively.	Hypoglycemia definition not specified.	The mixed meal provoked dumping symptoms postoperatively in four patients, who experienced nausea to a maximal score of 30 mm on the VAS score and one patient had minor palpitations (score 10 mm). Prevalence of hypoglycemia in patients not stated.	Study aims to describe early post-gastric bypass hormonal changes. The oral test meals were designed to cause little side effects (such as dumping). Patients were tested very early in the postoperative state.

Table 2b: Studies of the Mixed Meal Tolerance Test (MMTT) as hypoglycemic stimulus in patients after upper gastrointestinal surgery and in control populations. (continued)

Study Author, year	Patients (number)	Controls (number)	Definition of hypoglycemia	outcome	remarks
Valderas <i>et al.</i> , 2012 (46)	Patients (n=8) after gastric bypass surgery with neuroglycopenic complaints suggestive of postprandial hypoglycemia.	Same patients undergoing same tests after acarbose (100 mg) pretreatment.	< 2.8 mmol/l.	The mixed meal tolerance test was able to provoke hypoglycemia (with mild symptoms) in 5 out of the 8 patients.	Acarbose treatment was able to prevent hypoglycemia in all patients with concomitant decrease in insulin and GLP-1 concentrations.
Laurenus <i>et al.</i> , 2014 (29)	Gastric bypass patients with hypoglycemia-like symptoms (n=8)	Gastric bypass patients with no hypoglycemia-like symptoms (n=8)	Hypoglycemia definition not specified.	Symptomatic patients perceived more complaints but showed a similar response of glucose, insulin and incretins after a mixed meal tolerance test when compared to asymptomatic patients.	The glucose nadir of individual patients was not specified. The asymptomatic group had a mean glucose of 2.6 mmol/l at 120 minutes of the test meal, suggesting hypoglycemia unawareness. Sigstad dumping score was used which is more specific for early dumping (see Table 1).
Salehi <i>et al.</i> , 2014 (47)	Patients with recurrent symptomatic hypoglycemia after gastric bypass surgery (n=9), patients who were asymptomatic after gastric bypass surgery (n=7) and healthy control subjects (n=8).	Same patients undergoing same tests after GLP-1 receptor antagonist exendin (9-39) (Ex-9) during continuous intravenous treatment	<2.8 mmol/l.	During the MTT, blood glucose levels decreased to < 2.8 mmol/l in 8 of the subjects with symptomatic hypoglycemia. None of control subjects developed hypoglycemia	Infusion of Ex-9 corrected hypoglycemia in all patients with symptomatic hypoglycemia after gastric bypass surgery. The findings are consistent with reports that increased GLP-1 activity contributes to hypoglycemia after gastric bypass.
Salehi <i>et al.</i> , 2014 (48)	Patients after gastric bypass surgery with a history of predominantly neuroglycopenic symptoms (n=24) or with only autonomic symptoms (n=12)	Patients after gastric bypass surgery without symptoms of postprandial hypoglycemia (n=29) and healthy body mass index-matched control subjects without prior surgery (n=11)	Symptoms consistent with hypoglycemia associated with blood glucose <2.8 mmol/l and relief of symptoms immediately after carbohydrate ingestion (Whipple's triad). Studies were terminated if subjects developed symptomatic hypoglycemia.	12 of the 24 patients with predominantly neuroglycopenic symptoms developed hypoglycemia. 3 of the 29 patients of the control group developed hypoglycemia. No data specified for patients with autonomic symptoms only or healthy controls.	In patients after gastric bypass surgery with a clinical history of hypoglycemia, hyperinsulinemia is the result of inappropriate insulin secretion and reduced insulin clearance which is most pronounced in subjects who report neuroglycopenic symptoms.

CGM, continuous glucose monitoring; n, number, GLP-1: glucagon-like peptide 1; VAS, visual analogue scale.

The 650 controls had an oGTT with sample collection every 30 minutes for the first 2 hours and hourly thereafter until 5 hours. None of them had a history of diabetes, glucose intolerance or diseases that could influence glucose tolerance. Their mean age was around 40 years, half of the patients were male and 14% were obese. This study is of particular importance because although all of these patients were without complaints suggestive of postprandial hypoglycaemia, 25% had nadir glucose beneath 3.0 mmol/l (54 mg/dl) and 10% below 2.6 mmol/l (47 mg/dl). Most of the patients had their glucose nadir at 180 minutes, although it was not uncommon for it to occur later. The authors showed that the glucose nadirs of patients with suspected meal-induced hypoglycaemia overlapped with the controls, and concluded that an accurate diagnosis of hypoglycaemia requires that symptoms develop concurrently with low blood sugar and remain absent at other times. In addition, the authors stated that low postprandial plasma glucose can only be considered as one of the criteria in diagnosing functional hypoglycaemia, along with a relationship between food intake, timing of symptoms, correlation of symptoms and low glucose levels, and reproducibility of test results.

The first published observation of the oGTT in patients after gastric-bypass surgery came a year later. In this study by Halverson and co-workers, patients after gastric-bypass surgery were compared with morbidly obese patients prior to gastric bypass and healthy non-obese individuals.⁴¹ There were no significant differences in basal glucose concentrations for any of the groups. However, the rate of fall of the plasma glucose was faster in the postoperative group versus the morbidly obese controls (lowest glucose concentrations at 150 minutes versus 270 minutes, respectively). Half of the group of postoperative patients developed hypoglycaemia (defined as ≤ 2.7 mmol/l). The prevalence of hypoglycaemia in controls was not described as the main study focus was not on hypoglycaemia.

A decade later, Van der Kleij and co-workers presented their study in which patients with complaints of early and late dumping after previous gastric surgery were compared with asymptomatic patients after the same operation.¹⁸ They found that the lowest glucose in the control group was 2.7 mmol/l without complaints of hypoglycaemia or dumping. However, 64% of patients with symptoms of dumping had a glucose level beneath 2.7 mmol/l; this cut-off level was chosen on the basis of the lowest glucose concentration in the asymptomatic control group. Van der Kleij concluded that dumping is more recognizable by symptoms than by nadir glucose, possibly because of the poor correlation between symptoms and nadir glucose after oGTT.

Recently, more investigations on this subject have been published. In an interesting study, Kim *et al.* performed a 75g oGTT in patients with and without symptoms of hypoglycaemia after gastric bypass.¹⁵ The symptomatic patients had minimally different test results compared with the asymptomatic patients. The authors concluded that the oGTT was not able to discriminate between the presence and absence of symptomatic late dumping. However, this study lacks adequate description of time points after 180 minutes, when delayed hy-

poglycaemia can still occur. Furthermore, recurrent hypoglycaemia in the control group may have lead to hypoglycaemia unawareness, a phenomenon that may be accompanied by defective glucose counter-regulation (reduced epinephrine and glucagon responses) to hypoglycaemia.

Arts *et al.* used the oGTT to evaluate treatment with octreotide in patients after gastric-bypass surgery with complaints of post-gastric bypass hypoglycaemia. Eighty per cent of the patients developed hypoglycaemia with the oGTT before treatment, and treatment markedly improved the prevalence.³¹ Roslin *et al.* performed two studies on abnormal glucose tolerance testing in 2011 and 2013; the second probably being an extension of the first study.^{16,42} They concluded that abnormal oGTT results are a common finding after gastric bypass surgery because 68-72% of the patients had reactive hypoglycaemia defined as < 3.3 mmol/l (60 mg/dl). No control group was used. In 2011 Paik *et al.* used the oGTT to test for early gastric cancer in patients with gastrectomy and concluded that patients with intestinal bacterial overgrowth had significantly lower plasma glucose levels than those without intestinal overgrowth.¹⁷ Itariu *et al.* tested non-diabetic patients before and after a bariatric procedure, predominantly the gastric bypass.⁴³ They tested until 120 minutes and half of all patients developed low glucose (< 3.3 mmol/l), although none had hypoglycaemic complaints.

Discussion on the use of the oGTT

In conclusion, the oGTT very frequently shows hypoglycaemia after gastric-bypass surgery, even in the absence of symptoms suggestive of late dumping. The diagnostic accuracy of this test is therefore likely to be low. In addition, studies in a control population show that the normal postprandial glucose distribution often extends to what is considered the hypoglycaemic range. Therefore, the normative values are not firmly established. Clinicians should also be aware that hypoglycaemia unawareness may develop as a consequence of recurrent hypoglycaemia, making it even more difficult to distinguish between the presence and absence of symptoms related to post-gastric bypass hypoglycaemia. Accordingly, the guideline for evaluation and management of adult hypoglycaemic disorders from the Endocrine Society published in 2009 rejected the use of the oGTT for testing postprandial hypoglycaemia.⁴⁴

Provocative testing, the mixed meal tolerance test

The mixed meal tolerance test (MMTT) (Tables 3 and 4) has been developed as an alternative to the oGTT due to increased understanding that a 75g glucose load without the addition of other macronutrients is not physiological.⁴⁴ Some researchers have not used standardized meal tests but used orange juice, toast with jam and muffins or other solid food instead. Although these meals seem to better resemble eating habits at home and provoke symptoms in these patients, they are difficult to reproduce in the setting of research. We therefore have not included those studies in this review.

The composition of the MMTT has also not been standardized (see Table 3). It must also be noted that although the total glucose load is lower than in the oGTT, enhanced insulin secretion is observed by co-ingestion of a free amino acid/protein mixture and induction of a certain degree of insulin resistance by free fatty acids. Goldfine and colleagues were the first to publish results of the MMTT in patients after gastric bypass surgery.⁴⁵ They tested 12 patients with neuroglycopenia and compared them to patients without complaints of post-gastric bypass hypoglycaemia, as well as to healthy obese and non-obese volunteers. All patients with signs of neuroglycopenia developed hypoglycaemia after the MMTT. In patients after gastric bypass surgery without symptoms of dumping, three of nine patients developed hypoglycaemia below 3.3 mmol/l. None of the volunteers developed hypoglycaemia. Unfortunately, the test duration was only 2 hours and true nadirs were often not established due to the lack of documentation of subsequent increase in glucose concentrations. The authors showed that post-gastric bypass hypoglycaemia was associated with a robust insulin secretory response and a high incretin response. Indeed, establishing the hyperinsulinemic origin of this hypoglycaemic disorder can be of added value in preventing confusion with other hypoglycaemic disorders that are not the consequence of excessive insulin secretion.

In 2011, Salehi *et al.* reported on patients with recurrent hypoglycaemia after gastric bypass and compared them with asymptomatic individuals with previous gastric bypass surgery and healthy non-operated control subjects (30). In patients with a history of hypoglycaemia, 9 of 11 patients (82%) developed nadir glucose below 2.8 mmol/l, while this was only present in 2 of 12 control subjects (17%). Valderas *et al.* studied eight patients after gastric bypass surgery with neuroglycemic complaints suggestive for hyperinsulinemic hypoglycaemia.⁴⁶ They tested patients before and after treatment with acarbose. The MMTT provoked hypoglycaemia (glucose below 2.8 mmol/l) in five of eight patients, and acarbose treatment prevented hypoglycaemia in all of them.

Table 3: Contents of Mixed Meal Tolerance Test used as (hypoglycemic) stimulus in patients after upper gastrointestinal surgery and in control populations.

	Product	Volume (ml)	Energy (kcal)	Carbohydrate (g)	Protein (g)	Fat (g)	Duration of test (minutes)
Goldfine <i>et al.</i> , 2007 (45)	Ensure®	240	250	40	9	6	120
Halperin <i>et al.</i> , 2011 (55)	Ensure®	240	250	40	9	6	120
Jacobsen <i>et al.</i> , 2012 (52)	Nutridrink®	200	300	35	11	12	200
Valderas <i>et al.</i> , 2012 (46)	Ensure Plus®	237	355	50	13	11	180
Laurenus <i>et al.</i> , 2014 (29)	113 g Resource Addera Plus, 113 g Nutrical and 98 g cold water.	300	443	100	5.7	1	180
Salehi <i>et al.</i> , 2011, 2014, 2014 (30,47,48)	Ensure Plus®	237	350	51	13	11	180/180/300

Table 4: Levels of Evidence and Grades of Recommendation

Level of evidence	Type of evidence
I	Evidence from meta-analysis of multiple, well-designed, controlled studies (randomized trials with low false-positive and low false-negative errors)
II	Evidence from at least 1 well-designed, quasi-experimental study (randomized trials with high false-positive and high false-negative errors)
III	Evidence from well-designed, quasi-experimental studies (nonrandomized, controlled, single-group, pre-post, cohort, and time or matched case-control series)
IV	Evidence from well-designed, non-experimental studies (comparative and correlational descriptive and case studies)
V	Evidence from case reports
Grade of recommendation	Level of evidence
A	Level I evidence or consistent findings from multiple studies (level II, III, or IV)
B	Level II, III, or IV evidence with generally consistent findings
C	Level II, III, or IV evidence with inconsistent findings
D	Little or no systematic empirical evidence

In 2014, Laurenus *et al.* compared patients with and without symptoms of hypoglycaemia.²⁹ Hypoglycaemia was not specified in this paper at the individual patient level. However, the asymptomatic group had a mean glucose of 2.6 mmol/l at 120 minutes, suggesting hypoglycaemia unawareness. Symptomatic patients perceived more complaints but showed a similar response of glucose, insulin and incretins after MMTT compared with asymptomatic patients. In 2014, Salehi *et al.* compared patients with recurrent hypoglycaemia after gastric bypass ($n=9$) with asymptomatic patients and healthy controls.^{47,48} Almost all patients (eight of nine) with recurrent symptomatic hypoglycaemia developed nadir glucose below 2.8 mmol/l, and none of the controls did. After receiving an infusion with the GLP-1 receptor antagonist exendin, hypoglycaemia was prevented in all symptomatic patients. From the same group came a second study with more patients: 24 patients with a history of neuroglycopenic symptoms after gastric bypass surgery were compared with 29 patients without symptoms of hypoglycaemia after gastric bypass surgery.^{47,48} Approximately half of all patients with symptoms of neuroglycopenic symptoms developed hypoglycaemia with a MMTT, whereas only three of the 29 controls did.

Discussion on the use of the mixed meal tolerance test

In conclusion, the MMTT holds promise as a more physiological stimulation test for the detection of post-gastric bypass hypoglycaemia compared to the oGTT. Several studies show the effects on glucose, insulin, incretins and diabetes resolution after gastric bypass surgery, but diagnostic performance of this test for the detection of post-gastric bypass is still not extensively studied. Some studies show better specificity of this test in asymptomatic patients; however no normative data are present for healthy subjects with regard to the induction of hypoglycaemia. Further validation of this test is needed involving studies in patients with and without symptoms and in healthy volunteers.

Comparison of the oral glucose tolerance test and the mixed meal tolerance test

In two older studies, researchers compared the oGTT with the MMTT.^{49,50} In these studies, the MMTT failed to induce hypoglycaemia in patients with symptoms of postprandial hypoglycaemia. The MMTT was not given as a fully liquid meal but rather as a mixture of drinks and food of firmer consistency (e.g. a standard breakfast of eggs, bread, muffins, orange juice, and milk). Also, patients with prior gastrointestinal surgery were often excluded.

Marena *et al.* compared the MMTT with the oGTT in healthy volunteers and patients with mild or severe diabetes mellitus and used 75g glucose (oGTT) or a mixed meal containing bread, fruit and ham (590 kcal and 44% carbohydrates).⁵¹ They concluded on the basis of the response of incretins that the MMTT was a more physiological test and better in characterizing patients with impaired glucose tolerance and non-insulin-dependent diabetes mellitus. Jacobsen *et al.* performed three different provocation tests in eight patients before and soon after gastric bypass (i.e. within five months).⁵² Complaints of nausea, palpitations, pain and perspiration were also evaluated using a VAS questionnaire at various timepoints postprandially. No differences were seen between the oGTT with 25 or 50g before and after surgery. However, during the MMTT, an earlier peak response and a quicker return to baseline was seen after surgery, in spite of lower glucose concentrations at the start of the test. No hyperinsulinemic hypoglycaemia occurred during the tests. They concluded that the oGTT is easier to perform but less comparable with daily life and that minor differences are easier overlooked using the oGTT.

Several studies confirm that the MMTT is a more physiological stimulus for induction of a hypoglycaemia than the oGTT. However, although a normal breakfast of bread, milk, eggs, etc. better resembles eating habits during daily life, it is far from reproducible for research. The best stimulus in this setting to provoke hypoglycaemia seems to be the MMTT performed with a standardized liquid meal. The duration of the test must be at least 210 minutes, to be sure that the nadir glucose is reached and glucose concentrations have returned to normal. No consistency in a positive test result is present because some consider plasma glucose concentrations of less than 2.8 mmol/l (50 mg/dl) indicative of post-gastric bypass hypoglycaemia^{30,46,48}, while others use cut-off levels of 3.3 mmol/l (60 mg/dl)^{44,45}.

The use of Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) enables us to measure glucose levels continuously over a longer period of time. This has obvious advantages as monitoring can be performed during daily activities and provides insight into eating patterns and related episodes of hypoglycaemia. For diagnostic purposes, a blinded sensor is preferred to prevent any form of conscious or unconscious influencing. Patients should be instructed to keep a diary during CGM, recording time of complaints, type of complaints, time of meals and their size and composition (i.e., an assessment of carbohydrate content). CGM represents an evolving technology that has made considerable progress in overall accuracy. However, the accuracy

of CGM in the hypoglycaemic range is poor, and trends are more important than absolute concentrations.⁵³ Indeed, several investigators have used CGM systems and found that glucose variability is exaggerated after gastric bypass, that subgroups exist according to hyperglycemic pattern in these patients, and that treatment with diet and acarbose improves glycemic excursions.⁵⁴

Comparison of the continuous glucose monitoring and the mixed meal tolerance test

Halperin *et al.* compared CGM with the MMTT in patients with neuroglycopenia after gastric bypass.⁵⁵ Nine of ten subjects with neuroglycopenia developed hypoglycaemia (defined as glucose below 3.8 mmol/l) during CGM, and three of nine on MMTT. In asymptomatic subjects, three of six had asymptomatic hypoglycaemia during CGM, and three of five on MMTT. Therefore, the sensitivity and specificity to detect clinically significant hypoglycaemia was 90% and 50% for CGM and 33% and 40% for MMTT. The authors concluded that asymptomatic hypoglycaemia after gastric bypass surgery is more frequent than commonly recognized and that CGM may be a valuable diagnostic tool for clinicians evaluating patients for post-bypass hypoglycaemia.

Recently, Kefurt *et al.* published a study in which they investigated a series of 40 patients, regardless of symptoms of dumping.⁵⁶ CGM was performed for five consecutive days and followed by MMTT. The incidence of hypoglycaemia during normal daily life (checked with CGM) was 75% and with MMTT it was 29%. Thirty-eight per cent of the patients had nocturnal hypoglycaemia. Thus CGM detected more patients with hypoglycaemia and the authors concluded that CGM has a role in screening on post-gastric bypass hypoglycaemia and evaluating treatment.

Functional imaging

Although post-gastric bypass hypoglycaemia is most likely the result of diffuse β -cell hyperplasia, several authors found focal β -cell hyperplasia⁵⁷, single⁵⁸ or multiple insulinomas⁵⁹, or a combination of nesidioblastosis and an insulinoma⁶⁰ in post-gastric bypass patients. In cases of atypical presentation (e.g. nocturnal hypoglycaemia) or insufficient treatment response, it may be necessary therefore to perform additional imaging studies because other disease entities should be treated differently. No comparative studies are performed on imaging modalities with regard to post-gastric bypass hypoglycaemia for diagnostic purposes. However, in a case report De Heide *et al.* showed increased whole pancreatic 11C-HTP- and 18F-DOPA tracer uptake in a patient with post-gastric bypass hypoglycaemia.⁶¹ The rationale for these scans is that both Positron Emission Tomography (PET) scans have been successfully applied to image neuroendocrine tumours.^{62,63} Additional studies are necessary to establish its value in a diagnostic work up for post-gastric bypass hypoglycaemia.

CONSIDERATIONS AND RECOMMENDATIONS FOR THE DIAGNOSIS OF POST-GASTRIC BYPASS HYPOGLYCAEMIA

Considerations:

1. Post-gastric bypass hypoglycaemia is almost exclusively observed after upper gastrointestinal tract surgery in which food enters the small bowel directly and the duodenum is bypassed. Complaints are provoked by ingestion of carbohydrate-rich food, and symptoms usually occur between 1 and 3 h postprandially.
2. The purpose of the laboratory evaluation is to document low blood glucose together with signs and symptoms attributable to hypoglycaemia, and to observe that these complaints are relieved when the glucose levels are normal again (Whipple's triad).
3. The sole use of existing questionnaires is limited, considering the fact that none of them is validated for the diagnosis of post-gastric bypass hypoglycaemia.
4. Physicians should be aware that some patients may develop hypoglycaemia unawareness and therefore appear to lack symptoms.
5. The use of capillary blood glucose (finger-prick) measurements is insufficiently reliable to document hypoglycaemia. The use of CGM has potential in patients after gastric bypass surgery for measuring glucose variability or a relation between onset of symptoms and glucose nadirs. However, because of the limited experience and number of publications, it can not currently be recommended.
6. Two tests have emerged in literature for the provocation of meal-induced hypoglycaemia: the oGTT and the MMTT. Both tests are performed in a clinical setting, guaranteeing skilled observation by healthcare workers as well as blood glucose measurements with high accuracy in the hypoglycaemic range. In addition, the hyperinsulinemic origin of hypoglycaemia can be documented. The sensitivity and specificity of both provocation tests are largely unknown and far from optimal. The MMTT provides a more physiological stimulus and may therefore be the preferred test.
7. Clear cut-off values have not been established and differences exist between investigators in a research setting. Glucose levels below 3.3 mmol/l (60 mg/dl) and 2.8 mmol/l (50 mg/l) are both advocated as a positive test result for confirmation of post-gastric bypass hypoglycaemia. Lower glucose values add to the specificity of this diagnostic test at the expense of reduced sensitivity.
8. In case of an atypical presentation of post-gastric bypass hypoglycaemia, e.g. the presence of hypoglycaemia during night hours or the absence of a typical relation to meals, further diagnostic work-up is necessary. Although in our opinion rare, in such cases, an insulinoma may be suspected and a 72-hour fasting test is indicated. Additionally, an 18F-DOPA-PET can differentiate between an insulinoma with focal uptake in contrast to the enhanced uptake in the entire pancreas seen in patients with post-gastric bypass hypoglycaemia.

Recommendations

1. Perform diagnostic testing only in patients with a high *a priori* chance of post-gastric bypass hypoglycaemia. (*level of evidence: III; grade of recommendation: C*)(Table 4);
2. Confirm the diagnosis of symptomatic post-gastric bypass hypoglycaemia by combining a symptom score aimed at identification of hypoglycaemic complaints together with a provocation test, preferably the MMTT. (*level of evidence: III; grade of recommendation: C;*)
3. Use a glucose below 3.3 mmol/l as a sensitive cut-off value for meal-induced hypoglycaemia during oGTT or MMTT. (*level of evidence: III; grade of recommendation: C*);
4. Do not use capillary glucose measurements, CGM or nuclear imaging modalities for the diagnosis of post-gastric bypass hypoglycaemia. (*level of evidence: III; grade of recommendation: C*);
5. Perform additional testing in patients with an atypical disease presentation, e.g. by performing a 72-h fast (*level of evidence: V; grade of recommendation: D*).

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Chapter 3

Dumping syndrome after esophageal,
gastric or bariatric surgery: pathophysiology,
diagnosis, and management

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Obes Rev. 2017 Jan;18(1):68-85.

ABSTRACT

Background

Dumping syndrome, a common complication of esophageal, gastric or bariatric surgery, includes early and late dumping symptoms. Early dumping occurs within 1 hour after eating, when rapid emptying of food into the intestine triggers rapid fluid shifts into the intestinal lumen and release of gastrointestinal hormones, resulting in gastrointestinal and vasomotor symptoms. Late dumping occurs 1-3 hours after carbohydrate ingestion, caused by an incretin-driven hyperinsulinemic response resulting in hypoglycemia. Clinical recommendations are needed for the diagnosis and management of dumping syndrome.

Methods

A systematic literature review was performed through February 2016. Evidence-based medicine was used to develop diagnostic and management strategies for dumping syndrome.

Results

Dumping syndrome should be suspected based on concurrent presentation of multiple suggestive symptoms after upper abdominal surgery. Suspected dumping syndrome can be confirmed using symptom-based questionnaires, glycemia measurements, and oral glucose tolerance tests. First-line management of dumping syndrome involves dietary modification, as well as acarbose treatment for persistent hypoglycemia. If these approaches are unsuccessful, somatostatin analogues should be considered in patients with dumping syndrome and impaired quality of life. Surgical re-intervention or continuous enteral feeding may be necessary for treatment-refractory dumping syndrome, but outcomes are variable.

Conclusions

Implementation of these diagnostic and treatment recommendations may improve dumping syndrome management.

Abbreviations

GLP, glucagon-like peptide

GIP, glucose-dependent insulintropic polypeptide or gastric inhibitory polypeptide

VAS, visual analogue scale

sst, somatostatin receptor subtype

OGTT, oral glucose tolerance test

GI, gastrointestinal

VIP, vasoactive intestinal peptide

LAR, long-acting release

INTRODUCTION

Dumping syndrome is a frequent complication of esophageal, gastric, or bariatric surgery. Alterations in gastric anatomy or interference with its intrinsic innervation disturb gastric emptying mechanisms and allow a substantial amount of undigested food to reach the small intestine too rapidly.^{1,2} Dumping syndrome is not a single disease entity but, instead, consists of a constellation of symptoms that can be categorized as early dumping or late dumping symptoms.^{1,2} Early dumping syndrome occurs within the first hour after a meal. Because of the hyperosmolality of the food, rapid fluid shifts occur from the plasma compartment into the intestinal lumen, resulting in hypotension and a sympathetic nervous-system response. Early dumping is characterized by gastrointestinal (GI) symptoms such as abdominal pain, bloating, borborygmi, nausea, and diarrhoea, and vasomotor symptoms such as fatigue, desire to lie down after meals, flushing, palpitations, perspiration, tachycardia, hypotension, and, rarely, syncope.^{1,2} In contrast, late dumping usually occurs 1 to 3 hours after a meal and is a result of an incretin-driven hyperinsulinemic response after carbohydrate ingestion. Hypoglycemia-related symptoms are related to neuroglycopenia (fatigue, weakness, confusion, hunger, and syncope) and autonomic/adrenergic reactivity (perspiration, palpitations, tremor, and irritability).^{1,2} Moreover, dumping syndrome cannot always be discretely separated into early and late dumping symptoms but, instead, is an entire disease spectrum whereby patients can develop early dumping, late dumping or both. Furthermore, early dumping symptoms may have resolved in some patients before late dumping symptoms present.

The prevalence of early and late dumping symptoms depends on the type and extent of surgery, as well as the definition of dumping syndrome used by study investigators. Thus, considerable heterogeneity may exist among different study populations, making it difficult to accurately compare results. Therefore, in acknowledgement of these differences, this systematic review includes a description of the study population where relevant. Dumping syndrome has been reported to occur in approximately 20% of patients who undergo vagotomy with pyloroplasty, in up to 40% of patients after Roux-en-Y gastric bypass or sleeve gastrectomy, and in up to 50% of patients who undergo esophagectomy.³⁻⁷ Dumping syndrome has also been reported to occur after Nissen fundoplication in children and in adults.^{8,9} In recent years, bariatric surgery has become the leading cause of postoperative dumping syndrome.¹⁰ Bariatric surgery results in major alterations to the anatomy and function of the GI tract.¹¹ Various types of bariatric surgery have been used in recent years, including the Roux-en-Y gastric bypass, sleeve gastrectomy, biliopancreatic diversion, vertical banded gastroplasty, and laparoscopic adjustable gastric band. The sleeve gastrectomy, vertical banded gastroplasty, and the laparoscopic adjustable gastric band are restrictive procedures, in which the volume capacity of the proximal stomach is reduced. The Roux-en-Y gastric bypass and biliopancreatic diversion are considered malabsorptive procedures

because they interfere with the normal digestion and absorption of food.¹¹ After bariatric surgery, dumping syndrome has mainly been reported in patients who underwent Roux-en-Y gastric bypass and interventions involving partial gastrectomy.¹¹ Among 450 patients who underwent a Roux-en-Y gastric bypass or sleeve gastrectomy, approximately one third (34.2%) reported postoperative symptoms consistent with postprandial hypoglycemia.¹² The mechanisms underlying dumping syndrome after bariatric surgery are numerous and remain to be fully elucidated.¹¹

Early dumping syndrome is the most frequent type of dumping syndrome and may occur in isolation or in association with late symptoms. Isolated late dumping (hypoglycemia as the only symptom) affects up to 25% of patients.^{5,13} Symptoms suggestive of early and late dumping syndrome may be severe and persist in some patients many years after surgery.^{6,14} Among 129 patients who underwent gastric bypass surgery, 12% reported severe fatigue after eating (half were so tired that they needed to lie down), 7% reported severe nausea, and 6% severe fainting.¹⁴ Approximately, 12% had persistent dumping symptoms 1 to 2 years after surgery, especially postprandial fatigue necessitating lying down; 7% had persistent nausea and 6% had persistent fainting.¹⁴

Dumping syndrome may result in either weight loss or weight gain. In severe cases, dumping syndrome is associated with a substantial reduction in quality of life and significant weight loss as a result of avoidance of food intake.¹⁵ Patients with severe dumping syndrome may experience weight loss of up to 30% of their preoperative weight.¹⁶ However, although it has previously been suggested that dumping symptoms might be essential for weight loss after bariatric surgery, a prospective series demonstrated that weight loss after Roux-en-Y gastric bypass was not dependent on the presence of dumping symptoms, and other studies suggest that some patients with dumping syndrome may exhibit weight gain.^{4,17,18} Furthermore, a Swedish nationwide cohort study of 5,040 post-gastric bypass patients demonstrated that approximately 1% were hospitalized for hypoglycemia and/or related disorders at a median of 2.7 years after surgery.¹⁹ Patients were also at increased risk for confusion, syncope, epilepsy, and seizures after gastric bypass surgery.¹⁹ Symptoms can be emotionally distressing, leading to anxiety and apprehension. Because of the large number of patients undergoing bariatric surgery, it is important to educate clinicians about how to recognize and manage dumping syndrome. Therefore, this systematic review was conducted to develop uniform guidance about the management of dumping syndrome.

SEARCH METHODOLOGY

A literature search of the PubMed database was performed to identify relevant literature published through February 2016. Search terms included 'dumping syndrome' combined with 'symptoms,' 'pathophysiology,' 'management,' 'diet,' 'pectin,' 'guar gum,' 'glucoman-

nan,' 'acarbose,' 'somatostatin analogue,' 'octreotide,' 'lanreotide,' 'pasireotide,' 'diazoxide,' 'nifedipine,' 'glucagon-like peptide 1 (GLP-1) receptor antagonist,' 'surgery,' and 'continuous enteral feeding.' The reference lists from retrieved articles were also reviewed for relevant publications. The search results were manually reviewed to eliminate commentaries and correspondence/letters related to the clinical study publications. Applying these quantitative and qualitative filters reduced the search results to approximately 160 potentially relevant citations. Each of the selected publications was reviewed for management approaches for dumping syndrome, and consensus recommendations were developed by an interdisciplinary team (endocrinologist, gastroenterologist, nutritionist, and bariatric surgeon) to provide uniform practical guidance to the different specialists involved in the management of dumping syndrome. A systematic review of diagnostic approaches for dumping syndrome was not performed, but the most widely used approaches are described herein. A more in-depth review of the diagnosis of dumping syndrome has recently been published.²⁰

PATHOPHYSIOLOGY

The pathophysiological mechanisms involved in dumping syndrome are incompletely understood. Relatively few recent studies have been devoted to elucidating the mechanisms involved in early and late dumping syndromes, and much of our current knowledge is based on older literature.²¹ Symptoms of early and late dumping syndrome appear to be caused by distinct pathophysiological mechanisms.

Early Dumping

Several concurrent phenomena contribute to the development of early dumping symptoms.^{3,22-25} Gastric surgery reduces gastric volume or removes the barrier function of the pylorus, resulting in the rapid delivery of a substantial amount of undigested solid food to the small intestine, thereby bypassing the larger part of the stomach (Figure 1).¹ Esophageal surgery may also impair gastric retentive capacity because the accompanying vagotomy causes rapid liquid emptying. Hyperosmolar nutrients in the small bowel presumably cause a shift of fluid from the intravascular compartment (ie, plasma) to the intestinal lumen, resulting in a reduction in plasma volume, tachycardia, and, rarely, syncope. Movement of fluid into the small bowel may also cause distention and contribute to cramp-like contractions, bloating, and diarrhoea. Whether this fluid shift contributes to the pathophysiology of dumping syndrome or is mainly a consequence of this process remains unknown. In favor of the latter interpretation, intravenous fluid substitution is not effective in preventing early dumping symptoms.²⁶ Another important mechanism involved in the pathophysiology of early dumping syndrome (and also late dumping syndrome as described below) involves the increased release of multiple GI hormones including vasoactive agents (e.g. neurotensin and

Figure 1. Pathophysiology of dumping syndrome. Abbreviations: GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; VIP, vasoactive intestinal peptide.

vasoactive intestinal peptide(VIP)), incretins (e.g. gastric inhibitory polypeptide (GIP) and GLP-1), and glucose modulators (e.g. insulin and glucagon).^{12,23,24} Enhanced release of these GI hormones may induce disorganized GI motility and inhibit secretion, as well as elicit hemodynamic effects; for example, neurotensin and vasoactive intestinal polypeptide induce splanchnic vasodilation that results in hypotension and systemic hemoconcentration.²⁷

Late Dumping

In contrast to the multiple pathophysiologic factors involved in early dumping syndrome, the pathophysiology of late dumping is largely attributable to the development of hyperinsulinemic or reactive hypoglycemia.^{3,22-25} Rapid delivery of undigested carbohydrates to the small intestine results in high glucose concentrations that induce a hyperinsulinemic response, resulting in subsequent hypoglycemia and related late dumping symptoms.²⁸ Enteral glucose administration is known to induce enhanced insulin release relative to intravenous administration, a process known as the incretin effect. Two GI hormones are believed to play a pivotal role in the incretin effect: glucose-dependent insulinotropic polypeptide or gastric inhibitory polypeptide and GLP-1. An increased GLP-1 response has been reported

in patients after gastric surgery, and a positive correlation has been observed between increasing GLP-1 levels and insulin release.²⁹ An additional study suggests that that GLP-1 analogues may actually stabilize glucose levels in patients with postprandial hypoglycemia after gastric bypass surgery.³⁰ Therefore, an exaggerated GLP-1 response appears to be the key mediator of the hyperinsulinemic and hypoglycemic effect that is characteristic of late dumping syndrome.^{18,29} However, the precise mechanism by which GLP1 contributes to glucose homeostasis and late dumping syndrome is likely to be complex and remains to be fully elucidated.

DIAGNOSIS

Population at Risk

Dumping syndrome should be suspected based on the concurrent presentation of multiple suggestive symptoms in patients who have undergone gastric or esophageal surgery.¹ A carefully obtained medical history and thorough symptom evaluation are very important for the accurate diagnosis of dumping syndrome. Profound fatigue after meal ingestion, with the need to lie down, is an important clinical clue. Various approaches can be used to confirm the presence of dumping syndrome, including symptom-based questionnaires, glycemia monitoring, oral glucose challenge testing, and gastric emptying studies. An additional diagnostic evaluation may also be necessary to exclude conditions that can present with similar symptoms (e.g. postoperative complications, strictures, adhesions, and insulinoma). Hypoglycemia unawareness may develop as a result of recurrent hypoglycemia, making it even more difficult to diagnose late dumping syndrome in patients who have undergone gastric bypass surgery.²⁰

Symptom-Based Questionnaires

Symptom-based questionnaires, such as the Sigstad's score and the Arts' dumping questionnaire can be used to identify patients with clinically meaningful dumping symptoms. Sigstad's score was developed to separate patients with or without postoperative dumping syndrome in the era of peptic ulcer surgery¹⁷, while Arts' dumping questionnaire was designed to differentiate between early and late dumping symptoms. The Sigstad's scoring system assigns points to each dumping symptom, and the total points are used to calculate a diagnostic index.³¹ A diagnostic index >7 is suggestive of dumping syndrome whereas a score <4 suggests that other diagnoses should be considered. Patients receive an oral glucose tolerance test (oGTT) prior to using the Sigstad's scoring system to score and grade symptom severity. The primary focus of the Sigstad's scoring system is to identify early dumping by diagnosing signs and symptoms such as a high pulse rate or increased hematocrit indicative of hypovolemia. The diagnostic accuracy of the Sigstad's scoring questionnaire in bariatric patients or after

upper GI cancer surgery has not been established.⁶ Arts *et al.* developed a dumping-severity score in which symptoms of early and late dumping (eight and six symptoms, respectively) were scored on a 4-point Likert scale.¹⁵ This questionnaire has been tested on patients with early and late dumping, and was shown to be effective at discriminating between the two sets of symptoms and was responsive to somatostatin analogue therapy, but was never formally validated.¹⁵ A relatively recent report also describes the use of a visual analogue scale (VAS) survey to evaluate early and late dumping syndromes in more than 1,000 patients after gastrectomy for gastric cancer.³² This survey used a very low cutoff for dumping complaints (VAS score >10 mm), and a single item on the questionnaire was sufficient to label patients as symptomatic for late dumping.³²

Glycemia Measurements

Single plasma glucose measurements, whether scheduled or random, can be performed during clinic visits after gastric or esophageal surgery. Although the diagnostic value of a single glucose measurement is low, its clinical value increases when evaluated in conjunction with late dumping symptoms. To date, no definitive guidance regarding cutoff values for plasma glucose has been established, but some clinicians consider plasma glucose concentrations <2.8 mmol/L (50 mg/dL) to be indicative of post-gastric bypass hypoglycemia, whereas others regard levels <3.3 mmol/L (60 mg/dL) diagnostic of hypoglycemia.³³ Capillary glucose measurements (finger prick) are not considered valid because of their lack of accuracy in the hypoglycemic range. Continuous glucose monitoring may be beneficial in complex cases of dumping syndrome.³⁴⁻³⁶

Provocative Testing

Clinical suspicion of dumping syndrome can be confirmed using provocative tests such as the oGTT or mixed-meal tolerance test.³⁷ In the glucose tolerance test, patients with suspected dumping syndrome ingest 50 g or 75 g of glucose in solution after an overnight fast. Blood glucose concentrations, hematocrit, pulse rate, and blood pressure are measured before and at 30-minute intervals up to 180 minutes after ingestion. The oGTT is considered positive for early dumping based on the presence of an early (30 minutes) increase in hematocrit >3% or an increase in pulse rate >10 beats/min after 30 minutes, the latter being regarded as the most sensitive indicator of early dumping syndrome.¹ Test results are positive for late dumping based on the development of late (60-180 minutes postingestion) hypoglycemia.¹ In the mixed-meal tolerance test, patients with suspected dumping syndrome ingest a mixed meal containing carbohydrates, fats, and proteins after an overnight fast.^{18,38} Blood samples are collected before meal ingestion and at 30-minute intervals for up to 2 hours afterward to monitor glycemic and insulin profiles. The mixed-meal tolerance test is considered positive for late dumping syndrome in patients who develop hypoglycemia between 60 and 180 minutes after meal ingestion.

The use of provocative testing to diagnose dumping syndrome is associated with several challenges. Provocative testing can be difficult in patients with small gastric pouches as a result of gastric or bariatric surgical procedures. Furthermore, the oGTT frequently detects post-gastric bypass hypoglycemia in patients with and without symptoms, as well as in healthy individuals.²⁰ Therefore, the diagnostic accuracy of this test is low and normative values have not been firmly established.²⁰ As a result, clinical practice guidelines for adult hypoglycemic disorders developed by the Endocrine Society do not support the use of the oGTT for diagnosing postprandial hypoglycemia.³⁹ The mixed meal tolerance test holds promise as a more physiologic stimulation test for the detection of post-gastric bypass hypoglycemia.^{20,40} Some studies demonstrate improved specificity of this test in asymptomatic patients; however normative values have not been established for healthy individuals.²⁰ Further validation of the mixed meal tolerance test is needed in patients with and without hypoglycemia symptoms, as well as in healthy individuals. Because there is currently no optimal approach for the diagnosis of dumping syndrome, provocative testing is still commonly used in some countries to diagnose hypoglycemia in the safety of a medical testing facility.²⁰

Gastric Emptying Studies

The rate of gastric emptying may also be used to confirm a diagnosis of dumping syndrome. A gastric emptying scintigraphy test involves eating a bland meal that contains a small amount of radioactive material, and measuring the rate of gastric emptying at hourly intervals until 4 hours after the meal. However, gastric emptying studies generally have low sensitivity and specificity, probably because the process of rapid gastric emptying occurs soon after ingestion, a phase that is not adequately assessed in most studies. Furthermore, the duration of the entire study of up to 4 hours is integrated into a single value (half emptying time), which may neutralize the rapid initial emptying effect.^{3,15,37}

DIFFERENTIAL DIAGNOSIS

A differential diagnosis should also be considered in patients with suspected dumping syndrome.

Early Dumping

Symptoms of cramp-like contractions, bloating, and diarrhoea in patients with a history of upper GI surgery may also occur as a consequence of complications such as stenosis, fistula formation, adhesions and ischemia. A marginal ulcer or gastritis is generally characterized by pain during meals, acid reflux, and nausea, and the diagnosis can be confirmed via gastroscopy. Symptoms of stenosis of anastomoses are similar to symptoms of marginal ulcer accompanied by dysphagia, and the diagnosis can be confirmed via gastroscopy or a barium or gastrografin swallow. Internal herniation generally results in pain, sometimes colic pain,

a sensation of fullness quickly after meals, sometimes ileus and vomiting and no vegetative symptoms. A diagnosis of internal herniation can be confirmed via computed tomography or diagnostic laparoscopy. The main characteristics of obstipation are a feeling of fullness, pain, and defecation only once in 3 days. Symptomatic gallstone disease is characterized by colicky pain attacks, with an urge to move, nausea, and, often, vomiting. Pain generally lasts for at least 1 hour. Diagnoses can be confirmed with an ultrasound showing gallbladder stones and blood testing confirming liver function abnormalities after colic.

Late Dumping

A differential diagnosis of hyperinsulinemic hypoglycemia is important in patients with late dumping symptoms. Late dumping occurs during the postprandial period (1-3 hours after eating). In contrast, an insulinoma, which is extremely rare, should be considered if fasting hypoglycemia occurs (i.e. not provoked by a meal).^{41,42} A fast of up to 72 hours (usually 48 hours) in a supervised hospital setting to assess hypoglycemia and the pathological lack of decrease in insulin secretion may be indicated in case of doubt.^{39,41} Surreptitious use of glucose-lowering medications (e.g. sulfonylurea derivatives or insulin) should also be excluded in each case, which can be determined via a sulfonylurea and C-peptide assay, respectively. In the case of hypoglycemia resulting from exogenous insulin injection, C-peptide levels are inappropriately low at the time of hyperinsulinemic hypoglycemia. Finally, postprandial syncope may be similar to loss of consciousness, and the two conditions may be difficult to differentiate, especially in elderly patients.

TREATMENT

Treatment approaches for dumping syndrome include dietary modifications, pharmacologic interventions and, possibly, surgical re-intervention or continuous tube feeding. Some treatments are indicated solely for late dumping (e.g. acarbose), whereas others are potentially beneficial for both early and late dumping (e.g. somatostatin analogues). The effectiveness of some of these approaches has not been clearly established as most studies included relatively few patients and were not adequately controlled. The level of evidence and grade of recommendation, as described in Table 1, supporting the use of each of these approaches in dumping syndrome is provided.

Dietary Modification (level of evidence: III; grade of recommendation: B)

Dietary modification is the initial approach used to manage dumping syndrome and is usually beneficial for a majority of patients.^{3,10,16,43-47} Therefore, proper patient education about dietary modification is very important and should be repeated before all subsequent treatment approaches. In addition, clinicians caring for patients after bariatric surgery should be aware of

Table 1: Levels of Evidence and Grades of Recommendation

Level of Evidence	Type of Evidence
I	Evidence from meta-analysis of multiple, well-designed, controlled studies (randomized trials with low false-positive and low false-negative errors)
II	Evidence from at least 1 well-designed, quasi-experimental study (randomized trials with high false-positive and high false-negative errors)
III	Evidence from well-designed, quasi-experimental studies (nonrandomized, controlled, single-group, pre-post, cohort, and time or matched case-control series)
IV	Evidence from well-designed, non-experimental studies (comparative and correlational descriptive and case studies)
V	Evidence from case reports
Grade of Recommendation	Level of Evidence
A	Level I evidence or consistent findings from multiple studies (level II, III, or IV)
B	Level II, III, or IV evidence with generally consistent findings
C	Level II, III, or IV evidence with inconsistent findings
D	Little or no systematic empirical evidence

dietary approaches for the management of dumping syndrome. Clinicians should advise patients with dumping syndrome to reduce the amount of food consumed at each meal. Patients should also delay fluid intake until at least 30 minutes after meals. Rapidly absorbable carbohydrates should be eliminated from the diet to prevent late dumping symptoms such as hypoglycemia. Instead, patients should be advised to eat a diet consisting of high-fiber and protein-rich foods; consumption of fruit and vegetables should be encouraged whereas alcoholic beverages are better avoided. Patients should also eat slowly and chew well. Education about the glycemic index of different foods may also be helpful for patients with dumping syndrome. If these recommendations are not effective or are not followed properly, patients should be advised to lie down for 30 minutes after meals to delay gastric emptying and reduce the symptoms of hypovolemia.^{1,16}

Dietary Supplements (level of evidence: III; grade of recommendation: C)

Dietary supplements that increase the viscosity of food (e.g. guar gum, pectin, and glucomannan) slow the rate of gastric emptying and delay glucose absorption. A number of short-term studies involving the ingestion of up to 15 g of guar gum or pectin with each meal have demonstrated the efficacy of these dietary supplements in slowing gastric emptying, reducing GI hormone release, improving hyperglycemia, and controlling dumping symptoms (Table 2).⁴⁸⁻⁵⁷ A single study reported that glucomannan significantly improved glucose tolerance but had no effect on glucose absorption in children with dumping syndrome who underwent various types of gastric surgery.⁵⁷ However, the palatability and tolerability of many dietary supplements are poor. Because dietary supplements are high in fiber some patients may experience gas and bloating. Furthermore, dietary recommendations to delay fluid intake until at least 30 minutes after meals means that consumption of viscous, gel-forming dietary supplements with dry food may pose a choking hazard and cause bowel obstruction as a result of a delay in the transit of food through the GI tract.

Table 2: Summary of Pectin, Guar Gum, and Glucomannan Studies in Dumping Syndrome

Study	Design	Treatment	Results
Jenkins <i>et al.</i> (48)	Case series N = 9	Pectin 14.5 g, single administration before OGTT ^a	<ul style="list-style-type: none"> • Normalized glycemia • Prevented hypoglycemic symptoms
Jenkins <i>et al.</i> (49)	Case series N = 11	Pectin 14.5 g, single administration before OGTT ^a	<ul style="list-style-type: none"> • Significantly reduced high postprandial levels of glucose, insulin, and enteroglucagon • Reduced hypoglycemia
Leeds <i>et al.</i> (50)	Case series N = 12	Pectin 15 g, single administration before OGTT ^a	<ul style="list-style-type: none"> • Improved glycemia and vasomotor symptoms • Reduced insulin levels • Prolonged gastric emptying
Lawaetz <i>et al.</i> (51)	Case series N = 4	Pectin 15 g, single administration before OGTT ^a	<ul style="list-style-type: none"> • Reduced vasomotor symptoms • Decreased levels of insulin, glucagon, neurotensin, and GIP • Slowed initial gastric emptying
Andersen <i>et al.</i> (52)	Case series N = 5	Pectin 5 g, single administration before meal ^a	<ul style="list-style-type: none"> • No effect on symptoms or gastric emptying rate
Speth <i>et al.</i> (53)	Double-blind, randomized, controlled study N = 9	Acarbose 50-100 mg, pectin 4.2 g, acarbose 50 mg plus pectin 4.2 g, placebo, after standard breakfast	<ul style="list-style-type: none"> • Acarbose and acarbose plus pectin inhibited postprandial hyperglycemia and hypoglycemia • Acarbose plus pectin inhibited hyperinsulinemia • Acarbose, pectin, and combination reduced hypoglycemic symptoms
Harju <i>et al.</i> (55)	Double-blind, controlled study N = 11	Guar gum 5 g or placebo with meals for 1 week	<ul style="list-style-type: none"> • Improved dumping symptoms
Harju <i>et al.</i> (54)	Double-blind, controlled study N = 11	Guar gum 5 g or placebo after a meal	<ul style="list-style-type: none"> • Slowed gastric emptying
Harju <i>et al.</i> (56)	Case series N = 16	Guar gum 5 g with a glucose challenge meal ^a	<ul style="list-style-type: none"> • Improved symptoms
Kneepkens <i>et al.</i> (57)	Case series N = 8	Glucomannan 1.3 g before OGTT ^a	<ul style="list-style-type: none"> • Significantly improved glucose tolerance • No effect on glucose absorption

^aEfficacy was determined by comparing assessments performed before and after treatment.

Abbreviations: OGTT, oral glucose tolerance test; GIP, glucose-dependent insulinotropic polypeptide or gastric inhibitory polypeptide.

Pharmacologic Intervention

Pharmacologic intervention plays an important role in the management of dumping syndrome in patients who fail to respond to dietary modification. Several studies have evaluated acarbose or somatostatin analogues in patients with dumping syndrome (described in detail below). The efficacy and tolerability of other pharmacologic agents have mainly been presented as case reports, and clinical evidence supporting their use in dumping syndrome is more limited.

Acarbose (level of evidence: III; grade of recommendation: B)

Acarbose is an α -glycosidase hydrolase inhibitor that slows carbohydrate digestion in the small intestine, thus blunting postprandial hyperglycemia and subsequent hypoglycemia.

Several small studies demonstrated that acarbose improved glucose tolerance, reduced GI hormone release, reduced the incidence of hypoglycemia, and improved symptoms in patients with dumping syndrome (Table 3).^{9,34,53,58-66} However, the use of acarbose as a treatment approach for dumping syndrome is limited by the fact that it affects only late dumping symptoms and may result in side effects related to carbohydrate maldigestion, such as bloating, flatulence, and diarrhoea.

Somatostatin Analogues (level of evidence: II; grade of recommendation: A)

Somatostatin analogues are an effective treatment option for patients with well-established dumping syndrome who fail to respond to and/or do not tolerate initial dietary modification and acarbose treatment. Somatostatin analogues target various steps in the pathophysiology of dumping syndrome, including delaying gastric emptying, delaying transit through the small intestine, inhibiting the release of GI hormones, inhibiting insulin secretion and inhibiting postprandial vasodilation.^{15,67-78} Somatostatin inhibition of GLP-1 secretion is mediated via activation of the somatostatin receptor subtype (sst) 5, with a lesser effect through sst2.⁷⁹ Both short- and long-acting formulations of somatostatin analogues have demonstrated efficacy by slowing gastric emptying, improving hypoglycemia, and reducing early and late dumping symptoms (Table 4).^{15,66,80-95}

Somatostatin analogues may be administered subcutaneously three times daily as a short-acting formulation or intramuscularly once every 2 to 4 weeks as a long-acting formulation. Short-acting formulations may be more effective at improving some dumping symptoms such as hypoglycemia^{15,82,83,85}; however, the need for repeated injections throughout the day is often a major limitation to the long-term administration of short-acting formulations. Long-acting formulations are preferred by patients because of less frequent administration and the associated improvements in quality of life.^{15,89} The most common adverse events associated with somatostatin analogues are diarrhoea, nausea, steatorrhea, gallstone formation and pain at the injection site. Despite the occurrence of steatorrhea, which is generally mild, patients with dumping syndrome who receive long-term somatostatin analogue therapy experience a weight gain of approximately 1%.¹ Gallstone formation may influence treatment selection for dumping syndrome.^{96,97} Furthermore, during both short-treatment and long-term treatment, a proportion of patients with dumping syndrome do not respond to currently available somatostatin analogues.^{1,15,87-89} Somatostatin analogues have not received regulatory approval for the treatment of dumping syndrome.

Pasireotide is a multireceptor-targeted somatostatin analogue with high affinity for 4 of the 5 somatostatin receptor subtypes, including sst2 and sst5. The affinity of pasireotide for sst5 is higher than that of octreotide.^{98,99} A recent case report demonstrated that pasireotide inhibited GLP-1 and insulin release more effectively than octreotide, resulting in improved control of postprandial hyperinsulinemic hypoglycemia after a gastric bypass (100). A pilot study also demonstrated that pasireotide suppressed the increase in pulse rate and late

Table 3: Summary of Acarbose Studies in Dumping Syndrome

Study	Design	Treatment	Results
McLoughlin <i>et al.</i> (58)	Case series N = 10	Acarbose 100 mg or placebo single administration before OGTT	<ul style="list-style-type: none"> Improved glycemia and symptoms Reduced increase in plasma levels of GIP and insulin No change in gastric emptying rate
Gerard <i>et al.</i> (59)	Double-blind, randomized, controlled study N = 24	Acarbose 100 mg or placebo single administration before OGTT	<ul style="list-style-type: none"> Improved reactive hypoglycemia Reduced increase in plasma levels of insulin Inhibited glucose-induced glucagon suppression
Lyons <i>et al.</i> (60)	Double-blind, randomized, controlled study N = 13	Acarbose 50 mg or placebo single administration before standard breakfast	<ul style="list-style-type: none"> Significantly attenuated hyperglycemia Reduced increase in plasma levels of GIP, enteroglucagon, and insulin No effect on plasma levels of neurotensin, VIP, and somatostatin No significant effect on symptoms No significant reduction in the number or severity of dumping attacks Most patients preferred acarbose
	n = 9	Acarbose 50 mg TID or placebo for 1 month	
Hasegawa <i>et al.</i> (61)	Case series N = 6	Acarbose 50-100 mg 3 times daily before meals for 1 month ^a	<ul style="list-style-type: none"> Attenuated glucose and insulin fluctuations Improved dumping symptoms
Ozgen <i>et al.</i> (62)	Case series N = 21	Acarbose 150 mg/day before meals for 2 weeks and 300 mg/day for the remainder of the 3-month treatment period ^a	<ul style="list-style-type: none"> Reduced early hyperglycemic and hyperinsulinemic response Reduced reactive hypoglycemia
Ng <i>et al.</i> (9)	Case series N = 6	Acarbose 12.5 mg before a meal ^a	<ul style="list-style-type: none"> Improved postprandial hypoglycemia
De Cunto <i>et al.</i> (63)	Case series N = 4	Acarbose 25-100 mg before meals ^a	<ul style="list-style-type: none"> Stabilized postprandial glucose
Valderas <i>et al.</i> (64)	Case series N = 8	Acarbose 100 mg before a meal ^a	<ul style="list-style-type: none"> Avoided postprandial hypoglycemia Reduced hyperinsulinemic response Reduced GLP-1 secretion
Ritz <i>et al.</i> (34)	Case series N = 8	Acarbose 50-100 mg, 3 times per day for 6 weeks ^a	<ul style="list-style-type: none"> Eliminated dumping symptoms Improved CGM profile
Speth <i>et al.</i> (53)	Double-blind, randomized, controlled study N = 9	Acarbose 50-100 mg, pectin 4.2 g, acarbose 50 mg plus pectin 4.2 g, placebo, after standard breakfast	<ul style="list-style-type: none"> Acarbose and acarbose plus pectin inhibited postprandial hyperglycemia and hypoglycemia Acarbose plus pectin inhibited hyperinsulinemia Acarbose, pectin, and combination reduced hypoglycemic symptoms
Vilarrasa <i>et al.</i> (66)	Multicenter, retrospective, systematic case series N = 22	Alpha-glucosidase inhibitors ^b 50 mg/8 hours orally	<ul style="list-style-type: none"> 4 patients (18%) had a partial response^c

^aEfficacy was determined by comparing assessments performed before and after treatment.

^bAlpha-glucosidase inhibitor not specified.

^c50% reduction in the number and severity of hypoglycemic events.

Abbreviations: OGTT, oral glucose tolerance test; VIP, vasoactive intestinal peptide; GIP, glucose-dependent insulinotropic polypeptide or gastric inhibitory polypeptide; CGM, continuous glucose monitoring.

Table 4: Summary of Somatostatin Analogue Studies in Dumping Syndrome

Study	Design	Treatment	Results
Subcutaneous Octreotide			
Hopman <i>et al.</i> (80)	Double-blind, randomized, controlled study N = 12	Octreotide 50 µg vs placebo before OGTT	<ul style="list-style-type: none"> Improved symptoms and suppressed postprandial rise in pulse rate Reduced peak insulin and increased nadir glycemia Slowed GI transit
Primrose and Johnston (81)	Double-blind, randomized, cross-over, controlled study N = 10	Octreotide 50 µg or 100 µg vs placebo before OGTT	<ul style="list-style-type: none"> Reduced early dumping and abolished late dumping symptoms Suppressed early dumping-associated changes in hematocrit and pulse rate Inhibited hypoglycemia
Tulassay <i>et al.</i> (82)	Double-blind, randomized, controlled study N = 8	Octreotide 50 µg vs placebo before OGTT	<ul style="list-style-type: none"> Suppressed rise in pulse rate, hematocrit, and plasma levels of VIP Prevented postprandial hypoglycemia Inhibited rise in plasma insulin and GIP
Geer <i>et al.</i> (83)	Double-blind, randomized, controlled study N = 10	Octreotide 100 µg vs placebo before OGTT	<ul style="list-style-type: none"> Prevented symptom development including late hypoglycemia Inhibited rise in plasma levels of glucose, glucagon, pancreatic polypeptide, neurotensin, and insulin Slowed gastric emptying and GI transit
Richards <i>et al.</i> (84)	Double-blind, randomized, controlled study N = 6	Octreotide 100 µg vs placebo before OGTT	<ul style="list-style-type: none"> Prevented symptom development Induced phase III migrating motor complex in the small intestine Decreased postprandial intestinal motor activity
Gray <i>et al.</i> (85)	Double-blind, randomized, cross-over, controlled study N = 9	Octreotide 100 µg vs placebo before OGTT	<ul style="list-style-type: none"> Suppressed symptoms and rise in pulse rate Inhibited insulin release Prevented hypoglycemia
Hasler <i>et al.</i> (86)	Double-blind, randomized, cross-over, controlled study N = 8	Octreotide 50 µg vs placebo before OGTT	<ul style="list-style-type: none"> Suppressed symptoms and rise in pulse rate No effect on change in hematocrit, inhibition of insulin release, prevention of hypoglycemia, or gastric emptying rate
Arts <i>et al.</i> (15)	Single-arm, open-label study N = 30	Octreotide 50 µg for 3 days ^a	<ul style="list-style-type: none"> Suppressed rise in pulse rate and hematocrit Inhibited postprandial hypoglycemia and rise in insulin plasma levels Improved early and late dumping symptoms
Vilarrasa <i>et al.</i> (66)	Multicenter, retrospective, systematic case series n = 13	Octreotide 50/100 µg/12 hours	<ul style="list-style-type: none"> 3 patients (23%) had a complete response^b 5 patients (38.4%) had a partial response^c
Long-term Treatment With Subcutaneous Octreotide			
Geer <i>et al.</i> (83)	Double-blind, randomized, controlled study N = 10	Octreotide 100 µg vs placebo; mean treatment period, 15 months	<ul style="list-style-type: none"> Provided sustained symptom control Resulted in minimal side effects Provided stable fasting plasma glucose levels, normal liver function tests, and an average weight gain of 11% during a 12-month period Most patients able to resume employment
Vecht <i>et al.</i> (87)	Single-arm, open-label study N = 20	Octreotide 25-200 µg; mean treatment period, 37 months ^a	<ul style="list-style-type: none"> Provided early relief of early and late symptoms in all patients Long-term effects less beneficial Symptom relief persisted in 80% of patients at 3 months
Didden <i>et al.</i> (88)	Single-arm, open-label study N = 34	Octreotide 25-50 µg; mean treatment period, 93 months ^a	<ul style="list-style-type: none"> Provided early relief of early and late symptoms in all patients Long-term effects less beneficial 47% of patients discontinued therapy because of side effects or lack of efficacy

Table 4: Summary of Somatostatin Analogue Studies in Dumping Syndrome (continued)

Study	Design	Treatment	Results
Long-Acting Octreotide			
Penning <i>et al.</i> (89)	Single-arm, open-label study N = 12	Octreotide LAR 10 mg every 4 weeks for 6 months vs subcutaneous octreotide	<ul style="list-style-type: none"> Both formulations improved symptoms Octreotide LAR was superior at increasing body weight and improving quality of life
Arts <i>et al.</i> (15)	Single-arm, open-label study N = 30	Octreotide LAR 20 mg for 3 months vs subcutaneous octreotide 50 µg for 3 days	<ul style="list-style-type: none"> Both formulations had a beneficial effect on dumping symptoms, hypoglycemia, and pulse rate Subcutaneous octreotide was more effective than octreotide LAR in improving hypoglycemia Octreotide LAR was associated with significantly greater improvements in quality of life and was preferred relative to subcutaneous octreotide
Pasireotide			
Deloose <i>et al.</i> (90)	Double-blind, randomized, cross-over, controlled study N = 9	Pasireotide 300 µg vs placebo for 2 weeks	<ul style="list-style-type: none"> Suppressed increase in pulse rate and late hypoglycemia Increased peak glycemia Delayed gastric emptying

^aEfficacy was determined by comparing assessments performed before and after treatment.

^bComplete resolution of hypoglycemic events.

^c50% reduction in the number and severity of hypoglycemic events.

Abbreviations: OGTT, oral glucose tolerance test; GI, gastrointestinal; VIP, vasoactive intestinal peptide; GIP, glucose-dependent insulinotropic polypeptide or gastric inhibitory polypeptide; LAR, long-acting release.

hypoglycemia, and delayed gastric emptying.⁹⁰ However, pasireotide did not demonstrate a significant improvement in dumping symptoms, and approximately 20% of patients in the pilot study discontinued treatment because of GI events.⁸⁶ A recent phase 2, dose-escalation study evaluated the pharmacokinetics, efficacy, and safety of subcutaneous pasireotide followed by long-acting release (LAR) pasireotide in dumping syndrome (NCT01637272; N = 43).^{17,101} Pasireotide effectively controlled postprandial hypoglycemia and improved changes in pulse rate and hematocrit in patients with dumping syndrome. Both subcutaneous and LAR pasireotide were well tolerated, and no new safety signals were identified.¹⁰¹ Another phase 2 study, which compared the efficacy, safety, and quality of life of LAR lanreotide versus placebo in dumping syndrome, was recently completed, but no results have been published to date (NCT01923649).¹⁰²

Other Pharmacologic Interventions (level of evidence: V; grade of recommendation: D)

Other pharmacologic interventions, such as diazoxide, nifedipine, and exendin 9-39 have also been evaluated for the management of dumping syndrome. Diazoxide is a potassium channel activator that inhibits calcium-induced insulin release. Anecdotal evidence suggests that off-label diazoxide administered at doses ranging from 100 mg to 150 mg three times daily may be effective in the treatment of late dumping symptoms, but no effect on early symptoms is expected because of its mode of action.¹⁰³ A recent multicenter, retrospective,

systematic case series reported that treatment of six patients who developed hyperinsulinemic hypoglycemia after bariatric surgery with diazoxide (168.7 ± 94 mg/day orally) resulted in a partial response (defined as a 50% reduction in the number and severity of hypoglycemic events) in 3 patients (50%).⁶⁶ Nifedipine, a calcium channel blocking agent, successfully controlled persistent hyperinsulinemic hypoglycemia in a case report of an adult patient with dumping syndrome that occurred after gastric bypass surgery.¹⁰⁴ Administration of nifedipine in combination with verapamil to 10 patients who developed hyperinsulinemic hypoglycemia after bariatric surgery resulted in a partial response in five patients (50%).⁶⁶ Continuous infusion of the GLP-1 receptor antagonist exendin 9-39 has recently been shown to correct hypoglycemia after gastric bypass, which may result in a new therapeutic approach for the management of dumping syndrome. The benefit observed with exendin 9-39 therapy is consistent with the role of GLP-1 in the development of postprandial hypoglycemia after gastric bypass.¹⁸ Because these pharmacologic interventions have only been evaluated in small studies, current evidence supporting their efficacy in dumping syndrome is generally quite limited.

Surgical Re-intervention or Continuous Enteral Feeding

Despite the availability of several effective therapeutic options, some patients will continue to experience treatment-refractory dumping syndrome. Surgical re-intervention or continuous enteral feeding are additional therapeutic approaches that can be considered in this situation.

Surgical Re-intervention (level of evidence: IV; grade of recommendation: C)

Most patients with postprandial hypoglycemia after Roux-en-Y gastric bypass respond to dietary modification and pharmacologic intervention. However, a subset of patients with severe post-Roux-en-Y gastric bypass hypoglycemia may respond inadequately, and surgical re-intervention may be considered. In general, surgical re-intervention procedures are largely ineffective, and some procedures (e.g. pancreatectomy) are rarely performed because of lack of effectiveness and high morbidity. A study of patients who underwent partial pancreatectomy because of noninsulinoma pancreatogenous hypoglycemia demonstrated that nearly 90% experienced recurrent symptoms suggestive of hypoglycemia.¹⁰⁵ Fewer than half of patients (48%) were deemed to have achieved a highly or moderately successful surgical outcome, and 25% experienced no apparent benefit.¹⁰⁵

Various surgical re-interventions have been used, including gastric tube placement, gastric bypass reversal with or without concomitant sleeve resection, and gastric pouch restriction (Table 5).^{66,103,105-123} A special consideration is the association between hypoglycemia after Roux-en-Y gastric bypass and nesidioblastosis that may result in serious and refractory neuroglycopenic symptoms, which respond to pancreatic resection and re-resection.¹²⁴ Because the development of hyperinsulinemic hypoglycemia after gastric bypass surgery is

not accompanied by islet hyperplasia or increased beta-cell turnover, nesidioblastosis has not been established as the cause of late dumping syndrome.¹²⁵

As shown in Table 5, approximately 24% of patients who underwent surgical re-intervention because of refractory severe post-Roux-en-Y gastric bypass hypoglycemia received a gastric bypass reversal^{66,103,106-113} and approximately 9% had gastric pouch restriction^{66,114,115}. Pancreatic resection, the most commonly reported procedure, was performed in approximately 67% of patients.^{103,105,107,114,116-123} Some patients underwent two or more consecutive surgical re-interventions or combined re-interventions for severe hypoglycemia. The proportion of patients with symptom resolution after each procedure was generally higher for gastric bypass reversal or gastric pouch restriction than for pancreatic resection. Complications of surgical re-intervention included recurrent symptoms, diabetes, and weight gain. Most surgical re-intervention studies were relatively small and presumably included highly selected patients, mean follow-up was short, and the methodology used to evaluate hypoglycemia was not consistent. Furthermore, the effectiveness of one surgical re-intervention procedure relative to another has not been evaluated in adequately controlled clinical studies. Conservative management approaches should be pursued before attempting surgical re-intervention as patients with dumping syndrome may experience symptomatic improvement over time.

Continuous Enteral Feeding (level of evidence: V; grade of recommendation: D)

An additional approach for the management of refractory dumping syndrome involves the provision of a constant supply of nutrients via a feeding jejunostomy. Anecdotal evidence suggests that continuous enteral feeding may be beneficial in avoiding dumping symptoms after meal ingestion; however, this approach is invasive and may impair quality of life.^{1,126} Restoring the original nutrient transit route via placement of a gastric tube in the remnant stomach was also reported to be effective.¹²⁷ Standardized liquid meal administration via a gastric tube demonstrated complete reversal of severe metabolic abnormalities including hypersecretion of insulin and incretin hormones such as GLP-1 compared with oral administration.¹²⁷ The authors of this publication also restored glucose homeostasis via the placement of a gastric tube in the remnant stomach of a patient who had undergone gastric bypass surgery (Dr. van Beek, unpublished observation). However, as these findings are based on individual case reports, clinical evidence supporting the use of continuous enteral feeding in the management of dumping syndrome is very limited.

CONCLUSION

Dumping syndrome is a well-known but under-recognized complication of esophageal and gastric surgery and is becoming increasingly prevalent with the rising incidence of bariatric surgery. Severe dumping syndrome, in particular, can result in disabling symptoms that im-

Table 5: Summary of Surgical Re-intervention Studies for Post-Roux-en-Y Gastric Bypass in Dumping Syndrome

Study	Patients	Procedure	Results
Gastric Bypass Reversal			
Patti <i>et al.</i> (99)(103)	Case report N = 1	Gastric bypass reversal	<ul style="list-style-type: none"> Ineffective in reversing hypoglycemia Partial pancreatectomy required
Campos <i>et al.</i> (106)	Prospective study N = 5	Gastric bypass reversal, n = 2; modified sleeve gastrectomy, n = 3	<ul style="list-style-type: none"> No postoperative episodes of neuroglycopenia No or minimal hypoglycemic episodes Hypocalcemia became responsive to oral replacement therapy
Lee <i>et al.</i> (107)	Case report N = 2	Gastric bypass reversal	<ul style="list-style-type: none"> Ineffective in reversing hypoglycemia
Vilallonga <i>et al.</i> (108)	Retrospective database analysis N = 9	Gastric bypass reversal; patients with marked normalization of the gastrostomy tube glucose tolerance test	<ul style="list-style-type: none"> No new episodes of severe hypoglycemia 3 patients received a concomitant sleeve gastrectomy Severe gastroesophageal reflux disease and/or chronic diarrhea reported by some patients
Vilarrasa <i>et al.</i> (66)	Multicenter, retrospective, systematic case series n = 3	Gastric bypass reversal	<ul style="list-style-type: none"> Hypoglycemia resolved in 2 patients (67%) Hypoglycemia persisted in 1 patient (33%) but was controlled by alpha-glucosidase inhibitors
Rao <i>et al.</i> (109)	Case report N = 1	Laparoscopic gastric bypass reversal	<ul style="list-style-type: none"> Marked reduction in hypoglycemia burden 9 months after reversal
Carter <i>et al.</i> (110)	Retrospective analysis N = 3	Sleeve gastrectomy	<ul style="list-style-type: none"> Dumping symptoms and hypoglycemia resolved 1 patient developed portal vein thrombus and seroma 2 patients were readmitted to hospital and required supplemental nutrition
Lakdawala <i>et al.</i> (111)	Case series N = 5	Laparoscopic conversion to sleeve gastrectomy	<ul style="list-style-type: none"> Dumping syndrome resolved No complications were reported
Huang <i>et al.</i> (112)	Case report N = 2	Laparoscopic conversion to loop duodenojejunal bypass with sleeve gastrectomy	<ul style="list-style-type: none"> Dumping symptoms resolved After 6 months, the Sigstad's score decreased to 2 points No complications were reported
Huang <i>et al.</i> (113)	Case report N = 1	Laparoscopic conversion to modified duodenal switch	<ul style="list-style-type: none"> Dumping symptoms resolved No complications were reported
Gastric Pouch Restriction			
Z'graggen <i>et al.</i> (114)	Case series N = 10*	Gastric pouch downsized; silastic (Fobi) ring around pouch, n = 6; adjustable band, n = 4	<ul style="list-style-type: none"> No new hypoglycemic episodes All had symptomatic improvement (assessed via the Sigstad score)
De Heide <i>et al.</i> (115)	Case report N = 1	Laparoscopic adjustable banding for pouch dilatation	<ul style="list-style-type: none"> Subjective improvement in symptoms
Vilarrasa <i>et al.</i> (66)	Multicenter, retrospective, systematic case series n = 1	Resection of the "candy cane" roux limb	<ul style="list-style-type: none"> Patient was symptom-free 1 year after procedure
Pancreatic Resection			
Patti <i>et al.</i> (103)	Case series N = 3	Distal pancreatectomy (80%), n = 2; subtotal pancreatectomy (85%), n = 1	<ul style="list-style-type: none"> 1 patient who previously had an unsuccessful gastric bypass reversal and distal pancreatic resection required a total pancreatectomy for recurrent symptoms 1 patient had improvements but still experienced episodes of hypoglycemia 1 patient had no hypoglycemic episodes

Table 5: Summary of Surgical Re-intervention Studies for Post-Roux-en-Y Gastric Bypass in Dumping Syndrome (continued)

Study	Patients	Procedure	Results
Clancy <i>et al.</i> (116)	Case report N = 2	Distal pancreatectomy (80%), n = 1; subtotal pancreatectomy (95%), n = 1	<ul style="list-style-type: none"> 80% pancreatectomy^b unsuccessful; pancreaticoduodenectomy required Subtotal pancreatectomy successful
Alvarez <i>et al.</i> (117)	Case report N = 1	Distal pancreatectomy	<ul style="list-style-type: none"> Symptom-free for >10 months
Barbour <i>et al.</i> (118)	Retrospective analysis N = 2	Distal pancreatectomy, n = 1; duodenum-preserving pancreatic head resection, n = 1	<ul style="list-style-type: none"> Symptoms resolved after distal pancreatectomy Patient with pancreatic head resection had persistent symptoms and underwent distal pancreatectomy
Z'graggen <i>et al.</i> (114)	Case series N = 3 ^a	Distal pancreatectomy and Fobi ring around gastric pouch, n = 2; distal pancreatectomy (50%-60%) and removal of pouch band, n = 1	<ul style="list-style-type: none"> No new hypoglycemic episodes
Rumilla <i>et al.</i> (119)	Case series N = 27	Partial pancreatectomy	<ul style="list-style-type: none"> 8 patients had recurrent or ongoing mild symptoms
Mathavan <i>et al.</i> (120)	Retrospective study N = 9	Distal pancreatectomy (80%)	<ul style="list-style-type: none"> 2 patients had complete symptom resolution 3 had occasional symptoms 2 had frequent symptoms 2 patients had severe symptoms refractory to medical therapy (calcium channel blockers, diazoxide, and octreotide) Both patients had extended (95%) pancreatic resection; 1 had resolution of symptoms and symptoms persisted in the second patient
Vanderveen <i>et al.</i> (105)	Retrospective chart review N = 33	Pancreatic resection	<ul style="list-style-type: none"> Approximately 40% of patients had moderate or highly successful surgical outcomes, with an improvement in hypoglycemic symptoms
Rabiee <i>et al.</i> (121)	Case report N = 1	Distal pancreatectomy (85%)	<ul style="list-style-type: none"> Symptoms resolved but elevated levels of GLP-1 persisted
Ceppa <i>et al.</i> (122)	Case report n = 1	Distal pancreatectomy	<ul style="list-style-type: none"> Hypoglycemia persisted and a total pancreatectomy was required
Qintar <i>et al.</i> (123)	Case report N = 1	Distal pancreatectomy (80%)	<ul style="list-style-type: none"> Full remission initially after surgery but hypoglycemia recurred after 6 months Hypoglycemia recurrence well-controlled by octreotide therapy
Lee <i>et al.</i> (107)	Case report N = 1	Distal pancreatectomy	<ul style="list-style-type: none"> Distal pancreatectomy was followed by gastric bypass reversal Gastric bypass reversal was ineffective in reversing hypoglycemia
Vilarrasa <i>et al.</i> (66)	Multicenter, retrospective, systematic case series n = 3 ^c	Partial pancreatectomy	<ul style="list-style-type: none"> Hypoglycemia resolved in 2 patients (67%)

^a2 additional patients (N = 12) with concomitant pancreatic resection excluded from the gastric pouch restriction subgroup but are included in the pancreatic resection subgroup. ^bResection of 80% of the total pancreatic volume starting from the pancreatic tail. ^cRoux-en-Y gastric bypass or other malabsorptive procedure. Abbreviation: GLP, glucagon-like peptide.

pair quality of life. No medications are currently approved for the management of dumping syndrome, and most of the currently available treatments have considerable limitations, including failure to target early symptoms and poor tolerability.

Our recommendations for the diagnosis and management of dumping syndrome are based on available published clinical information and are presented in Figure 2. Patients who have undergone esophageal or gastric surgery should be monitored for symptoms suggestive of early and late dumping. Suspected dumping syndrome should preferably be

Figure 2. Recommended diagnosis and management strategies for dumping syndrome. ^aLimited evidence only.

confirmed using symptom-based questionnaires, glycemia monitoring, or, probably most effectively, in a challenge using a modified oGTT or mixed-meal tolerance test. The differential diagnostic evaluation should also consider other postoperative conditions or complications that may present with similar symptoms. First-line management of dumping syndrome should focus on dietary modification for 3 to 4 weeks, with addition of acarbose treatment for patients who experience postprandial hypoglycemia. If dietary modification and acarbose treatment are unsuccessful, somatostatin analogue therapy should be considered in patients with dumping syndrome who are experiencing incapacitating symptoms and impairment in quality of life. Short- and long-acting somatostatin analogue therapy should be attempted for 2 weeks and for 2 months, respectively. Based on patient preference, long-acting somatostatin analogue formulations are probably the treatment of choice because they require less frequent administration and have less impact on quality of life compared with short-acting somatostatin analogues. However, short-acting somatostatin analogues seem to provide the most rigorous control of pulse rate and glycemia fluctuations associated with dumping syndrome. Surgical re-intervention or continuous gastric/enteral feeding may need to be considered in some patients with treatment-refractory dumping syndrome, but the outcomes of these approaches are poorly studied and tend to be more variable.

Finally, effective management of dumping syndrome requires close collaboration between specialists trained in recognizing and treating dumping symptoms, including those with expertise in gastroenterology, endocrinology, surgery, and nutrition. Given the increase in bariatric procedures and, thereby, the potential for an increase in the prevalence of dumping symptoms, prospective clinical studies are needed to evaluate the occurrence of dumping syndrome and to assess the effect of early detection and treatment of clinical symptoms on weight loss and quality of life.

ACKNOWLEDGEMENTS

Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals. We thank Ann Marie Fitzmaurice, PhD (ProEd Communications, Inc.) for editorial assistance.

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Part II

Improving understanding of dumping
syndrome

Chapter 4

The short- to mid-term symptom prevalence of dumping syndrome after primary gastric-bypass surgery and its impact on health-related quality of life.

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Surg Obes Relat Dis. 2017 Sep ;13(9): 1489 -1500

ABSTRACT

Background

Early and late dumping are complications of gastric bypass surgery. Early dumping occurs within an hour after eating, when the emptying of food into the small intestine triggers rapid fluid shifts into the intestinal lumen and the release of gastrointestinal hormones, resulting in gastrointestinal and vasomotor symptoms. Late dumping occurs between 1 and 3 hours after carbohydrate ingestion and is caused by an exaggerated insulin release, resulting in hypoglycaemia. Almost no data are currently available on the prevalence of early and late dumping or their impact on health-related quality of life (QoL).

Objectives

To study the prevalence of early and late dumping in a large population of patients having undergone a primary Roux-en-Y gastric bypass (RYGB) and its effect on QoL.

Setting

Cross-sectional study at a single bariatric department in the Medical Center Leeuwarden, The Netherlands between 2008 and 2011.

Methods

In 2013 this descriptive cohort study approached by email or post all patients who underwent a primary RYGB in the setting between 2008 and 2011 in one hospital. These patients were asked to fill in standardized questionnaires measuring their QoL (RAND-36), anxiety and depression (HADS), fatigue (MFI-20) and any disease specific indicators of early and late dumping syndrome.

Results

The questionnaire was completed and returned by 351 of 613 patients (57.1%) and 121 nonobese volunteers. Participants were mostly female (80%), aged 42 (40 – 54 years), with an excess weight loss of 76.8% [IQR 61 – 95] after RYGB surgery 2.3 [IQR 1.6 – 3.4] years earlier. Self-reported complaints of moderate to severe intensity suggestive of early and late dumping were present in 18.8 and 11.7% of patients, respectively. Patients with early and late dumping demonstrated significantly lower scores on the RAND-36 and HADS compared to patients without dumping. No differences were seen in the MFI-20 scores between patients with or without early and late dumping.

Conclusion

In this descriptive cohort, self-reported complaints suggestive of early and late dumping of moderate-to-severe intensity were, respectively, 18.8 and 11.7% in a cohort after primary gastric bypass surgery. These complaints were associated with markedly reduced health related quality of life.

INTRODUCTION

Morbid obesity is a growing health care problem in the world. Its prevalence is increasing and, consequently, weight-loss strategies are needed. Weight-loss surgery is the most effective way to achieve sustained weight loss, resolve comorbidity, and improve rates of survival.¹ One of the most frequently performed weight loss operations is the laparoscopic Roux-en-Y gastric bypass (RYGB). This is an effective procedure but it is known to result in several long-term side effects, with some beneficial effects (rapid transit time, stimulation of L cells and secretion of GLP-1 and therefore remission of diabetes) as well as adverse effects such as dumping syndrome.^{2,3}

Two variants of dumping syndrome have been differentiated – namely, early and late dumping – and distinct pathogenic mechanisms have been proposed for both variants. Early (hypovolemic) dumping is probably caused by the entry of undigested food in the small bowel. Relative intravascular volume contraction and hemoconcentration occur as a consequence of an osmotic shift of fluids from the intravascular compartment into gut lumen. A drop in plasma volume, elevation of the hematocrit, and an acceleration of the heart rate have been observed in patients with early dumping in response to an oral hyperosmolar glucose load. Symptoms start between a few minutes to an hour after a meal and include autonomic symptoms as sweating, palpitations, drowsiness, and the need to lie down. Late dumping (also known as post-gastric bypass hypoglycemia) is in general ascribed either to a reset of incretins after bypassing the duodenum (foregut theory) or to the entry of undigested food in the jejunum (hindgut theory).^{4,5} Consequently, increased levels stimulate beta cells in the pancreas, which in turn induce an increase in the postprandial production of insulin. This phenomenon starts soon after a meal and results between 1 and 3 hours later in typical symptoms related to hypoglycemia such as sweating, drowsiness, trembling or even coma. Usually, these symptoms of late dumping start 1-3 years after gastric bypass operation.⁴

The incidence of early dumping after gastric bypass – measured by questionnaire or hematocrit change – is estimated to be between 12 and 42%.⁶⁻⁹ Svennevig et al. reported on self-reported symptom prevalence for patients after gastrectomy for gastric ulcer.⁸ They reported a prevalence for early dumping of 14% for daily symptoms and 19% of the patients had symptoms occasionally. Laurennius et al. reported a prevalence of early dumping of 12%, measured with a self-developed questionnaire.⁶ The prevalence of late dumping as assessed by oral glucose tolerance test or mixed meal tolerance test is estimated between 17 and 68%.^{7,10-12} No data are available in literature with regard to self-perceived complaints of late dumping after RYGB.

The treatment for dumping begins with modifications to the diet, mainly to eliminate or reduce the intake of carbohydrates. The second step is medication (ranging from Acarbose to Liraglutide), followed by revisional procedures such as undoing the gastric bypass or performing a (partial) pancreatectomy.¹³

Quality of life (QoL) after weight loss surgery is improved in comparison with that of obese volunteers not undergoing weight loss surgery.^{1,14-16} In addition, the improved QoL is reported to be relatively stable for years after surgery.¹⁵ However, it is unknown to what extent early and late dumping influence health-related QoL in patients after gastric-bypass surgery.

Therefore, our aim is to investigate both the symptom prevalence of dumping after primary gastric bypass surgery by the dumping severity score and its associated impact on health-related QoL. The prevalence of self-reported complaints was compared with healthy controls with no history of gastric surgery, to test whether the same complaints are prevalent in a group of healthy, nonobese volunteers.

METHODS

Study population, patient group

For this descriptive cohort study, we created a database of all patients who underwent a primary Roux-en-Y gastric bypass at single bariatric center between 2008 and 2011. Preoperative assessment of patients eligible for surgery included counselling by dietician and psychologist in order to exclude people with non-adjusted eating patterns or eating disorders. If detected, these issues were addressed before any surgery was considered. All patients were screened before operation according to the criteria outlined by the International Federation for Surgery of Obesity and metabolic disorders (IFSO).¹⁷

In 2013, all patients were invited to participate in a questionnaire survey. Four rounds of invitations were sent (3 by post and one by email). For the purpose of this study, all patients who underwent primary gastric bypass were selected, but patients with a history of earlier stomach operation were excluded. Other operations were not a reason for exclusion. Records for individual patients were completed by data review. The study protocol was approved by the Regional Ethical Review Board of the Medical Centre, Leeuwarden.

Weight Loss

The ideal weight of every patient was estimated based on a target BMI of 25. The percentage of excess weight loss (%EWL) was calculated as $((\text{operative weight} - \text{follow-up weight}) / \text{operative excess weight}) \times 100$. The Total Weight Loss (TWL) was calculated as $((\text{operative weight} - \text{follow-up weight}) / \text{operative weight}) \times 100$. We used the weight and height of patients at their last outpatients visit and we calculated from this EWL and TWL. We compared the weight measured at outpatient clinic with self-reported weight of the patients.

Operation details

All 3 surgeons performing the RYGB operations complied with a standardized operation technique on all patients. Routine antibiotics prophylaxis was administered. The pouch

was created by linear stapling (Ethicon Endo-Surgery, Inc, Cincinnati, USA). We started the creation of the pouch approximately 4-5 cm below the gastroesophageal junction at the lesser curvature. The estimated volume of the pouch was 30-60cc. The biliopancreatic limb was measured at 80cm from the angle of Treitz. With this loop, the gastroenterostomy was made by linear stapling and the anterior defect was closed with sutures. An alimentary limb of 150 cm was measured and the enteroenterostomy was fashioned with the endoscopic linear stapler and interrupted sutures. Confirmation of integrity of both anastomoses was performed by methylene and air-leak testing after introduction of a gastric tube by the anaesthesiologist. In the event of leakage, additional sutures were placed. After testing for both anastomoses, the Roux-en-Y construction was completed by dividing the loop with linear stapling between the two anastomoses. Mesenteric defects were not closed.

Group of volunteers

To evaluate whether our study was identifying abnormal symptoms or the normal gastrointestinal complaints associated with oral intake (i.e. the “after-dinner dip”), we also presented the dumping severity score to a group of healthy, nonobese volunteers.

For this we asked more than hundred healthcare workers working on the operation room or the outpatient department of the medical center to complete our questionnaire. Volunteers with diabetes mellitus or a history of a gastric operation were excluded. The volunteers completed the same questionnaire regarding on their complaints of early and late dumping as well as questions about use of medication. A power analysis to calculate the minimum number of volunteers for adequate study power was 98 (alpha 0,05 and power 90%, assuming the prevalence for early and late dumping was zero in the volunteer group and in the gastric bypass group 10%).

Questionnaires

Dumping severity score (Table 1a and 1b). The prevalence of early and late dumping can be estimated by several questionnaires assessing subjective complaints; however, none of these is adequately validated. The Dumping Severity Score (DSS) was ultimately chosen because it is the only questionnaire available that differentiates between early and late dumping. In addition, it uses a simple scale to estimate severity of the complaints. The dumping severity score, based on symptom pattern descriptions in the literature, is using a 4-point Likert scale.¹⁸ The patient was asked to grade the intensity (0 = absent; 1 = mild; 2 = moderate and 3 = severe, interfering with daily activities) of 8 early dumping symptoms (within 1 hour after food ingestion) and 6 hypoglycemia symptoms (more than 1 hour after food ingestion).¹⁸

To assess the psychological impact of these complaints we also asked if this provoked anxiety or insecurity. Patients were asked if they had complaints as mentioned in the dumping severity score in the last month.

Table 1a: Questionnaire for early dumping symptoms

Do you experience any of the following complaints within one hour after eating a meal?

	No complaints	Mild	Moderate	Severe, interfering with daily activities
Sweating	0	0	0	0
Flushes	0	0	0	0
Dizziness	0	0	0	0
Palpitations	0	0	0	0
Abdominal pain	0	0	0	0
Diarrhoea	0	0	0	0
Bloating	0	0	0	0
Nausea	0	0	0	0
I feel scared, anxious or troubled by these complaints	0	0	0	0

Table 1b: Questionnaire for late dumping symptoms

Do you experience any of the following complaints in the period between one and 3 hours after eating a meal?

	No complaints	Mild complaints	Moderate complaints	Severe, interfering with daily activities
Sweating	0	0	0	0
Palpitations	0	0	0	0
Hunger	0	0	0	0
Drowsiness/unconsciousness	0	0	0	0
Tremor	0	0	0	0
Irritability	0	0	0	0
I feel scared, anxious or troubled by these complaints	0	0	0	0

We defined a high suspicion of early dumping as someone having 3 or more symptoms (including at least one autonomic symptom) with an intensity of 2 or 3 (i.e., moderate or severe, interfering with daily activities) on the early dumping severity score. A high suspicion of late dumping (post-gastric bypass hypoglycemia) was defined as having 3 or more symptoms (including at least one neuroglycopenic symptom) with an intensity of 2 or 3 (i.e., moderate or severe, interfering with daily activities) on the late dumping severity score. Mild symptoms were not included.

Additional questions (on self-measured blood glucose levels, the occurrence of neuroglycopenia and the potential related use of health care and treatment) were asked with regard to dumping, weight development, comorbidities and use of medication. These responses were checked against the data collected at the patients' last outpatient visits.

Quality of life questionnaires

RAND-36.

HR-QoL was measured with the RAND-36 questionnaire, which contains 36 questions on various aspects of general wellbeing over the preceding four weeks. The items are formulated as statements or questions with Likert scale response options. These are organized into 8 sections (physical functioning, physical problems, bodily pain, general health, vitality, social functioning, emotional problems and mental health) linearly converted to a scale of 0 to 100. The first 3 sections measure physical health, the last 3 measure mental health, and the general health and vitality scales are sensitive to both physical and mental health outcomes. Higher scores represent better QoL.¹⁹ Normative data by age are available for the Dutch population.²⁰ The RAND-36 is almost identical to the 36-item Short Form Health Survey (SF-36).

Multidimensional Fatigue Inventory-20.

The Multidimensional Fatigue Inventory-20 (MFI-20) records fatigue. It contains 20 statements organized into 5 sections (general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue). Each section has a maximum score of 20.²¹ Higher scores indicate a higher level of fatigue or impairment. Dutch normative data were derived from Smets et al.²²

Hospital Anxiety and Depression Scale.

The Hospital Anxiety and Depression Scale (HADS) consists of 14 statements divided into 2 sections related to anxiety and depression.²³

Each item is scored on a scale of 1-3, with higher scores per section indicating more severe anxiety or depression. Clinical depression or anxiety are indicated by a score of 6 or higher on the depression scale or 7 or higher on the anxiety scale out of 21. Dutch normative data were derived from Spinhoven et al.²⁴

Hypoglycemia Fear Scale-II.

The Hypoglycemia Fear Scale II (HFS-II) is a 33-item questionnaire with 2 subscales that measure behaviors to avoid hypoglycemia and its negative consequences and worries about hypoglycemia.^{25,26} Responses are made on a 5-point Likert scale where 0 = Never and 3 = Always. We used the 12-item Worry subscale which has a score range of 0 - 72 with higher scores indicating increased fear of hypoglycemia. The HFS-II is a widely used measure in clinical trials, has been translated into more than 20 languages, and has demonstrated reliability and validity in type 1 diabetic patients.²⁷

Statistics

Data are presented as mean ($\pm$ standard deviation), median [interquartile ranges, IQR], frequencies or percentages where appropriate. Differences were assessed with unpaired *t* tests (for continuous variables) or Chi-square tests (for categorical variables). An alpha level of 0.05 was used for determining statistical significance. For graphical representation, study population mean with 95% confidence intervals are shown. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, Inc., Armonk, NY, USA), version 22.

RESULTS

Response

In the period between 2008 and 2011, a total of 615 patients at the Center underwent a primary laparoscopic RYGB for morbid obesity. Of this group, 2 patients died during follow up (both of malignancies). Thus, 613 patients were contacted and asked to participate in this study. The invitation was declined by 42 patients (6.8%). Despite repeated invitations 211 patients did not respond. The questionnaire was completed and sent back by 360 patients. Nine of the returned questionnaires were not usable because they could not be linked to the correct patients. Thus, the number of questionnaires for the patient group analyzed for this study was 351 (57.3%).

The questionnaire was also completed by 121 health care workers.

Demographics

In the patient group participants were mostly female (80%), and the group of volunteers contained 74 females (61.2%). The mean age for the patient and volunteer group was 46 ± 10 years and 42 ± 12 years respectively ($p < 0.001$). No significant differences was seen between the self-reported weight and the weight at the outpatients clinic. (Table 2a and 2b).

The weight and body mass index (BMI) during the study was significantly different between patients and volunteers: weight 86 ± 19 kg and BMI 29 ± 5.6 kg/m² versus weight 74 ± 12 kg and BMI 23 ± 2.9 (both $p < 0.001$). In the volunteer group the maximum BMI was 33, and 30% of the volunteers had a BMI above 25.

The median follow up for the patient group after surgery was 27 [IQR 20 – 34] months. The patient group had an excess weight loss of 76.8% [IQR 61 – 95%] and underwent RYGB surgery 2.3 [IQR 1.6 – 3.4] years earlier.

In the patient group, the participants were highly comparable in all aspects to those who had declined participation or who had not responded, with the exception of age - responders were slightly older (median [IQR]: 47 [39-53] versus 43 [36-51] years; p value = 0.02). No other differences were present.

Table 2a: Clinical characteristics of the study population at high suspicion for early dumping compared to patients at low suspicion.

	High suspicion group for early dumping	Low suspicion group for early dumping	P-value
Number	68	283	
Age (y)	46 [39; 53]	47 [40; 54]	0.824
Female (%)	62 (91.2)	220 (77.7)	0.011
Time between surgery and study (months)	31 [24;37]	26 [19; 33]	0.106
Time between surgery and last visit (months)	19 [14; 24]	20 [14; 26]	0.81
Weight and weight loss			
Weight at surgery (kg)	122 [111; 139]	131 [117; 147]	0.08
Lowest weight after surgery, self-reported (kg)	75 [66; 90]	83 [71; 99]	0.76
Current weight, self-reported (kg)	83 [73; 94]	87 [75; 103]	0.156
Weight at last outpatient visit (kg)	84 [74; 98]	91 [78; 107]	0.155
EWL at last outpatient visit (%)	76 [55; 90]	71 [54; 90]	0.759
TWL at outpatient visit (%)	29 [23; 37]	31 [23; 38]	0.545
Comorbidities preoperative			
Type 2 diabetes	20 (29.4)	84 (29.7)	1.000
Hypertension	29 (42.6)	128 (45.4)	0.786
Dyslipidemia	16 (23.9)	54 (19.6)	0.499
Sleep apnea	7 (10.3)	31 (11.0)	1.000
Comorbidities postoperative			
Type 2 diabetes, self-reported	11 (16.2)	26 (9.2)	0.121
Hypertension, self-reported	7 (10.3)	55 (19.4)	0.079
Dyslipidemia, self-reported	13 (19.1)	28 (9.9)	0.056
Sleep apnea, self-reported	0	13 (4.6)	0.081
Postoperative support and life style			
Support of dietician	9 (13.2)	8 (2.8)	0.002
Support of psychologist	7 (10.3)	26 (9.2)	0.817
Sport (more than 30 minutes per week)	37 (53.4)	164 (58)	0.313
Smoking	12 (17.6)	48 (17.0)	0.859
Treatment satisfaction			
Satisfaction with result of operation?	60 (88.2)	260 (91.9)	0.344
Would you do the operation again?	62 (91.2)	278 (98.2)	0.009

TWL = total excess weight loss

Data are median and interquartile ranges [IQR], or numbers and frequencies (percentages).

Symptoms of early and late dumping

In the patient group, the prevalence and severity of the individual symptoms of early and late dumping is shown in Table 3. Bloating, abdominal pain and nausea were the most frequent complaints in early dumping. For late dumping, the most frequent complaints were hunger, drowsiness and irritability.

Table 2b: Clinical characteristics of the study population at high suspicion for late dumping compared to patients at low suspicion.

	High suspicion group for late dumping	Low suspicion group for late dumping	P-value
Number	40	311	
Age (y)	41 [37; 49]	47 [40; 54]	0.034
Female (%)	35 (87,5)	247 (79,4%)	0.226
Time between surgery and study (months)	31 [20-41]	27 [19-33]	0.176
Time between surgery and last visit (months)	20 [14; 29]	20 [14; 26]	0.989
Weight and weight loss			
Weight at surgery (kg)	125 [116; 140]	130 [116; 146]	0.233
Lowest weight after surgery, self-reported (kg)	79 [68; 98]	81 [70; 98]	0.617
Current weight, self-reported (kg)	86 [74; 104]	86 [75; 102]	0.762
Weight at last outpatient visit (kg)	86 [73; 105]	90 [78; 107]	0.270
EWL at last outpatient visit (%)	77 [56; 104]	72 [54;90]	0.226
TWL at last outpatient visit (%)	32 [25; 39]	30 [25; 37]	0.505
Comorbidities preoperative			
Type 2 diabetes	11 (27.5)	93 (29.9)	0.754
Hypertension	15 (37.5)	141 (45.3)	0.339
Dyslipidemia	6 (15.0)	63 (20.3)	0.434
Sleep apnea	7 (17.5)	31 (10.0)	0.339
Comorbidities postoperative			
Type 2 diabetes, self-reported	4 (10,0)	33 (10.6)	0.906
Hypertension, self-reported	6 (15.0)	56 (18.0)	0.639
Dyslipidemia, self-reported	7 (17.5)	34 (10.9)	0.223
Sleep apnea, self-reported	7 (17.5)	31 (10.0)	0.504
Postoperative support and life style			
Support of dietician	8 (20.0)	9 (2.9)	<0.001
Support of psychologist	6 (15.0)	27 (8.7)	0.197
Sport (more than 30 minutes per week)	24 (60.0)	177 (46.9)	0.563
Smoking	5 (12.5)	56 (18.0)	0.387
Treatment satisfaction			
Satisfaction with result of operation?	31 (77.5)	289 (92.9)	0.001
Would you do the operation again?	34 (85.0)	306 (98.4)	<0.001

EWL = excess weight loss

Data are median and interquartile ranges [IQR], or numbers and frequencies (percentages).

In the volunteer group moderate-to-severe postprandial complaints were rare. Only 2 patients had some symptoms of early dumping (sweating, dizziness, palpitations, abdominal pain and diarrhea), and no differences were observed between volunteers whose BMI was below or above 25.

Table 3: Prevalence and intensity of early and late dumping symptoms.

<i>Early dumping</i>	Absent	Mild	Moderate	Severe, interfering with daily activities	Missing
Abdominal symptoms					
Abdominal pain (%)	50.0	29.5	14.8	5.1	0.6
Diarrhoea (%)	60.2	24.4	10.5	4.3	0.6
Bloating (%)	38.4	39.5	16.8	4.8	0.6
Autonomic symptoms					
Nausea (%)	50.0	30.7	15.3	3.7	0.3
Sweating (%)	70.5	17.0	9.7	2.6	0.3
Flushing (%)	67.0	18.2	10.5	3.7	0.6
Dizziness (%)	61.9	22.4	11.4	3.1	1.1
Palpitations (%)	64.5	20.7	11.6	3.1	0.0
I feel scared, anxious or troubled by these complaints (%)	69.3	21.3	8.8	0.6	0.0

<i>Late dumping</i>	Absent	Mild	Moderate	Severe, interfering with daily activities	Missing
Autonomic symptoms					
Sweating (%)	79.3	13.4	5.1	1.7	0.6
Palpitations (%)	77.6	15.6	5.7	0.9	0.3
Hunger (%)	56.5	23.6	17.3	2.0	0.6
Tremor (%)	66.8	19.9	10.2	2.6	0.6
Neuroglycemic symptoms					
Drowsiness/unconsciousness (%)	59.1	20.7	15.6	4.3	0.3
Irritability (%)	65.6	17.0	13.1	4.0	0.3
I feel scared, anxious or troubled by these complaints (%)	72.7	18.2	6.8	1.7	0.6

Data are numbers and frequencies (percentages)

For the symptoms of late dumping, 4 volunteers were moderately hungry 1 one had complaints of drowsiness; this was the similar for volunteers whose BMI below of above 25. Complaints of moderate or severe tremor, sweating and/or irritability were only seen in the group of volunteers with BMI of more than 25; this differed significantly from volunteers with BMI of less than 25, where 5 volunteers had complaints of tremor ($p = 0.028$), one had sweating ($p = 0.029$), and 2 suffered from irritability ($p = 0.004$). All the differences between patients and volunteers in the prevalence of symptoms were statistically significant ($p < 0.001$).

Identification of a population with high suspicion of early and late dumping

A high suspicion for early and late dumping based on self-reported complaints of moderate and severe intensity was present in 68 (18.8%) and 40 (11.7%) of the patients, respectively. Twenty-five patients (7% of the group) had a high suspicion for both early and late dumping.

In the volunteer group, only 2 volunteers suffered from early and late dumping. One (0.8%) had self-reported complaints of moderate-to-severe complaints of early dumping (0.8%) and 1 of late dumping (0.8%). No statistically significant differences were seen between the volunteers with BMI of above or below 25.

Differences between the patient and volunteer group were statistically significant ($p < 0.001$).

Characteristics of the patients with a high suspicion for dumping

The characteristics of patients with a high suspicion for early and late dumping are shown in Table 2a and 2b, respectively. Compared to those with a low suspicion, patients with early dumping were more often female. In contrast, patients with a high suspicion of late dumping were slightly younger than patients with a low suspicion but no gender difference was observed. More patients with a high suspicion of early and late dumping had support of a dietician. The patients with high suspicion of late dumping were less satisfied with the operation results, and fewer patients in both groups with high suspicion for dumping said they would not perform the operation again if they had the choice.

High suspicion of late dumping by other estimates in the patient group (Table 4).

Nearly 20% of patients reported a low self-measured blood glucose after a meal. Significant more patients with a high suspicion of late dumping (27.5 versus 12.3 %) reported a low self-measured blood-glucose level after a meal ($p = 0.015$). Loss of self-control (e.g., by disorientation, impaired speech, loss of consciousness) was reported by 7% of all patients. However, this was 20% in patients with a high suspicion of late dumping versus 5.6% in patients with a low-suspicion ($p = 0.001$). Hypoglycemia for which the help of others was necessary (severe hypoglycemia) occurred in 5.4% of patients. Contact with health care workers or institutions for hypoglycemia was 2.6%.

Self-treatment of dumping in the patient group (table 5a and 5b)

Patients with early and late dumping changed their eating pattern significantly more than patients without dumping symptoms; they changed the composition of their meals but no difference was seen in the intake of sugars, carbohydrates, or meat. Patients with symptoms of late dumping did not reduce their intake of vegetables (in contrast with patients without symptoms of late dumping). No difference was seen in vegetable intake for the patients with symptoms of early dumping. Patients with early dumping also changed the amount of food per meal.

Medical treatment of dumping in the patient groups (Table 4)

Three patients were treated for late dumping with medication (1 with long-acting Octreotide, 2 with Acarbose) at the time of the survey.

Table 4: Prevalence of self-measured hypoglycemia, neuroglycopenia and use of related health care.

	All patients 351	High suspicion group for late dumping 40	Low suspicion group for late dumping 311	P value*
Low self-measured blood glucose after a meal	70 (20.1)	16 (40.0)	54 (17.5)	0.003
Concentration of low self-measured blood glucose				
>4 mmol/L	9 (2.6)	0 (0)	9 (16.7)	
3-4 mmol/L	16 (4.5)	5 (12.5)	11 (3.6)	
2-3 mmol/L	24 (6.8)	6 (15.0)	18 (5.8)	
1-2 mmol/L	9 (2.6)	3 (7.5)	6 (1.9)	
Unknown	12 (3.4)	2 (5.0)	10 (3.2)	
Symptoms of neuroglycopenia #	26 (7.4)	8 (20.0)	18 (5.8)	0.001
Hypoglycemia for which help of others was necessary	19 (5.4)	5 (12.5)	14 (4.5)	0.003
Hypoglycemia for which help of health care workers or admission to hospital was necessary	9 (2.6)	4 (10.0)	5 (1.6)	0.07
Medical treatment for early or late dumping	8 (2.3)	2 (5.0)	6 (1.9)	0.223

Data are numbers and frequencies (percentages).

* P value of high suspicion versus low suspicion group for late dumping.

#Symptoms of neuroglycopenia include feelings of loss of control (e.g. disorientation, impaired speech, loss of consciousness)

Health related Quality of Life in the patient group

RAND-36, HADS, MFI-20 and HFS-II. Patients with early and late dumping had significantly lower scores on the RAND-36 and HADS questionnaires compared to patients without dumping (Figure 1a and 1b). No differences were seen in the MFI-20 scores (Figure 1a and b). The negative effects observed for health-related QoL, anxiety and depression were of similar magnitude in early and late dumping. In the Hypoglycemia Fear Scale (HFS-II) all 12 subscales were significantly different between patients with or low suspicion of late dumping (all $P < 0.001$). It is noteworthy that similar results were found in patients with early dumping (data not shown).

Weight loss and regain after primary RYGB in the patient groups (Table 2a and 2b)

Self-reported percentage of excess weight loss (%EWL) or weight regain were not different between patients with high or low suspicion of early or late dumping.

High suspicion of early and late dumping in patients without diabetes, with cured diabetes and with persistent diabetes postoperatively

The prevalence of medical treatment for diabetes postoperatively was approximately 10% (Tables 2a and 2b). No differences were seen in the prevalence of a high suspicion of early and late dumping in the patients without diabetes preoperatively, in patients with cured diabetes postoperatively or in patients with persistent diabetes (Table 6). Subgroup analysis

Figure 1a: Z-scores for RAND36, HADS and MFI in patients with a high and low suspicion of early dumping.

● Patients with a low suspicion of early dumping

■ Patients with a high suspicion of early dumping

Figure 1b: Z-scores for RAND36, HADS and MFI in patients with a high and low suspicion for late dumping.

● Patients with a low suspicion of late dumping

■ Patients with high suspicion of late dumping

according to type of medication was not possible due to very low numbers. But in the group at high suspicion for early dumping, 7.4% of the patients used insulin against 4.2% in the low-suspicion for early dumping ($p = 0.241$). In the group at high suspicion for late dumping group 5.5% of the patients used insulin against 4.8% in the low suspicion group ($p = 0.978$).

Table 5a: Change of food intake of study population at high suspicion for early dumping compared to patients at low suspicion.

	High suspicion group for early dumping	Low suspicion group for early dumping	P-value
Total	68	282	
Change of amount of food per meal	55 (80.9)	190 (67.4)	0.029
Change of frequency of meals	41 (60.3)	140 (49.6)	0.115
Change of content of meal	60 (88.2)	196 (69.5)	0.002
Fewer concentrated sweets	40 (66.7)	142 (72.4)	0.387
Less carbohydrates	39 (65.0)	111 (56.6)	0.250
Less vegetables	8 (13.3)	35 (17.9)	0.412
Less meat	34 (56.7)	109 (55.6)	0.886

Data are numbers and frequencies (percentages).

Table 5b: Change of food intake of study population at high suspicion for late dumping compared to patients at low suspicion.

	High suspicion group for late dumping	Low suspicion group for late dumping	P-value
Total	40	309	
Change the amount of food per meal	33 (82.5)	211 (68.3)	0.065
Change of frequency of meals	21 (52.5)	159 (51.5)	0.901
Change of content of meal	37 (92.5)	218 (70.6)	0.003
Fewer concentrated sweets	26 (70.3)	155 (71.1)	0.918
Less carbohydrates	25 (67.6)	124 (56.9)	0.223
Less vegetables	2 (5.4)	41 (18.8)	0.044
Less meat	18 (48.6)	124 (56.9)	0.351

Data are numbers and frequencies (percentages).

Table 6: Prevalence of a high suspicion for early and late dumping in patients without diabetes, with cured diabetes and with persistent diabetes postoperatively.

	Total number of patients 351	Early dumping 68	Late dumping 40
No type 2 diabetes,	255	37 (54.4)	30 (75)
Cured type 2 diabetes,	70	13 (19.1)	7 (17.5)
Persistent type 2 diabetes,	26	18 (26.5)	3 (7.5)
P-value		0.212	0.721

Data are numbers and frequencies (percentages).

P value for high versus low suspicion groups of early and late dumping, respectively

DISCUSSION

This study shows that complaints of moderate to severe intensity of both early and late dumping have a symptom prevalence of approximately 19 and 12%, respectively, at 2 to 3 years after primary gastric bypass surgery, and that they are associated with a markedly reduced health-related QoL as well as anxiety and depression.

Since the initial reports on late dumping (post-gastric bypass hypoglycemia) by Service et al.²⁸ and Patti et al.²⁹, increasing numbers of cases have been described and reviewed in the literature.³⁰ However, only 2 studies report on its prevalence. First, Lee et al. performed a study in which the Edinburgh hypoglycemia questionnaire was used in patients with gastric bypass or sleeve gastrectomy.³¹ Although of interest, it must be noted that this questionnaire is used and validated for hypoglycemia in the treatment of diabetes and not for late dumping.³² Lee found that the prevalence of complaints leading to high suspicion for hypoglycemia was 34%, which is much higher than the prevalence in our study. This discrepancy can be explained by the definition they adopted for suspected late dumping, which was based on the presence of 3 or more of 11 symptoms related to hypoglycemia. Their operational definition lacks specificity, for instance due to the potential absence of symptoms of neuroglycopenia. Furthermore, their results may be an overestimation of the true prevalence of late dumping due to enrichment with patients with early dumping because they did not distinguish between early and late postprandial complaints. In our study we divided early and late dumping by autonomic and neuroglycemic symptoms and therefore we think our prevalence is more accurate, although lower.

A second study on the prevalence of late dumping was published by Marsk et al., using several nation-wide registries in Sweden. They reported that obese persons who have undergone a gastric bypass have an increased risk of hospitalisation for diagnoses associated with late dumping, although only few patients (< 1%) were affected.³³ Interestingly, their results are consistent with self-reported prevalence of severe neuroglycopenia in our population (i.e., contact with health-care workers in 2.6% of the patients). Only one study describes the prevalence of early dumping based on a self-administered questionnaire. Svennevig et al. studied a group of more than 200 patients who had gastric resection for ulcer disease.⁸ Although investigated in a different patient population, their results are in agreement with our findings, with daily symptoms of early dumping reported in 14% of patients and occasional symptoms in 19.5%.

Several investigators studied dumping by means of a provocation test to elucidate its pathophysiology. The prevalence of late dumping in this studies is estimated between 17% and 68%.^{7,10-12} In the study by Kim et al., asymptomatic hypoglycemia was also found. This raises the possibility of hypoglycemia unawareness in patients with a gastric bypass, a finding which may affect the symptom prevalence.

In the literature, it is suggested that late dumping is associated with the presence of diabetes before or after gastric bypass.¹¹ In the present study, no differences were seen in the prevalence of early or late dumping in patients without type 2 diabetes, patients cured of type 2 diabetes, or those with persistent diabetes after operation. As noted by Banerjee et al., we also found no differences in weight loss or regain between patients with or without symptoms of late dumping in our large cross-sectional study.⁹

We also studied differences in self-treatment by changing dietary patterns. Patients with a high suspicion of early and late dumping reported a significant change in the composition, of their meals – but no differences were seen in the intake of carbohydrates or sugars, as would be expected of efficient self-treatment for symptoms of late dumping. This is most likely explained by the global character of this part of the questionnaire, lacking in depth information. It is also worth noting that self-reported food questionnaires have a reputation for being inaccurate.

QoL after weight loss surgery is improved in comparison with that of obese volunteers not having had weight loss surgery.^{1,14-16} In addition, the improved QoL after weight loss surgery is reported to be relatively stable for years after operation.¹⁵ This is the first study showing that early and late dumping is associated with a markedly reduced health-related QoL and mood. In addition, less patients with high suspicion of early and late dumping were satisfied with the results of their weight loss surgery, despite similar weight loss results compared to the low-suspicion groups, and more patients would not undergo the operation again.

Some limitations of our study need to be addressed. First, it is a single-center study and therefore its generalizability can be questioned. However, the patient selection, preoperative procedures, operative technique and postoperative care are in line with IFSO criteria and are highly comparable to those of other centers.¹⁷ Despite this, it would be very useful to confirm our data in a multicenter study. Also, the effect on early and late dumping of pouch size, limb length and diameter of anastomoses is not yet known. In our center, a standardized operation technique is used – but details will always be different between surgeons. We think that these minor differences will not affect dumping but this needs to be a subject of further study.

Secondly, although almost 60% of the invited patients responded to our questionnaire, it is possible that patients with postoperative complaints were more willing to participate in this study and this inclusion bias may have resulted in an overestimation of the dumping prevalence. Patients were asked to report symptoms of dumping within the past month, which may be long time for respondents to accurately recall symptoms. This could have biased our results, although it remains unclear in which direction. However, this period was chosen to stay in line with the well validated RAND-36, MFI and HADS in which the period of recall is also 4 weeks.

Thirdly, self-reported data on weight may also be less accurate, although a comparison between self-reported weights with the weight measured at the outpatient clinic revealed no difference between the two.

The difference in duration of follow-up per patient could be another limitation. If the prevalence of dumping is affected by time this may influence our results. It would be necessary to carry out longitudinal studies to gain more insight into this aspect.

The fifth and perhaps the most important limitation is that there is no validated questionnaire available for early and late dumping. The best-known questionnaire is the Sigstad score, which was initially developed as a clinical score for early dumping to be administered by a doctor.³⁴ Since then, some have used a modified Sigstad score as a patient questionnaire for postgastrectomy patients in case of ulcer disease.^{7,8} It is not widely used for late dumping. As indicated earlier, the Edinburgh hypoglycemia questionnaire is also not validated for late dumping. A newer and potentially more useful patient questionnaire is the Dumping Severity Score developed by Arts and al.¹⁸ This questionnaire is used for the evaluation of treatment response in patients with late dumping. Validated cutoff levels are not available. It is the only questionnaire available that differentiates between patients with early and late dumping.

For the purpose of this study we used an arbitrary predefined cutoff level for early and late dumping. This level was based on the presence of at least moderate complaints in 3 of 8 subscales for early dumping with at least one autonomic symptom and 3 of 6 subscales for late dumping with at least one neuroglycemic symptom. The rationale for these cutoff points is the self-reported burden of (daily) symptoms on more than one scale. Furthermore, the mandatory character of the presence of a symptom in any of the subscales leads to recognition of early and late dumping with enhanced specificity, thus excluding other diseases. It seems reasonable that this definition should identify a population that is at high suspicion for early and late dumping. It may even be that our definition is too strict, leading to an underestimation of the prevalence, considering that 20% of the patients in our group reported low glucose by means of self-measurement. Alternatively, validation of late dumping by verification of hypoglycemic episodes may also not yield a proper comparison, since late dumping after an oral glucose or mixed-meal tolerance test is reported to be up to 68%.¹¹ This high figure may reflect the ability of patients to respond with a hyperinsulinemic hypoglycemia after a certain stimulus but it is not likely to match daily complaints. In general the validation of questionnaires is a limitation in this field. The same applies for the HFS-II we used. This is only validated in a population with type 1 diabetes and not in a population of patients after gastric bypass surgery. Caution must therefore be applied in the interpretation of these results.

We compared our group of patients with healthy nonobese volunteers. This choice was made deliberately because we anticipated that obese prebariatric volunteers have a higher incidence of the after-dinner dip, because of different eating manners. We also did not ask

our presurgical patients because they were already in the screening procedure and could therefore see the questionnaire as an application form for bariatric surgery which in our opinion would also have biased the results. This, however, should however be subject of future research.

The prevalence of dumping varies with the different definitions of early and late dumping (i.e., whether it is self-reported, self-measured glucose, after tolerance test, etc). Severe late-dumping syndrome complaints requiring hospitalization are rare but the full spectrum of this disease is wider. Our results show that clinically significant complaints of dumping are prevalent and they can affect QoL and satisfaction with the operation. Therefore, we need to tell our patients before the operation that 1 in 5 will suffer from complaints that have an effect on overall wellbeing in daily life. In follow-up consultations, symptoms of early and late dumping must be checked so that advice and treatment can be given and a better QoL achieved. In future research, we have to find out whether screening for early and late dumping can identify more patients whose QoL could be improved with dietary advice, treatment and information on these syndromes.

CONCLUSION

In this descriptive cohort study, self-reported complaints suggestive of early and late dumping of moderate to severe intensity were, respectively, 18.8 % and 11.7% in a cohort after primary gastric bypass surgery and were associated with markedly reduced health related QoL.

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Chapter 5

Prevalence and pathophysiology of early dumping in patients after primary Roux-en-Y gastric bypass during a mixed meal tolerance test.

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Surg Obes Relat Dis. 2019 Jan;15(1):73-81

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ABSTRACT

Background

Early dumping is a poorly defined and incompletely understood complication after Roux-en-Y gastric bypass (RYGB).

Objective

We performed a mixed meal tolerance test in patients after RYGB to address the prevalence of early dumping and to gain further insight into its pathophysiology.

The study was conducted in a regional hospital in the northern part of the Netherlands.

Methods

From a random sample of patients who underwent a primary RYGB between 2008 and 2011, 46 patients completed the mixed-meal tolerance test. The dumping severity score for early dumping was assessed every 30 minutes. A sum score at 30 or 60 minutes of ≥ 5 and an incremental score of ≥ 3 points were defined as a high suspicion of early dumping. Blood samples were collected at baseline, every 10 minutes during the first half hour and at 60 minutes after the start.

Results

The prevalence of a high suspicion of early dumping was 26%. No differences were seen for absolute hematocrit value, inactive glucagon-like-peptide-1 and vasoactive intestinal peptide between patients with or without early dumping. Patients at high suspicion of early dumping had higher levels of active glucagon-like peptide-1 and Peptide YY.

Conclusion

The prevalence of complaints at high suspicion of early dumping in a random population of patients after RYGB is 26% in response to a mixed-meal tolerance test. Postprandial increases in both GLP-1 and PYY are associated with complaints of early dumping, suggesting gut L-cell over activity in this syndrome.

INTRODUCTION

Morbid obesity is a growing healthcare problem in the world and, consequently, effective weight-loss strategies are needed. Weight-loss surgery is the most effective way to achieve sustained weight loss, resolve comorbidity and improve survival.¹ Currently, one of the most frequently performed operations is the laparoscopic Roux-en-Y gastric bypass (RYGB). This procedure is effective but it is known to have several complications. One of these, early dumping, is poorly defined and incompletely understood. Early dumping represents a constellation of abdominal symptoms, including abdominal cramps, bloating and diarrhoea, which start within minutes after a meal and last for up to one hour. Early dumping is also accompanied by autonomic responses such as sweating, palpitations, drowsiness and orthostatic symptoms.

The prevalence of early dumping after gastric surgery has been estimated at 12-42%.²⁻⁴ The first shortcoming of these estimates is that there is no available gold standard to measure early dumping.⁵ Secondly, none of the studies used a meal-induced provocation in a random patient cohort, which would probably lead to a better estimate of the prevalence of early dumping syndrome.

Several concurrent phenomena can contribute to the development of early dumping.⁶ Due to the RYGB, the pylorus and the first part of the jejunum are bypassed, causing rapid delivery of undigested food to the small bowel. One theory suggests that these hyperosmolar nutrients cause a shift of fluid from the intravascular compartment (i.e. plasma) to the intestinal lumen, resulting in a reduction in plasma volume, tachycardia and hypotension.⁷ The triggers for these symptoms are not known. Another theory postulates that the increased release of multiple gastrointestinal (GI) hormones including vasoactive agents (e.g. neurotensin and vasoactive intestinal peptide [VIP]) and incretins (e.g. glucose-dependent insulintropic peptide [GIP] and glucagon-like polypeptide 1 [GLP-1]), as well as glucose modulators (e.g. insulin and glucagon), are involved in the onset of early dumping.⁸⁻¹¹ Enhanced release of these hormones may induce uncoordinated GI motility, inhibit secretion and elicit hemodynamic effects.⁸⁻¹¹ However, these studies were mainly performed in the pre-bariatric era with small groups of (preselected) patients and using an oral glucose-tolerance test, which is less reliable than a mixed-meal tolerance test (MMTT) in inducing a physiologic stimulus.¹² To address these methodological issues in prevalence estimations of early dumping and to gain further insight in its pathophysiology, we performed MMTTs in a random sample of patients after gastric bypass surgery.

METHODS

Study population

This study was conducted between February 2014 and March 2015. Patients aged 18-75 years who underwent primary RYGB between 2008 and 2011 in our centre were eligible for this study. The technique of the RYGB included an antecolic-antegastric Roux-en-Y reconstruction with 30-to 60 cc gastric pouch, a biliopancreatic limb length of 80 cm, and an alimentary limb length of 150 cm.¹³ We try to prevent dissecting the branches of the vagal nerve by strict perigastric dissection as we enter the lesser sac for performing the pouch.

Patients with diabetes mellitus at the time of the study or who had undergone a revisional procedure were excluded.

We estimated that we needed between 50 and 70 patients to participate in our study, to have enough patients with early dumping, assuming a prevalence of 18%.¹³ A participation rate of 50% was expected; therefore a random sample of 140 patients was created from the entire cohort (n=550 by means of the random sample function in SPSS [SPSS, Inc., Armonk, NY, U.S.A.]). After initial invitation by telephone, those willing to participate received additional study information. After at least one week of consideration, the patients were scheduled for MMTT after their informed written consent was obtained. A total of 51 patients participated. After the test we excluded 5 more patients because of a prior revisional operation (1 patient), withdrawal during the test (1 patient), and because of abdominal complaints before the start of the MMTT (3 patients). Therefore in total 46 patients were analyzed. The selection process, including reasons for exclusion, is shown in Figure 1.

Records for individual patients were completed by data review. The study protocol was approved by the hospital's Medical Ethical Review Board (RTPO 976 number 41604.099.12).

Study protocol

All scheduled patients underwent the MMTT in the morning after an overnight fast of at least 8 hours. Anthropometric measures were obtained before the test meal. Via a peripheral intravenous cannula, blood samples were obtained before the meal (t=0) and again at 10, 20, 30 and 60 minutes after the meal. Additionally, heart rate and blood pressure were measured. Perceived symptoms (documented by disease-specific questionnaires) were filled out by the patients before the meal and again at 30 and 60 minutes after the meal.

A 200-ml liquid nutrition supplement (Ensure Plus, Hoofddorp, the Netherlands; Abbot) containing 300 kcal, 12.5 g protein, 40.4 g carbohydrate (of which 13.8 g sugar), 9.84 g fat and 154.9 g water was used as a mixed meal. The patients were asked to finish the meal within 10 minutes.

Figure 1: CONSORT flow diagram showing the selection process.

Questionnaires and definition of early dumping

Symptoms of early dumping were assessed according to the dumping severity score (DSS) using a 4-point Likert scale as developed by Arts et al.¹⁴ Each patient was asked to grade the intensity (0 = absent; 1 = mild; 2 = moderate; and 3 = severe, i.e., interfering with daily activities) of 8 early-dumping symptoms.

Due to the explorative nature of this study, the group was divided into two sub-groups based on the sum score of the symptoms at 30 or 60 minutes, with all complaints weighted equally (Table 1). Patients with a sum score of ≤ 4 and the incremental score compared to baseline of ≤ 2 points compared with baseline were defined as low suspicion of early dumping. Patients with a sum score at 30 or 60 minutes of ≥ 5 and an incremental score of ≥ 3 points were defined as high suspicion of early dumping.

Table 1: Early dumping sum score during the Mixed Meal Tolerance Test in the low and high suspicion group of early dumping.

	Low suspicion of early dumping n=34	High suspicion of early dumping n=12	p-value
Early dumping sum score (t = 0 min)	0 [0; 0]	0 [0; 0.75]	0.627
Early dumping sum score (t = 30 min)	1 [0; 2]	6.5 [0; 9.75]	<0.001
Early dumping sum score (t = 60 min)	0 [0; 0]	3 [2; 4]	<0.001

Data are median and interquartile ranges [IQR]

Patients with a baseline sum score above 5 (n = 3) were excluded from analysis as they were considered to have abdominal complaints in the fasting state that would interfere with interpretation of postprandial symptoms.

Blood analyses

For hematocrit analysis, blood was collected in spray-coated ethylenediaminetetraacetic acid (EDTA) tubes; for glucose and insulin analysis, lithium-heparin tubes with a gel separator were used. For the measurement of Peptide YY (PYY), VIP, active GLP-1 and inactive GLP-1, blood was collected in pre-cooled tubes containing 15% aprotinin to which 50µl dipeptidyl peptidase 4 inhibitor (DPP4-010; Merck Millipore, the Netherlands) was added by injection through the cap directly prior to blood withdrawal without influencing the integrity of the pre-existing vacuum in the tube.¹⁵

The initial product GLP-1 (1–37) is susceptible to amidation and proteolytic cleavage, which gives rise to the 2 truncated and equipotent biologically active forms; GLP-1 (7–36) amide and GLP-1 (7–37). This proteolytic activation is the result of dipeptyl peptidase 4. All samples were centrifuged at 4°C and analyzed immediately or stored at -80°C until analyzed.

Hematology analysis was done using the Abbott Cell-Dyne Sapphire (Abbott, Abbott Park, Illinois, U.S.A.). Hemoglobin was measured spectrophotometrically using a Cell-Dyne Sapphire CN-free hemoglobin (HGB) reagent. The hematocrit was calculated by multiplying the mean of all measured red cell volumes by impedance analysis and the total red cell count (also based on the impedance analysis).

The glucose (hexokinase reaction) and insulin analyses (sandwich principle assay) were performed on a Roche analyser (Sandhofer Strasse 116, D-68305; Roche Diagnostics GmbH, Mannheim, Germany).

The concentrations of the active GLP-1, VIP, inactive GLP-1 and PYY were determined by using commercial enzyme-linked immunosorbent assay kits on a 2-plate enzyme-linked immunosorbent assay processing system (DS2, DYNEX Technologies, Chantilly, VA, USA), as per the manufacturer's instructions. The following commercial enzyme-linked immunosorbent assay kits were used for the active form and inactive form of GLP-1: IBL International (Hamburg, Germany) (code JP27784 and code JP27788); for human VIP: RayBiotech (Norcross,

GA, USA) (cat. # EIA-VIP); and for human PYY: Millipore Corporation (Billerica, MA, USA) (cat. # EZHPYYT66K). For the active and inactive form of GLP-1 and VIP, low and high-level internal quality controls (QCs) were prepared by selecting and pooling plasma containing 15% aprotonin and dipeptidyl peptidase 4 inhibitor. Low and high QCs for human PYY were provided by the manufacturer. The interassay variations of the low-level internal QC and the high-level internal QC were 57.0% and 43.7% for active GLP-1; 7.4% and 15.7% for inactive GLP-1; 62.0% and 54.1% for human VIP; and 12.1% and 17.2% for human PYY, respectively. Considering these variations, only within-subject changes from baseline were used for analysis.

Statistical analysis

Data are presented as mean $\pm$ standard deviation, median and interquartile ranges, IQR, and frequencies where appropriate. Relative within-subject changes from baseline were assessed by the formula $(\Delta/\text{baseline}) \times 100$.

The *t* test was used for calculating differences for normally distributed data; the Mann-Whitney *U* test for data that were not normally distributed was used, for categorical data a χ^2 test or a Fisher exact test (with expected cell counts <5) was used. Results were considered significant at $P < .05$. Graphs were created in GraphPad Prism (Graphpad Software Inc., La Jolla, CA, USA) using data calculated in SPSS version 23. For graphical representation, mean $\pm$ standard error of the mean are shown.

RESULTS

Data of 46 patients were available for analysis: 34 women and 12 men with a median age of 47 years (39 – 54). BMI was 46.1 kg/m² (42.0; 48.5) before RYGB and 31.2 kg/m² (28.6; 35.0) after surgery, resulting in an excess weight loss of 68.1% (54.9; 79.4) and a total weight loss of 33.1% (23.6; 37.7). Time between operation and MMTT was 46 months (39;54 months).

The study population (n=46) was representative of the entire surgical cohort (n=550) and of the random sample (n=140) in terms of age, sex, comorbidities before surgery, preoperative weight and postoperative weight at the time of the study (data not shown).

Table 2 shows the difference in patient characteristics between the patients with high and low suspicion for early dumping.

Prevalence of early dumping based on symptom scores.

The prevalence of a high suspicion of early dumping was 26% (12/46). Figure 2 panel A presents the DSS in our predefined groups with low and high suspicion of early dumping. The patients with high suspicion of early dumping peaked at 30 minutes followed by a decline without returning to baseline values at 60 minutes.

Table 2: Comparison of patient characteristics between patients at low and high suspicion of early dumping.

	Low suspicion of early dumping n=34	High suspicion of early dumping n=12	p-value
Age (y)	46 [39; 53]	52 [41; 58]	0.145
Female (%)	25 (74)	9 (75)	1.000
Time between surgery and study (months)	46 [39; 56]	47 [42; 54]	0.954
Weight and weight loss			
Weight at surgery (kg)	139 [127; 155]	131 [118; 141]	0.100
BMI at surgery	46 [42; 51]	46 [40; 48]	0.159
Weight at MMTT (kg)	93 [85; 113]	92 [76; 97]	0.086
BMI at MMTT	32 [29; 37]	30 [27; 33]	0.159
EWL at MMTT (%)	67 [50; 78]	73 [61; 88]	0.321
TWL at MMTT (%)	31 [24; 38]	32 [23; 39]	0.700
Comorbidities preoperative			
Type 2 diabetes	8 (23.5)	6 (50)	0.091
Hypertension	14 (41.2)	6 (50.0)	0.422
Dyslipidemia	4 (11.8)	4 (33.3)	0.108
Comorbidities postoperative			
Type 2 diabetes *	0	0	
Hypertension	7 (20.6)	2 (16.7)	0.568
Dyslipidemia	3 (8.8)	0 (0)	0.394

Data are median and interquartile ranges [IQR], or numbers and frequencies (percentages).

* Exclusion criteria

Baseline characteristics of the 2 groups showed no differences in demographics, prevalence of comorbidities, and percentages of excess and total weight loss.

A significant difference between the sum score of low and high suspicion of early dumping was present in all subscales of the DSS at 30 minutes except for flushing (Table 3). At 60 minutes, there were significant differences in dizziness and gastrointestinal symptoms nausea, bloating and abdominal pain (Table 3).

No differences were seen between the low and high suspicion of early dumping groups in the systolic and diastolic blood pressure and pulse rates at all time points (Figure 2 panels B and D). No differences were found between the groups in the absolute hematocrit value at all time points (Figure 2 panel C). However, the relative hematocrit at 30 minutes differed significantly between patients with low or high suspicion of early dumping (resp 0.32% versus 2.56% $p=0.039$). This difference is higher than the analysis variance.

Significant differences were seen in the postprandial response of active GLP-1 and PYY at 20, 30 and 60 minutes (Figure 3 panels A and C), whereas no differences in inactive GLP-1 and VIP were found between the 2 groups (Figure 3 panels B and D). No differences were seen between the groups in glucose or insulin concentrations (Figure 4 panels A and B).

Figure 2: Comparison between patients at low and high suspicion of early dumping for the sum score of early dumping (panel A), heart rate (panel B), haematocrit (panel C) and blood pressure (panel D).

Black line: high suspicion for early dumping

Grey line: low suspicion for early dumping

*** means $p < 0.001$

DISCUSSION

This study showed that 26% of the patients who had undergone a primary RYGB after a midterm follow up were suspected of early dumping based on symptom scores. Compared to patients with low suspicion of early dumping, these patients had a slightly increased haematocrit at 30 minutes but no differences in blood pressure or pulse rate. Furthermore, this study showed a difference in levels of active GLP-1 and PYY between patients with low and high suspicion of early dumping, suggesting that gut L-cells are involved in the pathophysiology of the syndrome.

Early dumping is seen as a sum of symptoms in most studies. The most widely used is the Sigstad score¹⁶, but the weighing of the symptoms and signs of this score is somewhat unclear and no distinction is made between early and late dumping (post-prandial hypo-

Table 3: Comparison of early dumping symptoms between the group at low and high suspicion for early dumping at 30 and 60 minutes after ingestion of the test meal.

	Low suspicion for early dumping n=34	High suspicion for early dumping n=12	P-value
At 30 minutes			
Transpiration	1 (2.9)	5 (41.7)	0.002
Flushes	2 (5.8)	2 (16.7)	0.220
Dizziness	4 (11.8)	9 (75)	<0.001
Palpitations	4 (11.8)	6 (50)	0.004
Abdominal pain	3 (8.8)	6 (50)	0.003
Diarrhoea	0	4 (33.3)	0.006
Bloating	11 (33.3)	10 (83.3)	0.002
Nausea	8 (24.3)	11 (91.7)	<0.001
At 60 minutes*			
Transpiration	1 (2.9)	1 (9.1)	4.33
Flushes	2 (5.9)	0	0.567
Dizziness	1 (2.9)	7 (63.6)	<.001
Palpitations	0	1 (9.1)	0.244
Abdominal pain	0	3 (27.3)	0.012
Diarrhoea	2 (5.8)	1 (9.1)	0.595
Bloating	4 (11.8)	6 (55.5)	0.004
Nausea	1 (2.9)	5 (45.5)	0.004

Data are numbers and frequencies (percentages).

*One patient did not fill in the questionnaire at 60 minutes

glycemia). Therefore, Arts et al. developed the DSS for the bariatric population in which patients rate the severity of 8 specific symptoms of early dumping on a 4-point Likert scale.^{14,17} This self-reporting DSS was used in the present study because of the possibility of grading the severity of symptoms and differentiating between early and late dumping. It has previously been used as a self-reporting symptom measure in a provocation setting in a bariatric population.¹⁷

Our findings support the conclusion that early dumping is still present in patients almost 4 years after RYGB, with a prevalence of 26%. In an earlier study of our group, we showed that moderate-to-severe symptoms (i.e., at least two abdominal and one autonomic) result in poor quality of life, highlighting the clinical relevance of this syndrome.¹³ The lower prevalence in the present study compared to studies describing higher prevalence can be explained by differences in syndrome definition, the use of a random sample as opposed to a preselected sample, the use of a MMTT instead of an OGTT, RYGB versus gastrectomy, and the longer postoperative period.^{6,12,18,19}

Figure 3: Comparison between patients at low and high suspicion of early dumping for the relative active GLP-1 (panel A), inactive GLP-1 (panel B), PYY (panel C) and VIP (panel D)

* P < 0.05

** P < 0.01

Figure 4: Comparison between patients at low and high suspicion of early dumping for glucose (panel A) and insulin (panel B).

Pulse rate increment and haematocrit increment have often been used to diagnose early dumping in accordance with the fluid shift theory.^{5,7,14,19} In our study, the pulse rate was not different between patients with low or high suspicion of early dumping. A difference in haematocrit of 3% is thought to be an objective measure of early dumping. However, in our study we only saw a difference of 2.6% between the two groups. Furthermore, whereas

many studies have found significant differences in the postprandial heart rate increment, this was not the case in our study.

Reasons for the difference in our study compared to the literature are the use of a random sample versus a selected population of patients with symptoms and the use of a formula without predefined cut-off points instead of a questionnaire.^{18,20,21} The question is whether this small difference in heart rate and haematocrit is clinically relevant or sufficient to support the fluid shift theory. A review by Vecht et al. has already questioned this supposed relationship.²⁰ The hypovolemia that has been described during early dumping is often estimated to be quite small (300-700ml) and could be considered tolerable; it is also present in nonoperated subjects and in patients after gastrectomy without complaints, which is in line with our findings.

Another theory behind early dumping is based on the influence of gut hormones. Studies comparing patients with symptoms of dumping to asymptomatic patients support the theory that these hormones are related to the pathogenesis of early dumping.⁷ Our study supports and extends this theory by finding increased concentrations of the L-cell hormones GLP-1 and PYY in patients with high suspicion of early dumping.

GLP-1 has multiple effects on several pathways, causing various symptoms, such as influence of the area postrema (causing nausea), stimulation of nitric oxide production (causing tachycardia and hypotension), vasodilatory effect on mesenteric, coronary and brachial arteries (causing hypotension); and influencing insulin secretion (causing vasodilation and normalisation of heart rates after 50-60 minutes).²²⁻²⁵ In support of this theory, treatment with somatostatin-analogues, known to diminish GLP-1 release from L-cells, has been successful in reducing early dumping complaints.^{14,26}

PYY is known to cause vasoconstriction, increase blood pressure, decrease intestinal motility and stimulate absorption of nutrients.²⁷⁻³¹ PYY is also shown to decrease VIP-induced secretory diarrhoea and inhibit intestinal chloride excretion.³² As these effects contradict those seen in the immediate reaction of early dumping, it has been suggested as a negative feedback mediator. The effect of PYY would occur after the first phase of signs and symptoms (peak is at 30 minutes), and it would be higher in the group with most complaints.^{20,33} In the present study, we found the concentrations of PYY to be significantly higher in the group with suggestive dumping than in the group with low suspicion. The peak was reached at 30 minutes, later than that of GLP-1, with subsided levels of hormones thereafter and decreased symptom-scores at 60 minutes. GLP-1, which is also released by the L-cells, is known to exert an inhibitory effect on PYY release and may therefore cause the delayed reaction of the PYY response seen in this study without reducing the level of the PYY release, explaining the later occurring peak in PYY compared to the GLP-1 (34). The anatomy change after RYGB is known to cause an increased density in GLP-1 and PYY producing L-cells in the perianastomotic jejunum, suggesting an increased direct stimulatory effect.³⁵ Furthermore, PYY-levels are also known to increase as a biological adaptation in gastrointestinal diseases

where higher amounts of undigested nutrients are present in the intestines and where VIP-levels are raised.^{32,36,37}

VIP is known to cause a cascade of postprandial reactions upon direct and indirect pathways: a strong vasodilator, it reverses normal intestinal absorption and causes secretory diarrhoea, stimulates gastrointestinal transit, relaxes vascular and nonvascular smooth muscle cells, increases heart rate, decreases diastolic blood pressure, and causes symptoms similar to those seen in early dumping.^{36,38,39} We had expected to see a higher concentration of VIP in the group high suspicion for early dumping, but we could not confirm this hypothesis in our study.

Some limitations of the study must be mentioned. First, for various reasons, most unrelated to dumping, only 46 patients of the 140 patients in the random sample were tested. The demographics of the tested patients were not different from the total group of operated patients but there is still a possibility of selection bias.

Secondly, we did not use a validated questionnaire for early dumping. After the start of our study (in 2013), Laurenus et al. validated the dumping symptom rating scale, a questionnaire with a 7-point Likert scale.² The questions addressing complaints are the same in the dumping symptom rating scale as they are in the DSS. One of the conclusions of Laurenus et al. was that the 7-point Likert scale should be changed to a four-point Likert scale, as used in the DSS.² Also, there is no definition of early dumping in the dumping symptom rating scale; this questionnaire is mainly made for screening in the outpatient clinic to select patients with severe complaints in 1 of the symptoms.

Third, the test meal for a MMTT is not standardized, which is a general shortcoming of meal tests. Although difficult, standardization should be recommended in order to compare studies in future research.

CONCLUSION

In conclusion, we found that 26 % of the patients who underwent a primary RYGB after a midterm follow up were highly suspected of early dumping. The gut hormones GLP-1 and PYY are increased in these patients and are therefore implicated in the pathophysiology of early dumping.

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Chapter 6

Prevalence of hypoglycaemia in a random population after Roux-en-Y gastric bypass during a meal test

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Endocr Connect. 2019 Jun 1.Epub ahead of print

ABSTRACT

Objective

Roux-en-Y gastric bypass (RYGB) is an effective way to induce sustainable weight loss and can be complicated by postprandial hyperinsulinemic hypoglycaemia (PHH). To study the prevalence and the mechanisms behind the occurrence of hypoglycaemia after a mixed meal tolerance test (MMTT) in patients with primary RYGB.

Design

This is a cross-sectional study of patients four years after primary RYGB.

Methods

From a total population of 550 patients, a random sample of 44 patients completed the total test procedures. A standardized mixed meal was used as stimulus. Venous blood samples were collected at baseline, every 10 minutes during the first half hour and every 30 minutes until 210 minutes after the start. Symptoms were assessed by questionnaires. Hypoglycaemia defined as a blood glucose below 3.3 mmol/L.

Results

The prevalence of postprandial hypoglycaemia was 48% and was asymptomatic in all patients. Development of hypoglycaemia was more frequent in patients with lower weight at surgery ($p = 0.045$), with higher weight loss after surgery ($p = 0.011$), and with higher insulin sensitivity calculated by Homeostasis Model Assessment indexes (HOMA2-IR $p = 0.014$) and enhanced beta cell function (insulinogenic index at 20 minutes $p = 0.001$).

Conclusion

In a randomly selected population four years after primary RYGB surgery 48% of patients developed a hypoglycemic event during a mixed meal tolerance test without symptoms, suggesting the presence of hypoglycaemia unawareness in these patients. The findings in this study suggest that the pathophysiology of PHH is multifactorial and not just the result of increased GLP-1 secretion.

INTRODUCTION

The laparoscopic Roux-en-Y gastric bypass (RYGB) is often used to achieve sustained weight loss, resolve comorbidity and improve survival in obese patients.¹

It is an effective procedure, but unfortunately it can be accompanied by long-term complications, such as late dumping syndrome, also known as Postprandial Hyperinsulinemic Hypoglycaemia (PHH).^{2,3}

PHH typically occurs 1-3 hours after a meal and can lead to autonomic and neuroglycopenic symptoms such as sweating, palpitations, hunger and drowsiness which may even result in coma.^{4,5} Studies have observed prevalence rates after primary gastric bypass surgery of 12% when assessed by means of questionnaires and up to 75% assessed by continuous glucose monitoring systems (CGMS).⁶ Glucagon-like peptide-1 (GLP-1) is assumed to play a pivotal role in the pathophysiology of PHH, most convincingly because the GLP-1 antagonist exendin 9-39 prevents postprandial hyperinsulinemia and the subsequent hypoglycaemia in people with severe symptoms of late dumping.^{7,8} Other gut hormones may also play a role after gastric bypass surgery, like peptide tyrosine tyrosine (PYY) in reducing appetite and suppress pancreatic secretion, and vasoactive intestinal peptide (VIP) in gluconeogenesis. The role of these hormones in PHH is not clear.^{9,10}

Although these studies have provided more insight into PHH, several (methodological) shortcomings should be mentioned. First of all, the questionnaires and symptom scales that were used for the assessment of the prevalence of PHH have not been validated. Further, these subjective methods do not take hypoglycemic unawareness into account, a phenomenon which is described in patient with diabetes who have frequent episodes of hypoglycaemia.¹¹ Diagnostic tools like CGMS have the advantage of monitoring glucose concentrations during daily activities, but the accuracy of CGMS in the hypoglycemic range is poor.¹² Also, this method can not be utilized to investigate the pathophysiology of PHH. Dynamic (or provocative) testing, however, can provide more insight into the pathophysiology, for instance by providing a standardized stimulus or meal in a laboratory while performing extensive hormone analyses. Older studies have used the oral glucose challenge as standardized stimulus, but nowadays this is considered not physiological accurate, therefore the mixed meal tolerance test (MMTT) is preferred.¹³ Smaller studies including up to ± 20 patients using the MMTT after gastric bypass have been performed comparing patients with spontaneous severe hypoglycemic symptoms to those without.^{14,15} These extremes of the spectrum of PHH have been informative but do not allow a proper evaluation of the real prevalence of PHH and its main driving mechanisms in those with milder or no symptoms. For this purpose a random selection of sufficient numbers of patients is necessary.

Therefore, we investigated the prevalence of PHH by venous sampling and by questionnaires during a MMTT in a random sample of patients with primary RYGB. Furthermore,

to gain insight in the mechanisms provoking hypoglycaemia, we performed gut hormone analyses and assessed the beta-cell function and insulin resistance with several indices.

PATIENTS AND METHODS

Study population

Details on the study design were described previously (16). In brief, non-diabetic patients aged 18-75 years who underwent primary RYGB between 2008 and 2011 in our centre were eligible to participate in the study. From the entire cohort (n=550), a random sample of 140 patients was drawn. All patients underwent an antecolic-antegastric Roux-en-Y reconstruction with a gastric pouch sized 30-60 cc, a biliopancreatic limb length of 80 cm, and an alimentary limb length of 150 cm (6). In total, 51 patients agreed to participate, but due to exclusion and withdrawal of consent only 44 patients were analysed. The selection process, as well as reasons for exclusion, is shown in Figure 1. One patient was registered as having a primary gastric bypass, but during test we found out she had gastric banding before, so she was excluded from analysis. The study protocol was approved by the hospital's Medical Ethical Review Board and all patients provided written informed consent. This study was conducted between February 2014 and March 2015.

Study protocol

All scheduled patients underwent the MMTT in the morning after an overnight fast of at least eight hours. Anthropometric measures were obtained before the test meal and throughout the test. Via a peripheral intravenous cannula, blood samples were obtained before the meal (t=0) and at 10, 20, 30 minutes followed by every half hour until 210 minutes after the meal. Before the beginning of the test and every 30 minutes until 210 minutes after the meal patients filled in symptom related questionnaires.

The mixed meal consisted of a 200 ml liquid nutrition supplement (Abbott Ensure S Plus) containing 300 kcal, 12.5 g protein, 40.4 g carbohydrate (of which 13.8 g sugar), 9.84 g fat and 154.9 g water. The patients were asked to finish the meal within 10 minutes.

Blood analyses

Venous blood for glucose and insulin analysis was collected in lithium-heparin tubes with a gel separator. For the measurement of Peptide YY (PYY), VIP, active GLP-1 and inactive GLP-1, blood was collected in pre-cooled tubes containing 15% aprotinin to which 50µl dipeptidyl peptidase 4 (DPP-4) inhibitor (Merck Millipore DPP4-010), which was added by injection through the cap directly prior to blood withdrawal without influencing the integrity of the pre-existing vacuum in the tube.¹⁷ All samples were centrifuged at 4°C and analysed immediately (glucose and insulin) or stored at -80°C until analysed (GLP-1, VIP and PYY).

Figure 1: CONSORT flow diagram

The glucose (hexokinase reaction) and insulin analyses (sandwich principle assay) were performed on a Cobas (Glucose with 701 module; insulin with 801 module) of Roche (Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim, Germany).

The concentrations of the active GLP-1, VIP, inactive GLP-1 and PYY were determined by using commercial ELISA kits on a two-plate ELISA processing system (DS2, DYNEX Technologies, Chantilly, VA, USA), as per the manufacturer's instructions. The following commercial ELISA kits were used for the active form and inactive form of GLP-1: IBL International, Hamburg,

Germany, code JP27784 and code JP27788. For human VIP: RayBiotech, Norcross, GA, USA, cat. # EIA-VIP. For human PYY: Millipore Corporation, Billerica, MA, USA, cat. # EZHPYYT66K. For the active and inactive form of GLP-1 and VIP, low and high-level internal quality controls (QCs) were prepared by selecting and pooling plasma containing 15% aprotinin and DPP-4 inhibitor (Merck Millipore DPP4-010). Low and high QCs for human PYY were provided by the manufacturer. The inter-assay variations of the low-level internal QC and the high-level internal QC were 57.0% and 43.7% for active GLP-1; 7.4% and 15.7% for inactive GLP-1; 62.0% and 54.1% for human VIP; and 12.1% and 17.2% for human PYY, respectively. Considering these variations, only within-subject changes from baseline were used for analysis. The maximum storage was thirty months. We did not analyse stability of the incretins, but we assume that with the precautions made (immediately storage) stability is warranted.¹⁷

Questionnaire

Symptoms were assessed during the MMTT with the dumping severity score (DSS) developed by Arts et al.¹⁸ This questionnaire is based on symptom pattern descriptions in the literature, using a four-point Likert scale. The patient is asked to grade the intensity (0 = absent; 1 = mild; 2 = moderate; and 3 = severe, interfering with daily activities) of eight early-dumping symptoms (within one hour after food ingestion) and six symptoms associated/attributioned with/to hypoglycaemia (more than one hour after food ingestion). These six hypoglycemic symptoms are either adrenergic (sweating, palpitations, hunger, tremor) or neuroglycopenic (irritability, drowsiness).¹⁸

If patients rated three or more symptoms at intensity 2 or 3 (i.e. moderate or severe, interfering with daily activities) on the DSS of which at least one was a neuroglycopenic symptom, this was considered a clinically relevant sign of postprandial hypoglycaemia based on previous research.⁶ To assess the psychological impact of these complaints we also asked if this provoked anxiety or insecurity. In addition to the DSS, all patients were asked to report any other accompanying symptoms.

During the test all patients were also observed and questioned for symptoms by the researchers.

DEFINITION OF PHH

Patients were divided into two groups, a group with hypoglycaemia defined as a postprandial glucose concentration < 3.3 mmol/L and a group without hypoglycaemia defined by postprandial glucose concentrations of ≥ 3.3 mmol/L in accordance with the guidelines(13). Symptomatic PHH was defined as hypoglycaemia in combination with a positive score on the DSS. Asymptomatic PHH was defined as hypoglycaemia without or with mild symptoms of neuroglycopenic or adrenergic symptoms.

Calculations of beta cell function and insulin sensitivity

In the fasting state:

HOMA-IR was calculated as the product of fasting baseline levels of circulating glucose and insulin divided by 22.5 ($\text{Basal}_{\text{gluc}} \times \text{Basal}_{\text{ins}} / 22.5$).¹⁹ The quantitative insulin sensitivity check index (QUICKI), was calculated by $1 / (\log(\text{fasting insulin in ng/ml}) + (\log(\text{fasting glucose in mg/dL})).$ ²⁰ HOMA- β was calculated with fasting glucose and insulin concentrations using the HOMA2 calculator available at <http://www.dtu.ox.ac.uk/homacalculator/index.php>.

In the postprandial state:

Insulin resistance was calculated using the formula of the product of the area under the curves (AUCs) of the circulating glucose and insulin responses ($\text{AUC}_{\text{gluc}} \times \text{AUC}_{\text{ins}}$) as used during an OGTT.²¹

Insulin sensitivity calculations were based upon the Matsuda index (MISI), and was calculated as $10000 / [\text{square root of (fasting glucose x fasting insulin)} \times (\text{mean glucose} \times \text{mean insulin})].$ ²² The insulin secretion index (ISI) was calculated by dividing the total area under the curve for insulin at 60 min by total area under the curve for glucose at 60 min.

The β -cell sensitivity was calculated by three different methods. Firstly, by the ratio of the area under the curves of the circulating insulin and glucose responses ($\text{AUC}_{\text{ins}} / \text{AUC}_{\text{gluc}}$).^{7,9} Secondly by the liquid mixed meal tolerance disposition index (LMTT-DI), which was calculated according the following formula; $\text{MISI} \times \text{ISI}.$ ¹⁰ Lastly, by the insulinogenic index calculated as the change in insulin concentration at 10, 20 or 30 min versus baseline divided by the change in glucose in the corresponding time period.

Statistical analysis

Data are presented as mean ($\pm$ standard deviation), median [Interquartile ranges, IQR], frequencies or percentages where appropriate.

In order to study the representativeness of the included study population, they were compared to the entire population and the random selection for age, sex, preoperative weight and preoperative comorbidities with independent Student's *t* tests and Fisher's Exact tests.

Differences between the group with hypoglycaemia and the group without hypoglycaemia were assessed with *t* tests (for continuous variables) or Chi-square tests (for categorical variables). An alpha level of 0.05 was used for determining statistical significance. For graphical representations, mean with standard error of the mean are shown. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, Inc., Armonk, NY, USA), Version 23.

RESULTS

Demographic characteristics

Data of 44 patients were available for analysis; 32 women and 12 men with a median age of 47 years [39; 56], all demographic characteristics are presented in Table 1. The study population was representative of the entire surgical cohort (n=550) in terms of age, sex, comorbidities before surgery, preoperative weight and postoperative weight at the time of the study (table 2).

Table 1: Comparison of patient characteristics between patients with and without hypoglycaemia.

	Patients without hypoglycaemia n=23	Patients with hypoglycaemia n=21	p-value
Age (years)	48 [42; 56]	42 [39; 56]	0.449
Female (%)	14 (61)	18 (86)	0.094
Time between surgery and study (months)	54 [44; 58]	43 [38; 53]	0.010
Weight and weight loss			
Weight at surgery (kg)	143 [128; 157]	130 [120; 147]	0.045
BMI at surgery	45 [43; 52]	45 [41; 48]	0.287
Weight at MMTT (kg)	99 [88; 118]	85 [79; 94]	0.001
BMI at MMTT	32 [30; 39]	29 [26; 32]	0.014
EWL at MMTT (%)	62 [48; 76]	78 [64; 92]	0.011
TWL at MMTT (%)	28 [22; 34]	33 [27; 41]	0.036
Comorbidities preoperative			
Type 2 diabetes	13 (57)	1 (5)	0.000
Hypertension	15 (61)	6 (29)	0.040
Dyslipidemia [#]	6(26)	3 (14)	0.462
Comorbidities postoperative			
Type 2 diabetes *	0	0	
Hypertension	6 (26)	4 (19)	0.902
Dyslipidemia	3 (13)	1 (5)	0.609

Data are median and interquartile ranges [IQR], or numbers and frequencies (percentages).

MMTT: mixed meal tolerance test. EWL: excess weight loss. TWL: total weight loss.

* Exclusion criteria

[#] Defined as patients using lipid lowering medication

Patients who developed hypoglycaemia during the MMTT were more often female, had a shorter follow up after surgery, had less often a history of type 2 diabetes, had a lower BMI and weight at the MMTT and had lost more (excess) weight after gastric bypass surgery (Table 1).

Table 2: Comparison between sample and entire surgical cohort of patients undergone primary gastric bypass

	Sample N = 44	Entire cohort N = 506	p-value
Age (years)	45.3 [38.1; 53.2]	44.4 [37.5; 51.5]	0.859
Female (%)	32 (72.7)	403 (79.6)	0.332
Comorbidities preoperative			
Type 2 diabetes	13 (29.5)	112 (22.1)	0.265
Hypertension	19 (43.2)	195 (38.5)	0.629
Dyslipidemia	9 (20.5)	84 (16.6)	0.535
Weight and weight loss			
Weight at surgery (kg)	137 [125; 150]	130 [116; 146]	0.820
BMI at surgery	45 [42; 48]	44 [41;48]	0.097
Last weight at outpatient clinic (kg)	95.0 [84.3; 106.8]	93.1 [82.0;110.0]	0.336
Last BMI at outpatient clinic	30 [26;33]	31 [27;35]	0.746
EWL (%)	75 [61; 92]	69 [53; 88]	0.263
TWL (%)	32 [28; 39]	30 [23; 37]	0.625

Data are median and interquartile ranges [IQR], or numbers and frequencies (percentages).

Glucose and insulin.

Hypoglycaemia was present in 21 patients (48%) occurring between 30 and 150 minutes, but mostly between 60 and 120 minutes (Figure 2). One patient started the MMTT with a fasting glucose concentration of 2.9 mmol/L, this increased to 9.5 mmol/L at 20 minutes after the meal and after 60 minutes the patient had a hypoglycaemia with a nadir glucose concentration of 1.7 mmol/L. Thirteen patients (30%) developed a hypoglycaemia with a nadir glucose concentrations below 2.8 mmol/L. Patients who developed a hypoglycemic episode had significantly lower glucose values at baseline and on all time points after ingestion of the meal except for 10, 180 and 210 minutes. Insulin concentrations were significantly higher at 10 and 30 minutes and significantly lower in the group with hypoglycaemia at baseline and in the late postprandial phase from 90 to 210 min.

Hypoglycaemia related symptoms.

No differences in moderate or severe hypoglycemic symptoms were seen between the group with hypoglycaemia versus group without hypoglycaemia (table 3).

In accordance with this, no symptoms of neuroglycopenia or adrenergic stimulation were observed by the investigators. .

Insulin sensitivity and beta-cell function

All indices of insulin resistance showed that insulin sensitivity was significantly higher in the group with hypoglycaemia compared to the group without hypoglycaemia (Table 4).

Figure 2: Glucose and Insulin levels in patients with and without a hypoglycemic event. Data are mean $\pm$ SEM.

* p value < 0.05, ** p value < 0.01, *** p value < 0.001

Table 3: Number of patients with (moderate and severe) symptoms in patients with (+) and without (-) hypoglycaemia

Minutes after meal	Sweating		Palpitations		Hunger		Tremor		Drowsiness		Irritability	
Hypoglycaemia	-	+	-	+	-	+	-	+	-	+	-	+
	23	21	23	21	23	21	23	21	23	21	23	21
-15	0	1 (5)	0	1 (5)	4 (17)	1 (5)	2 (9)	2 (10)	1 (4)	1 (5)	1 (4)	1 (5)
60-90	0	0	0	0	1 (4)	2 (10)	0	0	2 (9)	4 (19)	0	0
90-120	0	0	0	0	1 (4)	2 (10)	0	0	2 (9)	2 (10)	0	0
120-150	1 (4)	0	0	0	1 (4)	3 (14)	0	0	3 (13)	2 (10)	0	0
150-180	1 (4)	0	0	0	5 (22)	7 (33)	0	1 (5)	2 (9)	0	0	1 (5)
180-210	1 (4)	0	0	0	7 (30)	10 (48)	0	0	1 (4)	1 (5)	0	1 (5)

Data are numbers and frequencies (percentages). No significances were observed between both groups.

Table 4: Differences in beta cell function and insulin resistance

	No hypoglycaemia	hypoglycaemia	p-value
Insulin sensitivity			
HOMA2-IR	1.36 [0.68; 1.70]	0.72 [0.50; 1.01]	0.014
Quicki-index	0.147 [0.140; 0.164]	0.164 [0.157; 0.179]	0.011
MISI	4.3 [3.0; 7.8]	7.8 [4.7; 12.0]	0.014
ISI	9.9 [7.7; 14.1]	21.6 [11.3; 24.2]	0.001
Beta cell function			
HOMA2- β	121 [77; 158]	116 [99; 137]	0.685
LMTT-DI	36.9 [24.9; 48.0]	95.8 [68.5; 147.1]	0.000
Insulinogenic index			
0-10 min	21.0 [10.8; 43.4]	41.4 [23.1; 62.9]	0.012
0-20 min	19.7 [12.8; 29.0]	43 [25.3; 64.1]	0.001
0-30 min	19.1 [14.0; 34.7]	44.6 [26.6; 66.5]	0.600

MISI: Matsuda Index, ISI: Insulin Secretion Index, LMTT-DI: liquid mixed meal tolerance disposition index:

In contrast to the HOMA2- β which was not different between groups, the estimates of the postprandial beta-cell function showed an increased insulin secretion as calculated by the LMTT-DI and the insulinogenic index in the group with hypoglycaemia (Table 4).

Other intestinal hormones

The concentrations of PYY, total GLP-1 and VIP, measured as incremental AUC and relative peak were not different between both groups (Figure 3).

Figure 3: Changes in gut hormones from baseline (percentage change) of various gut hormones in patients with and without a hypoglycemic event. Data are mean $\pm$ SEM

DISCUSSION

In a random population four years after primary gastric bypass surgery 48% of patients developed a hypoglycemic event (< 3.3 mmol/l) without concurrent symptoms after a test meal. Patients who developed hypoglycaemia after a test meal were more often female and had lost more weight after their operation. In addition, they showed a higher insulin sensitivity (lower HOMA-IR and no prior history of type 2 diabetes) and an enhanced beta cell function in the postprandial phase.

This is the first study consisting of a randomly selected, sufficiently large number of patients with a mid-term follow up after primary gastric bypass surgery investigated with a

dynamic test of sufficient duration. Previous studies have shown that the prevalence of PHH assessed with an oral glucose tolerance test varied between 10.4% and 80% depending on the glucose load (75 or 100 gram) and cut-off value (2.8 or 3.3 mmol/L), and selection of the study population.²³⁻²⁷

The study by Raverdy et al. on the prevalence of PHH contains data 60 months after RYGB and found a prevalence of 7.9% of PHH.²⁸ However, they used an OGTT and measured only 30 and 120 minutes after oral ingestion with a definition of PHH with a glucose value lower than 2.8 mmol/L. We chose the MMTT as provocation test as the composition of this liquid meal with a combination of fat, protein and 40 grams of carbohydrate (of which 14 g sugar) resembles more a normal food intake. To study the prevalence of PHH in a daily life setting, the MMTT is therefore a better test than the OGTT.¹³

The first intriguing observation of our study is the high prevalence of PHH in combination with a total lack of related symptoms, as well as reported by patients, as observed by the researchers. This phenomenon is known as hypoglycaemia unawareness or hypoglycaemia associated autonomic failure (HAAF). It is frequently observed in people with type 1 diabetes on intensive insulin treatment who experience recurrent hypoglycaemia, but has also been suggested to occur during PHH in the bariatric population.¹¹ Our results are in line with Abrahamsson et al. who performed a stepwise hypoglycemic clamp study in patients before and 23 weeks after gastric bypass surgery.²⁹ They found that the hypoglycaemia symptom score but also the counterregulatory hormones glucagon, cortisol, catecholamine and sympathetic nerve response were much lower after surgery compared to before. One study investigated fifteen RYGB patients without known hypoglycaemia by means of CGMS and found that the patients had glucose concentrations below 3.3 mmol/L in 2.9% of the time and in 1.5% of the time these concentrations dropped below 2.8 mmol/L. The patients were unaware of their hypoglycaemia in four out of five (80%) times. Thus, it is plausible that the high prevalence of hypoglycaemia as seen in our study translates in daily life to recurrent hypoglycaemia, leading to hypoglycaemia induced autonomic failure and hypoglycaemia unawareness. This could also explain the discrepancy of the prevalence of PHH measured during dynamic tests and by means of questionnaires.

Not only after gastric bypass surgery, but also in patients who underwent a vertical banded gastroplasty with 30% weight loss a decrease in counterregulation to hypoglycaemia has been observed.³⁰ This suggests that the development of hypoglycaemia unawareness can not be attributed to a specific type of bariatric surgery. The second main finding in the current study is the observation of differences in insulin sensitivity and insulin secretion between the groups with and without hypoglycaemia. The group with hypoglycaemia had in comparison with the group without hypoglycaemia a lower preoperative weight, more postoperative weight loss and less likely to have a history of type 2 diabetes, these are all factors that are known to contribute to high insulin sensitivity. In these patients, this was supported by lower fasting glucose and insulin concentrations and a lower HOMA2-IR. Also contributing is the

increased insulin secretion in the first half hour of the test and the disposition index which was indicative of an enhanced postprandial beta cell function. Finally, the patients with a hypoglycemic event returned to lower insulin levels at later time points, this could reflect higher insulin sensitivity.

Our findings of higher insulin sensitivity and increased insulin secretion in patients with hypoglycaemia are in line with the prior studies.^{11,23} One of these studies was by Guarino et al. They performed an OGTT in patients who were all diabetic preoperatively, but the majority (74%) were at the time of testing postoperatively in remission.²³ Also, Vours et al. found that the patients after RYGB with hypoglycaemia during OGTT had an increased insulin secretion rate in the first 15 minutes. Just as in the current study, these patients had lost more weight postoperatively and were less frequently diagnosed with diabetes before surgery. However, they did not observe a difference in insulin sensitivity between patients with and without hypoglycaemia.¹¹ This discrepancy with the current study could be explained by the difference in the definition of hypoglycaemia which was a glucose concentration < 2.8 mmol/L in Vours et al, and < 3.3 mmol/L in ours. But it could also be caused by the difference in inclusion criteria, as they specifically included patients who experienced hypoglycemic symptoms during daily life, while in our current study a random sample was drawn and none of the patients with hypoglycaemia during the MMTT had clinically relevant symptoms. A more rapid glucose peak and higher GLP-1 response was found in patients with post gastric bypass hypoglycaemia suggesting a role for GLP-1 in the pathophysiology.^{23,31} Blocking the GLP-1-receptor by the GLP-1-receptor antagonist exendin 9-39 abolishes the occurrence of hypoglycaemia during a MMTT providing further evidence for a role of GLP-1 in the pathogenesis of PHH.³² Interestingly, we did not find differences in GLP-1, PYY and VIP concentrations between the group with hypoglycaemia versus the group without hypoglycaemia. Vours et al. also did not observe differences in GLP-1.¹¹ Difference in the stimulus, glucose versus a mixed meal, and selection of patients could be the explanation for this discrepancy. Moreover, the lower glucose concentration in the group with hypoglycaemia in our study was already present in the fasting state, which suggest that postprandial GLP-1 hypersecretion is not the only mechanism contributing to PHH. This may be a consequence of a higher glucose sensitivity but differences in hepatic glucose production by changes in glucagon concentrations or by changes in autonomic innervation have also to be considered. These mechanisms need to be studied further in detail.

Strength of our study is the random selection of patients with the cohort being comparable to the entire surgical cohort in terms of age, sex, comorbidities before surgery, preoperative weight and postoperative weight at the time of the study. Furthermore, we used a mixed meal tolerance test which is more close to normal food intake compared to an OGTT.

Some limitations of the study must be mentioned. Firstly, for various reasons, most unrelated to dumping, only 44 patients of the 51 patients in the random sample were tested, However, because most of these exclusions were due to problematic blood withdrawal, the

risk of bias is low. The demographics of the tested patients were not different from the total group of operated patients but there is still a possibility of selection bias.

Secondly, the test meal for a MMTT is not standardized, which is a general shortcoming of meal tests. Standardization should be recommended in order to compare studies in future research. Thirdly, patients were not tested before surgery and therefore other predictors beside the demographics can not be extrapolated from our study. Pigeyre et al. found in nondiabetic patients after RYGB that a normal glucose tolerance test and a lower HbA1c before surgery were predictors of the hypoglycaemia during a 75 gram OGTT 12 months after surgery.³³ Finally, for GLP-1, PYY and VIP only relative changes compared to baseline could be presented due to the (unexpected) large inter-assay variation.

CONCLUSION

In a randomly selected population mid-term after primary RYGB surgery 48% of patients developed a hypoglycemic event during a mixed meal tolerance test. No hypoglycemic symptoms accompanied these events suggesting the presence of hypoglycaemia unawareness in these patients. The findings in this study suggest that the pathophysiology of PHH is multifactorial and not just the result of increased GLP-1 secretion.

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Part III

Solving old problems, creating new ones

Chapter 7

Conversion of failed laparoscopic adjustable gastric banding to Roux-en-Y gastric bypass is safe as a single-step procedure

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Surg Endosc. 2015 Aug; 29(8): 2217-2223.

ABSTRACT

Background

Several different procedures have been proposed as a revisional procedure for treatment of failed laparoscopic adjustable gastric banding (LAGB). Laparoscopic Roux-en-Y gastric bypass (LRYGB) has been advocated as procedure of choice for revision. In this study, we compare the single- and two-step approaches for the revision of failed LAGB to LRYGB.

Method

All patients who underwent bariatric surgery were included in a prospective database. For the purpose of this study, patients who underwent revisional surgery from LAGB to LRYGB were selected. Records for individual patients were completed by data review. Complication rates were compared between both procedures and with complications rates reported in literature.

Results

Revisional gastric bypass surgery was performed in 257 patients. This was done as a planned single-step procedure in 220 (86%) patients without indications for acute band removal and in 32 patients as a 2 step procedure. Five patients were intraoperatively converted to a 2-step procedure based on poor pouch tissue quality. No postoperative mortality occurred in both groups. No differences in early major morbidity and stricture formation were seen between the two groups. Gastric ulceration was more frequently observed after 2-steps procedure (8.5 versus 1.7%, $p < 0.05$). In comparison with data reported in literature, the single-step procedure had similar to lower complication rates. Percentage excess weight loss two years after revisional gastric bypass procedure was, respectively, 53 versus 67% ($p=0.147$) for single- and two-step procedure.

Conclusion

In patients without indications for acute band removal, the planned conversion of gastric banding to Roux-Y gastric bypass can be safely done in a single step procedure without increase in morbidity and no difference in postoperative weight loss.

INTRODUCTION

Morbid obesity is a growing healthcare problem across the world. In the Netherlands, 35.4% of the adult population suffer from obesity and 11.8% of the adult population from morbid obesity.¹ Weight-loss surgery is the only way to achieve sustained weight loss, resolve co-morbidities and improve longevity.² Adjustable gastric banding has long been the first choice for weight-loss surgery as it is a relatively simple operation with low postoperative morbidity and mortality rates, especially since the introduction of the laparoscopic approach. Excess weight loss can be reached, ranging from 44% to 68 % after 4 years and from 38 to 46% in 10 to 12 years.³⁻⁶ In the long-term, a large proportion (25 %) of patients with gastric banding need revisional surgery because of disappointing weight-loss results or banding complications.⁶⁻⁸

The relative disadvantages of LAGB include the need for frequent follow-up and band adjustment, and there is potential for adverse band-related symptoms such as food intolerance, vomiting and reflux disease.⁶⁻⁹ In addition, late-complication rates after LAGB are common and even increase with time. The most frequent complications are band slippage, band erosion, pouch dilatation and port complications.^{6-8,10} For these reasons, the surgical revision rate is high. Even using the pars flaccida technique, revision is still substantial and ranges between 18 and 30% after 5-8 years.^{3,7,8}

Surgical options for patients with band complications, insufficient weight loss or weight regain include removal, repositioning or replacement of the band, or conversion to an alternative procedure, such as gastric sleeve, gastric bypass or duodenal switch.¹¹ In the case of failed gastric banding, the procedure of choice is removal of the gastric band and performance of a gastric bypass.¹² Conversion to gastric bypass is often performed as a two-step procedure but it can be performed as a one-step operation.¹³⁻¹⁵ However, there are no data available on the safety of the one-step procedure in a large population. For this reason we reviewed the early and late complications and the postoperative weight loss results of the conversion of failed LAGB to LRYGB as a one-step procedure in patients.

METHOD

Data

From January 2008 to December 2011, all patients who underwent bariatric surgery at the Centre for Obesity at the Medical Centre Leeuwarden were included in a prospective database. For the purpose of this study, we performed a retrospective review of prospectively collected data. Patients who underwent revisional surgery from LAGB to LRYGB were selected and analysed. Records for individual patients were completed by data review. Data are reported according to the STROBE statement.¹⁶

Patients

All patients were aged between 18 and 65 years at the time of the primary LAGB, in accordance with international guidelines.¹⁷ Indications for revisional procedures included: insufficient weight loss (<50% EWL), weight regain (>5 BMI points) with healthy lifestyle and diet or band-related complications in a well-motivated patient. Preoperative assessment of patients eligible for revisional surgery included counselling by dietician and psychologist in order to exclude non-adjusted eating patterns or eating disorders. If detected, these issues were addressed before surgery was considered.

Preoperative Procedures

All patients were preoperatively consulted with and received extensive information about the procedures, possible complications, expectations for weight loss, changes in lifestyle, eating behaviour and the importance of exercise. A gastrograffin swallow X-ray was routinely performed on all patients prior to surgery. In case of suspicion of ulceration or erosion, an endoscopic evaluation was performed. Dietary advice prior to surgery consisted of a three-week high-protein, low-carbohydrate diet.

Definition and Evaluation of Band Complications

All band complications were documented preoperatively, either by endoscopy, radiological imaging, or cultures from cutaneous fistula or access port (Table 1).

Band migration or slipping was visualised on a gastrograffin swallow. Band erosions were detected by gastroscopy. Band infection was defined by abscesses near the band on CT-scan or positive cultures from cutaneous fistula or access port. Pouch or oesophageal dilatation was also demonstrated by the gastrograffin swallow and failed to improve by emptying the band. Severe band intolerance was defined as dysphagia, odynophagia, vomiting or reflux interfering in daily life in the presence of a deflated band and in the absence of other band complications as described above.

One- or Two-Step Procedure

One-step procedures were planned after the preoperative preparations described above. In the two-step procedure, the removal of the band was planned briefly after presentation (depending on the severity of band complications) and the second step took place after the above preoperative procedure and was planned several months after band removal. Patients presenting with acute symptoms such as infection, migration or erosion of the band with an indication for acute band removal were booked for a two-step procedure. Patients with severe band intolerance in combination with slipping or pouch formation that did not improve by deflating, and who were not willing to wait for a planned one-step procedure, were also booked for a two-step procedure. All other patients were booked for a one-step procedure.

Table 1: Indications for revisional gastric bypass surgery in patients undergoing a one- and two-step procedure.

	One step N=220 (%)	Two step* N=37 (%)	p-value
<i>Band complications</i>			
Erosion	0	2 (5.4)	<0.001
Migration	7 (3.2)	2 (5.4)	0.496
Leakage of band	3 (1.4)	1 (2.7)	0.543
Slipping	15 (6.7)	9 (25.7)	<0.001
Dysmotility	38 (17.3)	12 (35.1)	0.012
Infection of band	0	1 (0.5)	0.681
Pouch formation	19 (8.6)	6 (13.5)	0.346
<i>Indications not related to band complications</i>			
Insufficient weight loss	81 (36.8)	8 (21.6)	0.072
Weight regain	63 (28.2)	13 (37.8)	0.234
Insufficient weight loss and weight regain	19 (8.6)	1 (5.4)	0.213
Reason unknown	19 (8.6)	2 (5.4)	0.507

Data are absolute numbers (percentage). P-value by Chi square.

*More indications in one patient possible

Operative Technique

We performed a standardised operation protocol in all patients. We used the six trocars technique and first removed the band and performed an adhesiolysis of the angle of His. The capsula of the band on the stomach was occasionally divided or removed. Then we continued to perform the bypass. The formation of the pouch was done by linear stapling (Ethicon Endo-Surgery, Inc, Cincinnati, USA). We started the creation of the pouch just below the scar tissue of the band, approximately 4-5cm below the gastro-oesophageal junction at the lesser curvature. The staple line of the pouch is created just outside the scarred and compromised tissue and therefore probably bigger than it would be in primary procedure. The estimated volume of the pouch was 60-80cc. The biliopancreatic limb was measured at 80cm from the angle of Treitz. With this loop, the gastro-enterostomy was made by linear stapling and the anterior defect was closed with sutures. An alimentary limb of 150cm was measured and the latero-lateral entero-enterostomy was fashioned with the endoscopic linear stapler and interrupted sutures. Control of integrity of both anastomoses was performed by methylene and air-leak testing after introduction of a gastric tube by the anaesthesiologist. In occurrence of leakage, additional sutures were placed. After testing for both anastomoses the Roux-en-Y construction was completed by dividing the loop with linear stapling between the two anastomoses. The technique of the one-step revisional procedure is also described by Hii.¹⁵ All anastomoses were covered by tissue col (Baxter). The mesenteric defects were not routinely closed. Operative procedure times were recorded for all operations, however, for 10 operations these data were not available. On the first postoperative day, a gastrograffin swallow was performed to check the integrity of the gastroenteric anastomosis in prospect of oral intake.

Postoperative Care

Patients were allowed to eat fluid meals for three weeks from the first postoperative day on in case of absence of leakage on the gastrograffin swallow. Most patients were discharged from hospital two to four days after revisional surgery and 24 hours after band removal. Before discharge, patients were informed about signs of complications and pressed to call the outpatient clinic or emergency department in case of fever, new severe abdominal pain, vomiting, melena, hematemesis and failure to eat. In the event of these alarm symptoms, gastrograffin swallows and blood tests for infections and/or CT-scanning were made to rule out leakage of anastomosis. Postoperative counselling was done by the surgeon at 4 weeks and 12 months after surgery and yearly thereafter. After surgery all patients were given a 2-year-long sequential group meeting programme, including counselling by a bariatric nurse practitioner and appointments with a dietician, a psychologist and a physiotherapist. Follow-up rates after 1 and 2 years (22-26 months) postoperatively were 93% and 75% respectively.

Definition of Postoperative Complications

Complications that developed within 30 days after surgery were classified as early complications. Major complications in this group included anastomotic leakage, intra-abdominal abscess formation, myocardial infarction, pulmonary embolism, cerebrovascular accident (CVA), any reoperation, and death.

Late complications were complications that developed more than 30 days postoperatively. We registered gastric ulcer formation or stricture of gastrojejunal anastomosis as late complications.

Weight Loss

The ideal weight of every patient was estimated based on a target BMI of 25. The percentage of excess weight loss (%EWL) was calculated as $((\text{operative weight} - \text{follow-up weight}) / \text{operative excess weight}) \times 100$.

Statistics

The analyses were all carried out using the PASW (SPSS, Inc., Armonk, NY, USA) Statistics 20 package. Data are presented as mean ($\pm$ standard deviation), median (ranges), frequencies or percentages, where appropriate. Chi-square with Yates correction for continuity was used for comparison of proportions. Significance was assumed for p values lower than 0.05.

RESULTS

Patient Characteristics

Between 2008 and 2011, 257 patients were treated for failed banding by removal of the band and construction of a Roux-en-Y gastric bypass. The median age of patients was 43 (range 23-70) and 83% were female. Gastric banding was performed in other hospitals in 173 patients (67%). The median time between LAGB and LRYGB was 57 months (range 7- 219) and follow up after revisional procedures was 29 months (range 1-69). The mean age in the one-step and two-step groups was 44 and 42 years respectively ($p = 0.252$). No difference in follow-up time was seen between the two patient groups (29 and 31 months, $p = 0.342$)

Indications and Planning of Revisional Surgery

Indications for revisional gastric bypass surgery in patients are shown in Table 1. A one-step procedure was performed in 220 patients (85.6%). The most frequent indications for revisional surgery in this group were related to insufficient weight loss or weight regain. Band-related complications were especially dysmotility, slipping and pouch formation. Some patients had more than one indication for revision. In 32 patients, a two-step procedure was planned and performed. The primary reasons for band removal in the two-step group were slipping, pouch formation or dysmotility in which conservative treatment failed and not insufficient weight loss or weight regain. In addition, five patients were planned as a one-step procedure but converted to a two-step procedure on the basis of surgical judgement of damage or poor tissue quality of the pouch (1 erosion; 2 perforations; 1 extreme pouch formation with thin wall and 1 suspicion of malignancy, which, during follow up, proved to be scar tissue). Two patients died in the follow-up period (one in each group), one of myocardial infarction and one after suicide by depression, both not attributable to surgery.

Peri-operative Details

Cumulative duration of both removal of gastric band and the performance of gastric bypass was respectively 118 minutes (range 57-315) and 222 minutes (range 114-331) for one- and two-step procedures ($P=0.000$). The average operation time of laparoscopic removal of the gastric band as the first step in the two-step procedure was 76 minutes (range 27-175). The average operation time of gastric bypass as the second step in the two-step procedure was 115 minutes (range 61-263).

Total postoperative hospital stay was three days (range 2-71) for one-step and five days (3-18) for two-step procedures ($P=0.201$), respectively.

Complications of Revisional Surgery

All patients were seen in outpatient clinics after 4 weeks, therefore, all early major complications could be scored. No mortality was seen after operation. The total early complication

rate for major morbidity was 4.6% in both groups combined (Table 2). No myocardial infarction, CVA or pulmonary embolism was seen. No differences were seen in stricture formation or leakage of the gastro-jejunal anastomosis between both procedures. The latter complication was treated in four patients by laparoscopy, drainage and, if possible, suture repair of the leak. Two patients received a stent and percutaneous drainage. One patient was treated by laparoscopic lavage of the abdomen and antibiotics. Hospital stay was prolonged in all patients with complications. One patient had a severe sepsis due to anastomotic leakage, which was treated on the ICU, total hospital stay in this patient was 71 days. The only difference in the late-complication rate was seen in the development of gastric ulcers, which was more frequent after two-step procedures than after one-step procedures (8.5% versus 1.7%, $p = 0.03$). The median time after revisional bypass for developing gastric ulcers was 21 months (range 7-30); for stenosis it was 13 months (range 9-17).

Table 2: Complications after revisional gastric bypass surgery in patients undergoing one- and two-step procedures.

	One step N=220	Two step N=37	P-value*	References review Coblijn(22)	References cohort Hii(14) N = 82
<i>Early postoperative complications</i>					
Leakage of gastroenterostomy	5 (2,3)	2 (5,4)	0.279	1.8%	
Intraabdominal abscess (no signs of leakage)	2 (0,9)	0	0.560		
Bleeding necessitating operation	1 (0,5)	0	0.681	0.9%	
Suspicion of leakage but negative laparoscopy	2 (0,9)	0	0.560		
Mortality	0	0		0%	
Total major morbidity	10 (4,6)	2 (5,4)	0.711		
<i>Late postoperative complications</i>					
Gastric ulcer formation	4 (1,8)	3 (8,1)	0.030		16 (2,4)
Stricture formation at anastomosis	1 (0,5)	1 (2,7)	0.151		19.5%

Data are absolute numbers (percentage). P-value by Chi square between one-step and two-step revisional procedures.

Weight Loss

Weight loss and BMI before and after primary gastric banding and revisional gastric bypass surgery are shown in Table 3. Thirteen patients gained weight after the revisional procedure, one by 10 BMI points, the others by within three BMI points. Twenty-five patients reached a BMI lower than 26 (10 of these were in the two-step group). The median Excess Weight Loss percentage (%EWL) 29 months after one-and two-step procedures was 53% (range -112- 181) and 67% (range -22-151; $p=0.147$) respectively.

Table 3: Weight and BMI development after primary gastric banding and at time of and after one- and two-step revisional gastric bypass procedures.

	One-step procedure			Two-step procedure			P-value
	Weight (kg)	BMI	%EWL	Weight	BMI	%EWL	
At gastric banding	135 (79-197)	46 (29-65)		133 (100-197)	43 (35-59)		0.978 [#]
Lowest reached after gastric banding	105 (60-169)	36 (22-55)		100 (57-142)	31 (20-42)		0.005 [#]
At revisional procedure	121 (65-211)	40 (25-70)		120 (72-160)	40 (25-51)		0.881 [#]
Last visit*	93 (56-199)	32 (20-66)		90 (60-139)	29 (20-42)		0.074 [#]
Total %EWL from gastric bypass			53% (-112-181)			67% (-23- 151)	0.147
Total %EWL starting from gastric banding			67% (-4-175)			77% (11-140)	0.027

Data are median (range)

*Median follow up 29 months after gastric bypass

[#]Calculated on BMI

DISCUSSION

In this large single-centre study, we show that a planned conversion of LAGB to Roux-Y gastric bypass can be safely done in a one-step procedure. Complication rates were comparable between one- and two-step procedures. Also, the need for conversion to a two-step procedure was low. Several studies already showed the feasibility of converting gastric banding to gastric bypass.^{18,19} This is the first study that shows the safety in a large homogenous cohort of more than 250 patients operated in a small period of time (four years).

Since complication rates after LAGB are common, the need for revisional procedures is increasing.^{6-8,10} Schouten et al. described a 'decision tree' for the treatment of failed banding.¹² They argued that in case of poor weight loss or banding complications such as pouch formation or erosion, conversion to gastric bypass must be proposed. Rebanding can only be considered in case of adequate weight loss and banding problems such as leakage or migration without other complications. Revision to another procedure can be done by either a one-step or two-step approach. The one-step procedure has the advantage of circumventing the need for a second operation 2-3 months later and thereby results in a shorter cumulative operation time and hospital stay.¹⁴ Several studies describe the one-step procedure without comparing it with a two-step procedure.^{13,18,20,21} In addition, a recent population-based study showed not only an increase in reoperations after gastric banding, but also that patients had more adverse outcome after revisional surgery than patients with primary gastric bypass.²² A recent review of literature by Coblijn showed higher complication rates of revisional procedures compared with primary procedures.²³

A disadvantage of the one-step approach could be the potentially higher risk of anastomotic leakage because of the fibrosis that is present after removal of the band. However, the series of Hii, Apers, and Van Nieuwenhoven, in which patients who underwent a one-step

procedure were compared with those who underwent a two-step procedure, showed no differences in anastomotic leakage.¹³⁻¹⁵ All these studies were limited to a relatively small patient group. In our large cohort we confirm their results.

Another possible disadvantage of the one-step procedure is anastomotic stricture formation, which is suggested to be significantly higher after the one-step approach.^{14,15} In both series, circular stapling is used. In our series, by contrast, we used linear stapling for creation of the gastroenterostomy, which may explain the differences. Significant differences in ulcer formation were seen in the two-step group; we have no straightforward explanation for this. In theory, the possibility exists that in the two-step approach the creation of the pouch is in vascular-compromised tissue because of scarring. In case of the one-step procedure, scar tissue is easily recognised and stapling takes place around this vascular compromised tissue.

Weight-loss results showed a difference between one- and two-step procedures of 14% (53 versus 67) without statistic significance. However, calculating from before gastric banding until the last visit after revisional procedure, the two-step group reached a lower BMI and a higher cumulative %EWL. This difference is due to the higher %EWL after gastric banding, in favour of the two-step procedure. In this group all patients suffered from banding complications such as dysmotility, slipping, etc. Therefore, intake was possibly lower than in the one-step group, and therefore they reached a higher %EWL. As a result we think that the cumulative %EWL from banding and gastric bypass is more indicative of the results than the %EWL after revisional gastric bypass alone.

Our study has an observational design and, therefore, bias could have been introduced. The indications for one- or two-step procedures were not strictly agreed upon in advance, and therefore, some patients with subjective severe complaints were given a two-step procedure. Furthermore, indications for one-step revisional surgery were predominantly insufficient weight loss or weight regain, while indications for two-step conversion were mainly due to complications. This selection may have led to unbalanced comparisons between both groups. On the other hand, it is a description of daily surgical practice and shows that with careful selection of patients the complication rates were excellent compared to both two-step procedures and those reported in the literature.²³

In general, we advise that patients with an acute indication for band removal, such as infection, slipping, migration or erosion, are more suitable for a separated two-step procedure, undergoing definitive gastric bypass several months after band removal. This is not only for safety reasons but also because these patients should be properly informed and prepared in terms of their expectations after gastric bypass. These aspects are usually time consuming and impossible to plan for prior to acute band removal. In all other patients, in our experience the majority, elective band removal can be safely combined with simultaneous gastric bypass surgery.

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Chapter 8

Long-term self-reported symptom prevalence
of early and late dumping in a patient
population after sleeve gastrectomy, primary,
and revisional gastric bypass surgery

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Surg Obes Relat Dis. 2018 Aug ;14(8): 1173-1181

ABSTRACT

Background

Early and late dumping are side effects of bariatric surgery. Almost no data are available on the prevalence of dumping after different surgical procedures.

Objectives

Comparison of the relative risks of dumping in a large population of patients having undergone primary Roux-en-Y gastric bypass (pRYGB), sleeve gastrectomy (SG), or revisional RYGB (, rRYGB, after removal of band).

Setting

Bariatric center of a teaching hospital

Methods

In this descriptive cohort study, all patients who underwent a pRYGB (n=615), SG (n=157) or rRYGB (n=274) between 2008 and 2011 were approached by mail and asked to complete and return a questionnaire of general and disease-specific questions related to dumping syndrome. Relative risks (RR) were calculated (mean with 95% confidence intervals) by comparing the prevalence of high suspicion for early and late dumping between different surgical procedure groups and primary gastric bypass surgery.

Results

The questionnaire was completed and returned by 593 (57%) of 1046 patients. Fewer patients with SG were at high suspicion of early dumping than after pRYGB (RR [95% confidence interval] 0.46 [0.22-0.99], $p = 0.049$). No differences for early dumping were seen between rRYGB and pRYGB (RR 1.21 [0.77-1.91], $p = 0.40$). More patients were at high suspicion for late dumping after rRYGB compared with after pRYGB (RR 1.78 [1.09-2.90] $p = 0.021$). No differences for late dumping were seen between SG and pRYGB (RR 0.59 [0.22-1.61], $p = 0.30$).

Conclusion

Fewer complaints of early dumping are reported after SG, while patients report more complaints of late dumping after rRYGB compared to pRYGB.

INTRODUCTION

Morbid obesity is a growing healthcare problem in the world. Its prevalence is increasing; consequently, effective weight-loss strategies are needed. Bariatric surgery is the most effective way to achieve sustained weight loss, resolve comorbidity and improve survival in morbidly obese persons.¹ Different surgical procedures are performed to obtain this durable weight loss.

In earlier days, gastric banding was thought to be a simple and effective way to lose weight. However, because of a high percentage of late complications such as slipping, erosion and migration, and disappointing weight loss results, many patients have their bands taken out and convert to another bariatric procedure.^{2,3} Currently, one of the most frequently performed weight-loss operations is the laparoscopic Roux-en-Y gastric bypass (RYGB). This is effective both as a primary procedure and as a revisional procedure in case of failure of gastric banding.⁴⁻⁶ Over the last few years, sleeve gastrectomy (SG) has gained popularity because of its relative simplicity and reduced risk of vitamin and mineral deficiency and steatorrhea.^{7,8}

One of the side effects of bariatric surgery in the long term can be dumping syndrome. Two variants have been distinguished, early dumping and late dumping. Early dumping is characterized by abdominal symptoms such as bloating, abdominal pain, and nausea, as well as autonomic symptoms such as sweating and flushes within 1 hour after a meal. Late dumping (also known as post-gastric-bypass hypoglycemia) is caused by a hyperinsulinemic hypoglycemic event 1 to 3 hours after a meal.^{9,10} Symptoms exist of neurological impairment because of reduced glucose availability to the brain (e.g., impaired judgment, irritability, confusion, seizures and coma) and autonomic/adrenergic symptoms (e.g., palpitations, tremor and anxiety) due to the release of counter-regulatory hormones, especially (nor) epinephrine. Mechanisms of early dumping are not well understood, but for late dumping glucagon-like peptide 1 is thought to play a crucial role in the exaggerated insulin release because glucagon-like peptide 1 receptor blockade abolishes hypoglycemia.^{11,12}

The prevalence of dumping syndrome is dependent on the diagnostic test used and the population being tested. Studies using provocation tests report the prevalence of early dumping at approximately 42% and of late dumping at as high as 72%.¹³⁻¹⁸ These studies using provocation tests have been criticized because of the absent relationship with daily complaints, and most of the tests are carried out in a selected group of patients with known symptoms. Studies on patient-reported outcomes after bariatric surgery regarding dumping complaints are scarce. Lee et al. showed that patients after bariatric surgery (RYGB and SG) had a prevalence of high suspicion for late dumping of 34% and that RYGB had an increased risk of developing late dumping compared with patients after SG (odds ratio 2.5).¹⁹ In addition, we recently estimated, in a large cohort study of patients after primary gastric bypass surgery that the prevalence of complaints suggestive of early and late dump-

ing of moderate-to-severe intensity would be 19 % and 12%, respectively. We also found that dumping syndrome was inversely related to quality of life, mood and postoperative treatment satisfaction.²⁰

Because various bariatric procedures are currently performed and the prevalence and consequences of dumping syndrome are likely to be of influence on treatment results and satisfaction, we assessed the effects of three different surgical procedures (SG, primary RYGB and revisional RYGB) on the symptom prevalence of early and late dumping.

METHODS

Study population

All patients who underwent bariatric surgery for morbid obesity at a teaching hospital in the Netherlands between 2008 and 2011 were included in a database. All patients were screened before their operation according to the criteria outlined by the International Federation for Surgery of Obesity and Metabolic Disorders.²¹ In 2013, all patients were invited by mail to participate in a questionnaire survey. Four rounds of invitations were sent out (3 by postal mail and 1 by e-mail). For the purpose of this study, all patients who underwent SG, primary gastric bypass and revisional RYGB were selected. Patients who had undergone extra revisional surgery were excluded. The Regional Ethical Review Board of the Medical Center Leeuwarden approved the study protocol (registered at ISRCTN, ISRCTN17666669).

Surgical technique

In all patients a standardized operation technique was used, and all 3 surgeons complied with this standard. Routine antibiotic prophylaxis was administered.

The techniques for primary and revisional gastric bypass are previously described (6). In short, we create a pouch of approximately 30-60 cc in primary gastric bypass and 60-80 cc in revisional bypass because we start the creation of the pouch beneath the scar tissue of the former banding. Most bands were placed in our and surrounding hospitals. The technique of band placing was mostly the so called “pars flaccida” technique, in which the anterior and posterior nerves of Latarjet are not preserved.

In both procedures we used the omentum-sparing procedure for creation of the pouch, in which the lesser sac was entered via perigastric dissection with care taken to preserve the anterior and posterior nerves of Latarjet.²²

The other difference with the primary RYGB technique is that we covered all our anastomosis at the end of the revisional procedure with tissue col (Baxter, Utrecht, the Netherlands).

Karmali et al. earlier described the technique of SG.²³ We started transection at 6 cm before the pylorus and used a 34-F gastric tube for calibration of the sleeve. The sleeve was made “floppy” around this tube.

Control of integrity of anastomoses or staple line was performed in all procedures by methylene and air-leak testing after introduction of a gastric tube by the anesthesiologist. In case of leakage, additional sutures were placed.

Patient groups

Primary gastric bypass

In total, 615 patients received a primary laparoscopic gastric bypass. Of this group, 2 patients died during follow-up (both of malignancies). Thus, 613 patients were contacted and asked to participate in this study. The questionnaire was filled in and returned by 360 patients; 9 were not usable because the questionnaires could not be linked to the right patients. Thus the total amount of questionnaires available for analysis was 351 (57.3%).

The participants in this study were highly comparable to the nonresponders, with the exception of age. Participants were slightly older (median [interquartile range]: 44 [37,49] versus 41 [40-54] years; $P = 0.02$). No differences were seen in excess weight loss, weight before operation, preoperative comorbidities (diabetes, hypertension and hyperlipidemia). This group has been previously described.²⁰

Sleeve gastrectomy

In total, 192 patients received SG. Of these, 35 patients had received a revisional procedure (1 duodenal switch, 1 mini gastric bypass, and 33 RYGB) and were excluded. Of the remaining 157 patients, 89 (57%) filled in the questionnaire and were included in this study. The participants were slightly older than the nonresponders (42 versus 38 years, $P = 0.02$) and had a lower weight before operation (127 kg versus 138 kg, $P = 0.011$). No differences were seen in excess weight loss and presence of preoperative comorbidities (diabetes, hypertension, and hyperlipidemia).

Revisional gastric bypass

In total, 274 patients underwent a revisional gastric bypass procedure. Of these, 153 (56%) filled in the questionnaire and were available for analysis in this study. No differences were seen between participants and nonresponders in terms of weight at revisional surgery and weight at last visit, or in prevalence of diabetes and remission of diabetes. The nonresponders were slightly older (45 versus 42 years, $P = 0.011$), and had more hypertension at the time of revisional surgery (32 versus 17%, $P = 0.005$).

Reason for former band placement was mostly because the other techniques were not available, or the banding procedure was suggested by the surgeon.

Questionnaires

Dumping severity score

The dumping severity score developed by Arts et al. was used for assessment of the severity of early and late dumping syndrome, using a 4-point Likert scale (Supplemental Tables 1a and 2a).¹⁷ Patients were asked to grade the intensity (0 = absent; 1 = mild; 2 = moderate and 3 = severe, i.e. interfering with daily activities) of 8 early dumping symptoms within 1 hour of food ingestion and of 6 hypoglycemia symptoms >1 after food ingestion.¹⁷ To assess the psychological impact of these complaints, we also asked if the symptoms provoked any anxiety or a feeling of unsafety.

Patients were classified based on the results of this questionnaire in 2 groups: high and low suspicion of dumping syndrome. We defined high suspicion of early dumping as someone with ≥ 3 moderate or severe symptoms, including at least one autonomic symptom, on the early dumping severity score. A high suspicion of late dumping (post-gastric bypass hypoglycemia) was defined with the presence of ≥ 3 moderate or severe symptoms, including at least 1 neuroglycopenic symptom, on the late dumping severity score. Additional questions were asked with regard to dumping (self-measured blood-glucose levels, the occurrence of neuroglycopenia and the potential related use of healthcare and treatment), weight development, comorbidities, and use of medication. These data were checked against the data collected at the last outpatient visit.

Statistics

Data are presented as mean ($\pm$ standard deviation), median (interquartile ranges), frequencies, or percentages where appropriate. Differences were assessed with *t* tests (for continuous variables) or Chi-square tests (for categorical variables). A *P*-value < 0.05 was used for determining statistical significance. Relative risks (RR) were calculated (mean with 95% confidence intervals) by comparing the prevalence of high suspicion for early and late dumping between different surgical procedure groups and primary gastric bypass surgery (the comparator). All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, Inc., Armonk, NY, USA), version 23.

RESULTS

Patient characteristics: comparison between sleeve gastrectomy and primary gastric bypass (Table 1)

The excess weight loss did not differ significantly between patients after SG and primary gastric bypass (72 versus 77%, *P* = 0.067). Follow-up time between surgery and study date was significantly shorter (27 versus 32 months, *P* < 0.001) for gastric bypass versus SG patients. Satisfaction with the results was equal between patients with SG and primary gastric bypass.

Table 1: Patient characteristics of patients after primary RYGB and sleeve gastrectomy

	Primary RYGB	Sleeve gastrectomy	P value
number	351	89	
Age (yrs)	46 [39; 53]	45 [38; 54]	0.349
Female (%)	282 (80.3)	73 (82.0)	0.766
Time between last surgery and study (months)	27 [19; 34]	32 [19; 42]	<0.001
Weight and weight loss			
Weight at primary surgery (kg)	129 [116; 144]	124 [112; 139]	0.092
BMI at primary surgery (kg/m ²)	43 [40; 48]	41 [39; 46]	0.08
Weight at revisional surgery (kg)			
Minimum weight after last surgery - self reported (kg)	81 [70; 98]	84 [75; 95]	0.255
Current weight - self reported (kg)	86 [75; 102]	89 [80; 98]	0.437
EWL from primary procedure to study (%)	77 [61; 95]	72 [57; 88]	0.067
Comorbidities preoperative			
Type 2 diabetes	104 (29.6)	21 (23.6)	0.294
Hypertension	157 (44.7)	32 (36.0)	0.150
Dyslipidemia	70 (19.9)	18 (20.2)	1.000
Sleep apnea	38 (10.8)	14 (15.7)	0.202
Comorbidities postoperative			
Type 2 diabetes - self reported	37 (10.5)	8 (9.0)	0.845
Hypertension - self reported	62 (17.7)	15 (16.9)	1.000
Dyslipidemia - self reported	41 (11.7)	13 (14.6)	0.470
Sleep apnea - self reported	13 (3.7)	4 (4.5)	0.758
Postoperative support and life style			
Support of psychologist#	33 (9.4)	12 (13.5)	0.246
Sport (more than 30 minutes per week)	199 (57.3)	53 (59.6)	0.911
Smoking	60 (17.1)	19 (21.3)	0.356
Treatment satisfaction§			
Satisfaction with result of operation (yes)	320 (91.2)	81 (91.0)	1.000
Would you do the operation again? (yes)	340 (96.9)	83 (93.3)	0.126

RYGB = Roux-en-Y gastric bypass; BMI = body mass index; EWL = excess weight loss.

Data are shown as numbers (percentage), mean $\pm$ standard deviation, or median and [interquartile range].

support of a psychologist is defined as regular visits to a psychologist to help coping eating or post-bariatric surgery problems.

§ with treatment satisfaction in the revisional group is meant the revisional operation (not the first operation or both)

Demographic characteristics as prevalence of co-morbidities, remission of co-morbidities, weight at surgery and age were not different between patients with SG and primary gastric bypass.

Patient characteristics: comparison between revisional and primary gastric bypass (Table 2)

Patients with revisional gastric bypass had lower prevalence of comorbidities than patients with primary gastric bypass at day of (revisional) surgery, but self-reported comorbidities at time of questionnaire were equal. Patients after revisional surgery were less satisfied than

Table 2: Patient characteristics of patients after primary RYGB and revisional RYGB

	Primary RYGB	Revisional RYGB	P value**
number	351	153	
Age (yrs)	46 [39; 53]	46 [42; 54]	0.138
Female (%)	282 (80.3)	128 (83.7)	0.456
Time between last surgery and study (months)	27 [19; 34]	25 [18; 34]	0.715
Weight and weight loss			
Weight at primary surgery (kg)	129 [116; 144]	130 [120; 146]	0.612
BMI at primary surgery (kg/m ²)	43 [40; 48]	45 [41; 48]	0.889
Weight at revisional surgery (kg)		118 [103; 130]	
Minimum weight after last surgery - self reported (kg)	81 [70; 98]	85 [77; 101]	0.063
Current weight - self reported (kg)	86 [75; 102]	90 [79; 103]	0.202
EWL from primary procedure to study (%)	77 [61; 95]	71 [50; 89]	0.039
Comorbidities preoperative			
Type 2 diabetes	104 (29.6)	32 (20.9)	0.049
Hypertension	157 (44.7)	49 (32.0)	0.008
Dyslipidemia	70 (19.9)	12 (7.8)	<0.001
Sleep apnea	38 (10.8)	6 (3.9)	0.003
Comorbidities postoperative			
Type 2 diabetes - self reported	37 (10.5)	24 (15.7)	0.105
Hypertension - self reported	62 (17.7)	35 (22.9)	0.174
Dyslipidemia - self reported	41 (11.7)	16 (10.7)	0.878
Sleep apnea - self reported	13 (3.7)	5 (3.3)	1.00
Postoperative support and life style			
Support of psychologist#	33 (9.4)	17 (11.1)	0.517
Sport (more than 30 minutes per week)	199 (57.3)	87 (58.2)	0.294
Smoking	60 (17.1)	28 (18.3)	0.702
Treatment satisfaction\$			
Satisfaction with result of operation (yes)	320 (91.2)	112 (73.2)	<0.001
Would you do the operation again? (yes)	340 (96.9)	134 (87.6)	<0.001

RYGB = Roux-en-Y gastric bypass; BMI: Body Mass Index; EWL: Excess Weight Loss

Data are shown as numbers (percentage), mean $\pm$ standard deviation, or median and [interquartile range].

Bold type *p*-values are significant ($p < 0.05$).

support of a psychologist is defined as regular visits to a psychologist to help coping eating or post-bariatric surgery problems.

\$ with treatment satisfaction in the revisional group is meant the revisional operation (not the first operation or both)

after primary gastric bypass (73.2 versus 91.2%, respectively, $P = <0,001$). More patients would not have had the gastric bypass operation done again if they had the choice (12.4% versus 3.1%, $P = <0,001$). Patients after revisional gastric bypass had less excess weight loss than patients after primary gastric bypass when calculated from the pre-bariatric weight (71 versus 77%, $P = 0,039$).

Table 3. Prevalence of self-reported moderate to severe symptoms of early and late dumping in patients after primary RYGB, sleeve gastrectomy, and revisional RYGB

	Primary RYGB 351	Sleeve gastrectomy 89	P value*	Revisional RYGB 153	P value**
<i>Early dumping</i>					
Abdominal symptoms					
Abdominal pain (%)	70 (19.9)	11 (12.5)	0.125	33 (21.6)	0.719
Diarrhoea (%)	52 (14.8)	7 (8.0)	0.115	31 (20.3)	0.151
Bloating (%)	76 (21.7)	21 (23.9)	0.669	39 (25.5)	0.359
Autonomic symptoms					
Nausea (%)	67 (19.1)	11 (12.5)	0.163	39 (25.7)	0.121
Sweating (%)	43 (12.3)	8 (9.1)	0.462	25 (16.3)	0.257
Flushing (%)	50 (14.2)	5 (5.7)	0.030	22 (14.4)	1.000
Dizziness (%)	51 (14.5)	7 (8.0)	0.114	30 (19.6)	0.188
Palpitations (%)	52 (14.8)	5 (5.7)	0.021	26 (17.0)	0.592
High suspicion of early dumping #	68 (19.4)	8 (9.1)	0.026	36 (23.5)	0.285
I feel anxious or insecure by above mentioned complaints (%)	33 (9.4)	6 (6.7)	0.534	26 (17.0)	0.016
<i>Late dumping</i>					
Autonomic symptoms					
Sweating (%)	24 (6.8)	2 (2.3)	0.131	16 (10.5)	0.209
Palpitations (%)	23 (6.6)	6 (6.7)	1.000	13 (8.5)	0.455
Hunger (%)	68 (19.4)	20 (22.5)	0.554	44 (28.8)	0.027
Tremor (%)	45 (12.8)	6 (6.7)	0.138	38 (24.8)	0.002
Neuroglycopenic symptoms					
Drowsiness/unconsciousness (%)	70 (19.9)	10 (11.2)	0.065	36 (23.5)	0.406
Irritability (%)	60 (17.1)	9 (10.1)	0.141	41 (26.8)	0.015
High suspicion of late dumping #	40 (11.4)	6 (6.7)	0.246	31 (20.3)	0.012
I feel anxious or insecure by above mentioned complaints (%)	30 (8.5)	9 (10.1)	0.677	24 (15.7)	0.027

RYGB: Roux-en-Y gastric bypass

Bold type p -values are significant ($p < 0.05$).

* P value of primary gastric bypass versus sleeve gastrectomy.

** P value of primary gastric bypass versus revisional gastric bypass.

A high suspicion of early dumping was defined as having three or more symptoms (including at least one autonomic symptom) with an intensity of 2 or 3 (i.e. moderate or severe, interfering with daily activities) on the early dumping severity score. A high suspicion of late dumping (post-gastric bypass hypoglycemia) was defined as having three or more symptoms (including at least one neuroglycopenic symptom) with an intensity of 2 or 3 (i.e. moderate or severe, interfering with daily activities) on the late dumping severity score.

Table 4. Prevalence of self-measured hypoglycaemia, neuroglycopenia and related consumption of health care in patients after primary gastric bypass, gastric sleeve and revisional gastric bypass surgery

	Primary RYGB 350 [§]	Sleeve gastrectomy 85 [§]	P value*	Revisional RYGB 148 [§]	P value**
Low self-measured blood glucose after a meal (%)	70 (20.0)	5 (5.9)	0.001	17 (11.5)	0.028
Concentration of low self-measured blood glucose			0.101		0.150
>4/mmol/L (%)	9 (2.8)	3 (3.5)		1 (0.7)	
3-4 mmol/L (%)	16 (4.6)	1 (1.2)		6 (4.1)	
2-3 mmol/L (%)	24 (6.8)	1 (1.2)		10 (6.8)	
1-2 mmol/L (%)	9 (2.6)	0 (0.0)		5 (3.4)	
Unknown (%)	12 (3.4)	3 (3.5)		13 (8.8)	
Symptoms of neuroglycopenia [#] (%)	26 (7.4)	0 (0.0)	0.02	15 (10.1)	0.564
Hypoglycemia for which help of others was necessary (%)	19 (5.4)	1 (1.2)	0.058	13 (8.8)	0.367
Hypoglycemia for which help of health care workers or admission to hospital was necessary (%)	9 (2.6)	0 (0.0)	0.214	7 (4.7)	0.350
Medical treatment for early or late dumping	8 (2.3)	0 (0.0)	0.369	6 (3.9)	0.231

RYGB = Roux-en-Y gastric bypass.

Bold type *p*-values are significant ($p < 0.05$).

[§] patients still using insulin are left out

* *P* value of primary gastric bypass versus sleeve gastrectomy.

** *P* value of primary gastric bypass versus revisional gastric bypass.

Symptoms of neuroglycopenia include feelings of loss of control (e.g. disorientation, impaired speech, loss of consciousness).

Perceived complaints of early dumping (Table 3)

Fewer patients with sleeve gastrectomy were at high suspicion of early dumping than after primary RYGB (RR [95% confidence interval] 0.46 [0.22-0.99], $P = 0.0497$). This finding was mainly based on the lower prevalence of palpitations and flushing in the SG group. No differences for early dumping were seen between revisional and primary RYGB (RR 1.21 [0.77-1.91], $P = 0.40$) but the emotional impact of these complaints was more often moderate to severe in patients having undergone a revisional procedure (17 versus 9%, $P = 0.016$).

Perceived complaints of late dumping (Table 3)

More patients after revisional RYGB were at high suspicion for late dumping compared to primary RYGB (RR 1.78 [1.09-2.90] $P = 0.021$). This was mainly based on the higher incidence of tremor, hunger and irritability in the revisional surgery group. The revisional surgery group had also more complaints of anxiety and feelings of unsafety as a consequence of these symptoms (8.5 versus 15.7%, $P = 0.027$). No differences for late dumping were seen between SG and primary RYGB (RR 0.59 [0.22-1.61], $P = 0.30$).

Late dumping by other estimates (Table 4).

In spite of similarly perceived complaints of late dumping between patients after SG,, fewer low-plasma glucose levels after the meal were noticed in patients after SG compared to those who had primary gastric bypass surgery. Also, less help by others for hypoglycemia and fewer neuroglycopenic complaints were reported. No differences between revisional and primary gastric bypass surgery were noted.

DISCUSSION

This study shows that self-reported symptoms of early and late dumping were observed after all the included bariatric procedures. However, SG showed a lower prevalence of early dumping while revisional gastric bypass surgery showed more late dumping compared with primary gastric bypass surgery.

The prevalence described in literature of early and late dumping symptoms depends on the type and extent of surgery, the definition of dumping syndrome used by study investigators, and whether the diagnosis is based on questionnaires, random lab or provocation tests. Papamargaritis et al. performed a prospective study after SG.¹⁴ They described that 10 out of 25 patients (40%) had complaints of dumping after 6 months and 33% after 12 months, according to Arts et al. questionnaire mainly due to early dumping.¹⁷ However, 8 patients had a hypoglycemia after an oral glucose tolerance test 6 months postoperatively (33%).¹⁴ More literature is available about gastric bypass and late dumping, which is present in 30% to 72% of the cases studied.^{9,24-26} These high percentages were all observed after provocation tests (oral glucose tolerance test, mixed meal tolerance test, continuous glucose monitoring). However, Lee and co-workers studied late dumping by means of questionnaire, with a response rate of 40% in patients after RYGB and SG.²⁷ They used the Edinburgh hypoglycemia questionnaire, developed for use in diabetic patients to measure the intensity of commonly experienced hypoglycemic symptoms. The prevalence in their total study population of a high suspicion for hypoglycemia was 34%. They found that gastric-bypass surgery, longer time since surgery, female sex, and preoperative symptoms of hypoglycemia were independent factors of a higher prevalence of late dumping. The odds of RYGB surgery in the high-suspicion group for hypoglycemia was 2.5 compared with the low-suspicion group. The increased prevalence of late dumping in this study compared with ours is likely to be a result of their operational definition of late dumping, in which patients were included in the high-suspicion group if they had only autonomic symptoms. In another study, Ramadan et al. compared patients after SG and RYGB at 1 and 6 months after surgery.²⁸ They invited patients with a Sigstad score ≥ 7 for a glucose-tolerance test and an orthostatic hypotension test. The Sigstad score is a questionnaire that was initially developed as a clinical score for early dumping to be administered by a doctor. The prevalence of late dumping in the SG

group was much lower than in our study (1.5% versus 6.7%), the prevalence in the RYGB was higher in patients with a stapled anastomoses of 3-cm long (18% after 6 months) and a lower prevalence of dumping after a hand-sewn technique 1.5-cm long (0% at 6 months). Of interest, the prevalence of dumping was also found to be positively associated with postoperative time, which may be the reason why Ramadan reported such low numbers at 6 months postoperatively.²⁷

The pathophysiology behind early and late dumping symptoms after different procedures can be explained in several ways. Much emphasis is given to plasma-glucose concentrations, insulin sensitivity and beta-cell glucose sensitivity.^{24,29} In addition, a strong association is seen between the levels of incretins in blood and the onset of dumping (especially late dumping).^{9,10,12} The entry of undigested food to the jejunum triggers the early onset of incretin production. It can be hypothesized that the quicker undigested food enters the jejunum, the higher the levels of incretins become and thus the higher the chance of dumping symptoms. Possible influencers of slowing or accelerating the entry of food into the small bowel are the function of the pylorus and the activity or integrity of the vagal nerve.³⁰ In agreement with this finding, Humphrey et al. found in a non-bariatric population of patients after vagotomy with or without pyloroplasty that in case of highly selective vagotomy less dumping occurred, and thus the function of the pylorus and/or vagal nerve plays a role.³¹ Our data are in agreement with this hypothesis, with fewer complaints in SG patients in whom pyloric function remains intact and more complaints in revisional gastric bypass patients in whom a higher likelihood of vagal nerve damage is present.

In addition, Frantzides et al. and Fujita et al. both published studies in which the vagal nerve was either damaged/transected or spared during a gastric bypass or a gastrectomy.^{22,23} Both showed that patients with the vagal nerve spared had lower prevalence of late dumping. This finding may also be relevant in patients with revisional gastric bypass surgery after gastric banding. In these cases, the band is usually placed high on the stomach and with the use of the pars flaccida technique in which the anterior and posterior branches of the vagal nerve are not preserved. For this reasons and scarring caused by banding causes vagal nerve entrapment, resulting in alterations in innervation. We propose that revisional gastric bypass after earlier gastric banding can, by damaging vagal nerve fibers, cause more complaints of late dumping.

Some limitations of the study must be mentioned. First, the participation rate was slightly < 60%, raising the possibly of an inclusion bias that may have resulted in an overestimation of dumping prevalence. The percentage of patients participating was equal in all surgical procedure groups. A second limitation is the fact that no validated questionnaire for early and late dumping is available.⁹ The only questionnaire that is available and that differentiates between the onset of complaints after eating and the kind of symptoms is the dumping severity score, which provides a quantitative assessment of symptom severity. By identifying high-suspicion groups for early and late dumping, and calculating odds ratios, relative effects

compared to the primary RYGB were calculated. This reduces the need for validation of the questionnaire.

A third limitation of the questionnaire is the lower prevalence of late dumping in case of development of hypoglycemia unawareness. Hypoglycemia unawareness is the phenomenon used in the diabetic population that a patient has no symptoms of the hypoglycemia. This phenomenon is also seen in patients with tightly controlled type 1 diabetes who have frequent episodes of hypoglycemia.³³ Our results show no difference in the prevalence of late dumping between SG and primary gastric bypass. However, significantly more patients reported low blood sugar levels after primary gastric bypass in comparison with SG (Table 4). This discrepancy between complaints versus self-reported measurements of glucose may also potentially be related to accessibility to a glucose meter, which may have differed between groups. Revisional gastric bypass patients reported significantly more complaints of late dumping, and they significantly more often reported low blood sugars but only a slightly raised prevalence of neuroglycopenia (Table 4). These 2 seemingly conflicting findings, potentially indicative of hypoglycaemia unawareness, may have played a role in the perceived complaints. Ten percent of the patients after revisional RYGB reported low to very low blood sugars (between 1.0 to 3.0), and this is also suggestive for increased severity of hypoglycaemia and therefore fits in the profile of hypoglycaemia unawareness. Other limitations of the study are the possibility of inducing bias due to a follow-up of only 2 to 3 years and that we used a retrospective cohort. With a follow-up of 2 to 3 years it is possible that we miss patients with a late onset of post-gastric bypass hypoglycaemia.

CONCLUSION

SG is associated with reduced complaints of early dumping, while revisional gastric bypass surgery after gastric banding is associated with more complaints of late dumping compared to primary gastric bypass surgery.

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Chapter 9

Summary, discussion of main findings and
future perspectives

SUMMARY

With the increase of morbid obesity around the world, there is a need for sustainable weight loss strategies. With the development of laparoscopic bariatric surgery resulting in durable weight loss with low short-term morbidity and mortality, these needs are fulfilled. In 2016 over 600.000 patients underwent bariatric surgery, and the number is still rising.¹ In the Netherlands in 2018 more than 10.000 patients were operated for morbid obesity in 18 hospitals.² Although bariatric surgery is very effective, these procedures are known to have several long term complications. The focus of this thesis is on early and late dumping. As the number of patients undergoing this type of surgery is risen every year, the number of patients affected by these complications is growing. Therefore, it is mandatory to gain more knowledge about these complications, and how to prevent them.

Early dumping is a poorly defined and incompletely understood disorder. Early dumping represents a constellation of abdominal symptoms, including cramps, bloating and diarrhoea, which starts within minutes after a meal and lasts for up to one hour. Early dumping is also accompanied by autonomic responses such as sweating, palpitations, drowsiness, and orthostatic symptoms.

The late dumping syndrome, which occurs one to two hours after ingestion of food, consists of symptoms such as sweating, drowsiness, trembling or even coma. Its classical name is nowadays more appropriately described as postgastric bypass hypoglycemia or postprandial hyperinsulinemic hypoglycemia (PHH). Over the course of the years in which we have studied this phenomenon we have decided that postprandial hyperinsulinemic hypoglycemia (PHH) was the best definition because this complication not only occurs after bariatric surgery but also after other gastric operations, and by using the name PHH it is less easily confused with early dumping.

This thesis describes the results of studies on the prevalence and pathophysiology of early dumping and PHH after the most common bariatric operations and the influence of these complications on quality of life.

Early dumping

In **Chapter 3**, we describe our current understanding of the pathophysiology of early dumping. Gastric surgery reduces gastric volume or removes the barrier function of the pylorus, resulting in the rapid delivery of substantial amounts of undigested solid food to the small intestine. Hyperosmolar nutrients in the small bowel presumably cause a shift of fluids from the intravascular compartment (i.e. plasma) to the intestinal lumen, resulting in a reduction of plasma volume with secondary complaints, such as tachycardia, and -rarely- syncope (hypovolemic theory).^{3,4} Movement of fluids into the small bowel may also cause distention and contribute to cramp-like contractions, bloating and diarrhea. Whether this fluid shift contributes to the pathophysiology of early dumping syndrome or is mainly a consequence of this

process remains unknown. Another important mechanism involved in the pathophysiology of early dumping syndrome involves the increased release of multiple gastrointestinal (GI) hormones including vasoactive agents (e.g. neurotensin and vasoactive intestinal peptide-VIP), incretins (e.g. gastric inhibitory polypeptide - GIP and glucagon-like-peptide-1 - GLP-1), and glucose modulators (e.g. insulin and glucagon) (incretin theory).⁵⁻⁷ For diagnosing early dumping syndrome the most important diagnostic tool is a good case history, preferably by using a questionnaire (**Chapter 3**). In **Chapter 4**, we studied the prevalence of early dumping and the impact on quality of life in people four years after primary gastric bypass, by means of a questionnaire. Over 18% of the patients reported moderate to severe symptoms of early dumping more than once a month, which caused significant interference with daily life. Patients with early dumping reported a lower quality of life score (tested with the RAND-36) and experienced more symptoms of depression and anxiety (as measured with the Hospital Anxiety and Depression Score-HADS) than patients without complaints. We could not demonstrate an effect of early dumping on the severity of complaints of fatigue (both groups were equally tired, tested with Multidimensional Fatigue Inventory - MFI-20).

Further studies using questionnaires revealed that patients who underwent a gastric sleeve procedure had a prevalence of early dumping of 9%, which was significantly lower than patients after primary RYGB ($p=0.026$) (**Chapter 8**). Patients after revisional RYGB (after removal of earlier gastric banding) had a prevalence of 23%, and this was not different from primary gastric bypass ($p=0.285$) (**Chapter 8**).

In addition to our studies using a questionnaire to assess complaints, we also studied symptoms of early dumping after a test meal. We designed this study to assess the prevalence of early dumping in a randomly selected population of patients four years after gastric bypass, and to gain insight into its pathophysiology. To test the hypovolemic theory we measured hematocrit, blood pressure and heart rate. To test the incretin theory we measured active and inactive GLP-1, VIP and Peptide YY (PYY). In **Chapter 5**, we report the results of this study. The prevalence of early dumping after this standardized stimulus (as measured with a symptom score) was 26%. Most patients reported the complaints thirty minutes after the intake of the liquid meal. No differences were seen in the objective parameters of dumping, such as heart rate, blood pressure and change in hematocrit between patients with or without symptoms of early dumping. However, the relative change in hematocrit at 30 minutes differed significantly between patients with low or high suspicion of early dumping (0.32% versus 2.56% $P = 0.039$). Significant differences were seen in the postprandial response of the hormones active (GLP-1) and PYY at 20, 30, and 60 minutes, whereas no differences in inactive GLP-1 and VIP were found between the two groups. No differences were seen between the groups in glucose or insulin concentrations. We concluded from this study that PYY and GLP-1 (and therefore intestinal L-cells) are likely to play a role in the pathophysiology of early dumping.

Treatment of early dumping starts with dietary modifications: reductions in the amount of food consumed during each meal, division of eating and drinking, eating slowly and chewing well, and consuming high-fiber and protein-rich food (**Chapter 3**). Some of the treatments for PHH also have an effect on early dumping (somatostatin analogues and acarbose) thereby promoting the thought that the pathophysiology of early dumping can have a relation with the pathophysiology of PHH (**Chapter 3**).^{8,9} Considering our finding of intestinal L-cell involvement, this seems plausible.

Postprandial hyperinsulinemic hypoglycemia (PHH)

PHH is almost exclusively observed after upper-gastrointestinal tract surgery in which food enters the small bowel directly and the duodenum is bypassed. Hypoglycemia is provoked by ingestion of carbohydrate-rich food, and symptoms usually occur between one and two hours postprandial. The purpose of the laboratory evaluation is to document low blood glucose together with signs and symptoms attributable to hypoglycemia, and to observe that these complaints are relieved when the glucose levels are normal again (Whipple's triad). Physicians should be aware that some patients may develop impairment of the awareness of hypoglycemia and therefore lack symptoms. In **Chapter 2** we describe five recommendations for diagnosing PHH:

1. Perform diagnostic testing only in patients with a high a priori chance of PHH.
2. Confirm the diagnosis of symptomatic PHH by combining a symptom score aimed at identification of hypoglycemic complaints together with a provocation test, preferably the MMTT.
3. Use a glucose level below 3.3 mmol/l as a sensitive cut-off value for meal-induced hypoglycemia during oGTT or MMTT.
4. Do not use capillary glucose measurements, continuous subcutaneous glucose measurement (CGM) or nuclear imaging modalities for the diagnosis of PHH.
5. Perform additional testing in patients with an atypical disease presentation, e.g. by performing a 72-h fast.

The pathophysiology of late dumping is largely attributable to the development of hyperinsulinemia relative to the ambient blood sugar leading to hypoglycemia (**Chapter 3**). Rapid delivery of undigested carbohydrates to the small intestine results in high glucose concentrations that induce a hyperinsulinemic response, resulting in subsequent hypoglycemia and related symptoms. When compared to intravenous glucose loading leading to the same glucose concentration, oral ingestion of glucose leads to a much higher insulin response, the so-called incretin effect.¹⁰ Two gastrointestinal hormones are believed to play a pivotal role in the incretin effect: GIP and GLP-1.¹⁰

The role of GLP-1 was confirmed in our study in which forty-four patients on average four years after primary gastric bypass were challenged by a mixed meal tolerance test (**Chapter**

6). This study also showed that the development of PHH could not be totally attributed to the increase of these hormones. Patients with hypoglycemia after MMTT showed a higher insulin sensitivity (lower HOMA-IR and no prior history of type 2 diabetes) and an enhanced beta-cell function in the postprandial phase. The role of GLP-1 in the development of PHH can be stressed by the finding that with blocking of the GLP-1 receptor by a GLP-1 receptor antagonist (Exendin 9-39), insulin responses to enteral glucose is reduced and PHH is prevented, but PHH is, as illustrated in our study, multifactorial in its pathogenesis.¹¹

The self-reported, and thus subjective, prevalence of PHH in a group of patients four years after primary gastric bypass is described in **Chapter 4** and was almost 12%. In this study we showed that patients who reported frequent symptoms of PHH had a lower quality of life (estimated with the RAND-36) and a higher incidence of symptoms of anxiety and depression (scored with the HADS), similar to patients with early dumping. No difference was seen in the prevalence of fatigue between patients with or without symptoms of PHH.

The objective prevalence in a randomly selected population on average four years after primary RYGB, as measured with a glucose lower than 3.3 mmol/L, is described in **Chapter 6**, and was found to be as high as 48%. All these patients with hypoglycemia reported almost no symptoms, tested with the same questionnaire as used in **Chapter 3**. This suggests impaired awareness for (severe) hypoglycemia in patients four years after primary gastric bypass, a finding that has also been reported by others.¹²⁻¹⁴

In earlier days, gastric banding was thought to be a procedure with low morbidity and mortality with good weight loss results. In the long-term, a large proportion of patients with gastric banding needed revisional surgery because of either disappointing weight-loss results or banding complications. In **Chapter 7** we described that in patients without indications for acute band removal, the planned conversion of gastric banding to Roux-Y gastric bypass can be safely done in a single-step procedure without increase in morbidity and no difference in post-operative weight loss. In **Chapter 8** we studied the self reported prevalence of PHH in this population. The prevalence was 30,2%, significantly higher in this patient-group compared to the primary gastric bypass patient group ($p=0.012$). We hypothesize that this difference is due to the damage of the vagal nerve by former gastric banding. Furthermore, we saw in this study that patients after gastric sleeve had a prevalence of self-reported hypoglycemia of almost 7%, slightly, but not significantly lower than the prevalence after primary gastric bypass suggesting that the assumed protective function of the pylorus is low. Also, in these patient groups (after gastric sleeve and revisional gastric bypass), hypoglycemia unawareness is suspected.

In **Chapter 3**, we propose a step-up approach in the treatment of PHH.

Patients who have undergone oesophageal or gastric surgery should be monitored for symptoms suggestive of dumping. First-line management of PHH should focus on dietary modification for three to four weeks, with the addition of acarbose treatment for patients who experience PHH. Acarbose is an α -glycosidase hydrolase inhibitor that slows carbohy-

drate digestion in the small intestine, thus blunting postprandial hyperglycemia and subsequent hypoglycemia.⁸ When dietary modification and acarbose treatment are unsuccessful, somatostatin analogue therapy should be considered in patients with dumping syndrome who are experiencing incapacitating symptoms and impairment in quality of life. Short-acting and long-acting somatostatin analogue therapy should be attempted for two weeks and for two months, respectively. Surgical re-intervention or continuous gastric/enteral feeding may be considered in some patients with treatment-refractory dumping syndrome, but the outcomes of these approaches are poorly studied and tend to be more variable.

DISCUSSION OF THE MAIN FINDINGS

For both early dumping and PHH, we showed that patients who suffer from dumping have lower quality of life, more anxiety and depression symptoms and more patients regret having the operation compared with those without dumping. To date no other studies have addressed this subject.

Early dumping

Before we started this study, the main thought about the pathophysiology of early dumping was that it was provoked by hypovolemia, induced by the rapid delivery of substantial amounts of undigested solid food to the small intestine. Hyperosmolar nutrients in the small bowel presumably cause a shift of fluids from the intravascular compartment (i.e. plasma) to the intestinal lumen, resulting in a reduction of plasma volume with secondary complaints, such as tachycardia, and – rarely - syncope. This hypovolemia could be observed by a change in hematocrit, a drop in of blood pressure and a higher pulse rate.^{3,4,15}

Our main finding after the MMTT was that these objective measurements for the hypovolemic therapy, leading to a robust change in haematocrit, could not be confirmed. In our study, we showed that, with early dumping, the L-cells seem to play an important role in the pathophysiology, as is also described by Ukleja.¹⁵ All the symptoms, which are well described in the Sigstad score, can be explained by the exaggeration of L-cell products such as GLP-1 and PYY. GLP-1 has multiple effects on several pathways, causing various symptoms, such as nausea, tachycardia, hypotension, and influencing insulin secretion (causing vasodilation and normalisation of heart rates after 50-60 minutes).¹⁶⁻¹⁹ In support of this theory, treatment with somatostatin-analogues, known to diminish GLP-1 release from L-cells, has been successful in reducing early dumping complaints.^{20,21} PYY is known to cause vasoconstriction, increase blood pressure, decrease intestinal motility and stimulate absorption of nutrients.²²⁻²⁶ In our study the peak of PYY is much later after the meal, which supports the theory that it acts as a negative feedback mediator. In fact, PYY is the predominant hormonal product of the more distant L cells in the intestinal tract.²⁶

PHH

In our study, two main findings emerged on PHH: the cause of PHH is multifactorial and the prevalence of asymptomatic PHH is very high.

Multifactorial cause of PHH

When we started with this study, the main thought was that post prandial hypoglycemia is the result of hyperinsulinemia due to an increase of GLP-1 by stimulation of the L-cells in the ileum and colon.^{6,27,28}

In our MMTT study (**Chapter 4**), we saw that the development of hypoglycaemia was more frequent in patients with lower weight at surgery, with higher weight loss after surgery, without prior diabetes and with higher insulin sensitivity, calculated by Homeostasis Model Assessment indexes and enhanced beta cell function. All these findings suggest a multifactorial cause of the hypoglycemia, which has also been reported by others.^{13,29} The precise mechanism for these differences are not known.

The other main finding was the discrepancy between the self reported prevalence of hypoglycemia in our questionnaire study and the prevalence of (asymptomatic) hypoglycemia in our MMTT study. This hypo-unawareness may be due to an impaired autonomic response to hypoglycemia after RYGB, which is indicative of hypoglycemia associated autonomic failure (HAAF). Hypoglycemia unawareness is recognized in patients with type 1 diabetes who are (too) strictly regulated and is characterized by a lack of adrenergic warning symptoms during a hypoglycemia. It is postulated that recurrent hypoglycemic episodes in patients with diabetes induce blunting of the adrenergic and hypothalamic-pituitary-adrenal (HPA)-responses to hypoglycemia and thereby diminish the counterregulation.^{14,30} Hypoglycemia unawareness has also been found by others, which confirms our findings.^{12-14,31}

There is considerable interaction between the vagal nerve and gut hormone release.^{32,33} An approach to view early dumping solely as an endocrine disorder may be too simplistic. The role of afferent and efferent vagal nerve endings may also be opposing in this matter.³⁴ In addition, nutrients, bile acids and, for example, gut microbiota may all play a role in early dumping and PHH.^{35,36}

In fact, the surgical procedure applied may thus be optimized considering the above to allow for optimal treatment results.³⁷ Combining treatments (for example medical treatment for obesity added to gastric bypass surgery) may yield favourable results not only in terms of weight loss, but also on PHH.³⁸

FUTURE PERSPECTIVES

Early dumping

From our studies, early dumping was found to be associated with increased PYY and GLP-1 concentrations immediately after ingestion of a meal. Its pathophysiology is therefore not so different from aspects of PHH in which GLP-1 production stimulates excessive amounts of insulin. Both disorders can be regarded as gut endocrine disorders or, more specifically, as hyperstimulation syndromes of the L-cells.

It remains, however unclear why some people react to the same food stimulus, while others do not. Some studies showed an important role for amino acids in stimulating L-cells via the calcium-sensing receptor and stimulating production of GLP-1 and PYY.³⁹⁻⁴¹ More research is necessary to see if this phenomenon plays a role in the development of early dumping.

Bile acid concentration increased significantly after RYGB. Most studies have shown this increase to be proportionate for all bile acid sub-types. Bile acids can regulate glucose metabolism through the expression of Takeda-G protein-coupled-receptor (TGR) 5 in L cells, resulting in a release of glucagon-like peptide 1 (GLP-1), and, therefore, play an important role in the pathogenesis of early dumping.⁴²⁻⁴⁴

Studies involving replicability of the MMTT and priming effects of food habits should be performed.

For proper treatment of severe early dumping that interferes with quality of life, it is important to distinguish early dumping from “normal” food intolerance which can be the consequence of, for example, eating too fast, not chewing well, or not separating eating and drinking properly.

A validated questionnaire for early dumping would be helpful to use in the outpatient setting. This questionnaire should not only contain a Likert-scale of severity of symptoms but also aspects of impact on quality of life and which foods trigger the symptoms. Based on this questionnaire, advice can be given to patients, such as changing eating habits or avoiding certain food products.

In patients with severe symptoms with an impact on quality of life, objective measurements are necessary to distinguish early dumping from PHH and other illnesses such as gastric ulcer, obstipation and gastrointestinal problems. Our MMTT study showed that pulse rate, blood pressure and hematocrit were not discriminatory findings. Future research should aim to discover better objective measures for diagnosing early dumping. Potential future directions for this may be found in imaging of entero-endocrine cell populations, gut biopsies, and markers of gut endocrine activity.

Change of operation technique (longer pouch, banded bypass) may have a preventive effect in the prevalence of early dumping, but may have some other disadvantages, such as variable weight loss, and migration or slippage of the band.

Post-prandial hyperinsulinemic hypoglycemia

The prevalence of PHH is higher in patients who had former gastric banding. This may suggest that a role is reserved for the vagal nerve. Fibres of the vagal nerve are dissected while creating the pouch, but with gastric banding, scar tissue is more evident and more fibres of the vagal nerve are at risk.⁴⁵ Future research should focus on the role of the vagal nerve in the pathophysiology of PHH, so that perhaps strategies can be developed to spare these fibres in bariatric surgery thereby preventing the development of PHH. After sleeve gastrectomy, the prevalence of PHH trends to be lower than after primary gastric bypass, but is not zero. This suggests that the pylorus does not prevent PHH. As the fibres of the vagal nerve are spared during this operation, studying the prevalence of PHH in patients after sleeve gastrectomy, and the role of incretins, can give us more insight into the pathophysiology of PHH for the whole group.

The MMTT study, shows that in nearly 50% of the patients after RYGB a hypoglycemic event can be provoked after a meal stimulus. This is intriguing because in clinical practice we do not see that 50% of our patients are struggling with this disorder. It may therefore be possible that certain patients who experience severe neuroglycopenia do not adapt to frequent hypoglycemia. In fact impaired hypoglycemia awareness may be seen as a 'normal' response, thus preventing symptoms.^{12,46} Future studies should address the neurological adaptation to hypoglycemia in those without compared to those with complaints.

A description in more detail of potential consequences of repeated hypoglycemia is essential. Do patients with repeated hypoglycemic events have fewer or more incidents after hypoglycemia, such as problems at work, or in any other domains, due to a lack of concentration?

In clinical practice, we see that a step-up approach in the treatment of PHH has a satisfactory effect. However, a small group of patients will only have short-term benefit from medical treatment and will need more medication every few months. Future research on treatment must focus on why these patients no benefit from treatment anymore. New treatment modalities based on the pathophysiology have to be developed. For example, GLP-1 antagonists, such as exendin 9-39, have a favourable role in the treatment of PHH in some patient groups.¹¹ But also potential new diabetes medication, such as the sodium-glucose transporter-2 (SGLT-2) inhibitors, are most likely new candidates for the treatment of PHH.

As in early dumping, the role of bile acids and amino acids have to be explored further to recover more of the pathophysiology and in order to find new, and possibly better and easier treatment modalities.³⁹⁻⁴¹

For those in which medical treatment is unsuccessful, surgical options must be studied in more detail, and a step-up approach in surgical treatments should be proposed and evaluated. Because of the small group of patients who need surgical therapy for PHH, bariatric departments in different hospitals should cooperate in these studies.

Prevention is better than cure. Because bariatric surgery is still a young discipline, there is ample room for improvement. Different surgical techniques are performed and developed. As shown in our study, sleeve gastrectomy is associated with a reduced chance of PHH but this procedure has other disadvantages, such as reflux and diminished weight loss over time. In two other procedures (Duodenal switch and Sadi-S), a gastric sleeve is performed and a single anastomosis (Sadi-S) or a Roux-en-Y anastomosis (duodenal switch) is performed at the beginning of the duodenum.

Although these procedures are promising due to their weight loss and resolution of co-morbidities, the long term consequences regarding the prevalence of PHH is not known yet. It is imperative that (new) surgical procedures must also be judged on the complications that arise, such as early dumping and PHH, because of their profound impact on quality of life.

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Chapter 10

Samenvatting, discussie van belangrijkste
bevindingen en toekomstig onderzoek

SAMENVATTING

Door de wereldwijde toename van mensen met morbide obesitas is er behoefte aan duurzame strategieën voor gewichtsverlies. Bariatrische chirurgie, tegenwoordig uitgevoerd door middel van laparoscopie met lage morbiditeit en mortaliteit, heeft zich bewezen als methode voor duurzaam gewichtsverlies. In 2016 ondergingen ruim 600.000 patiënten bariatrische chirurgie en het aantal stijgt nog steeds.¹ In Nederland werden in 2018 meer dan 10.000 patiënten geopereerd voor morbide obesitas in 18 ziekenhuizen.² Bariatrische ingrepen kennen echter ook hun keerzijde en er kunnen complicaties optreden. De focus van dit proefschrift ligt op vroege en late dumping. Door de groei in bariatrische chirurgie zullen er ook steeds meer mensen zijn met klachten die passen bij vroege en late dumping. Daarom is het belangrijk om meer kennis hierover te verzamelen en strategieën te ontwikkelen om deze complicaties te voorkomen.

Vroege dumping is een slecht gedefinieerde en onvolledig begrepen ziekte-entiteit. Het treedt op binnen enkele minuten na een maaltijd (duur maximaal 1 uur) en geeft een meerdere gastrointestinale symptomen (buikkrampen, een opgeblazen gevoel en diarree) en autonome reacties zoals zweten, hartkloppingen, slaperigheid en duizeligheid.

Het late dumpingsyndroom dat gekenmerkt wordt door een lage bloedsuiker (hypoglycemie), treedt doorgaans één tot twee uur na de inname van voedsel op. Het bestaat uit symptomen zoals zweten, slaperigheid, trillen of zelfs coma. De klassieke naam is post-gastric bypass-hypoglycemie of postprandiale hyperinsulinemische hypoglycemie (PHH). In de loop van de jaren waarin we dit fenomeen hebben bestudeerd, hebben we besloten dat postprandiale hyperinsulinemische hypoglycemie (PHH) de beste omschrijving is omdat deze complicatie niet alleen optreedt na bariatrische chirurgie, maar ook na andere maag-operaties en de naam PHH geeft minder verwarring met vroege dumping.

Dit proefschrift beschrijft de resultaten van studies naar de prevalentie en pathofysiologie van vroege dumping en PHH na de meest voorkomende bariatrische operaties en de invloed van deze complicaties op de kwaliteit van leven.

Vroege dumping

In **hoofdstuk 3** beschrijven we ons huidige begrip van de pathofysiologie van vroege dumping. Maagchirurgie vermindert het maagvolume of verwijdert de barrièrefunctie van de maagportier (pylorus), wat er voor zorgt dat een aanzienlijke hoeveelheid onverteerd vast voedsel snel in de dunne darm terecht komt. Deze hyperosmolaire voedingsstoffen veroorzaken vermoedelijk een verschuiving van vloeistoffen van het intravasculaire compartiment (dwz plasma) naar het darmlumen, resulterend in een vermindering van het plasmavolume met secundaire klachten, zoals tachycardie en - zelden- syncope (hypovolemische theorie).^{3,4} De toename van vocht in de dunne darm kan uitzetting van de darm veroorzaken en daardoor klachten geven als krampachtige samentrekkingen, opgeblazen gevoel en diarree. Of

deze vloeistofverschuiving oorzaak of gevolg is, is onbekend. Een mogelijk ander belangrijk mechanisme bij de pathofysiologie van het vroege dumping syndroom is de verhoogde afgifte van meerdere gastro-intestinale (GI) hormonen waaronder vasoactieve stoffen (bijv. Neurotensine en vasoactief intestinaal peptide-VIP), incretines (bijv. Gastric inhibitory polypeptide -GIP en glucagon-like protein -1 - GLP-1) en glucosemodulatoren (bijv. Insuline en glucagon) (incretinetheorie).⁵⁻⁷

Belangrijkste hulpmiddel voor het diagnosticeren van vroege dumping is de anamnese, bij voorkeur met behulp van een vragenlijst (**hoofdstuk 3**). Meer objectieve diagnostiek zouden een veranderingen in hematocriet of hartslag zijn na het eten (hypothese van hypovolemie). In **hoofdstuk 4** hebben we de prevalentie van vroege dumping en de impact op kwaliteit van leven bij mensen vier jaar na primaire gastric bypass onderzocht aan de hand van een vragenlijst. Meer dan 18 procent van de patiënten rapporteerde meer dan één keer maandmatige tot ernstige symptomen van vroege dumping te ervaren. Deze patiënten meldden een lagere kwaliteit van leven (getest met de RAND-36) en ervoeren meer symptomen van depressie en angst (gemeten met de Hospital Anxiety and Depression Score-HADS) dan patiënten zonder vroege dumping. We konden geen effect aantonen van vroege dumping op de ernst van klachten van vermoeidheid (beide groepen waren even moe (getest met Multidimensional Fatigue Inventory - MFI-20).

Negen procent van de patiënten die een gastric sleeve hadden ondergaan rapporteerden klachten van vroege dumping, wat significant lager was dan patiënten na primaire RYGB ($p = 0,026$) (**Hoofdstuk 8**). Patiënten na revisie RYGB (na verwijdering van eerdere maagband) hadden een prevalentie van 23%, dit verschilde niet significant van de patiënten na primaire RYGB ($p = 0,285$) (**Hoofdstuk 8**).

Naast het vragenlijst-onderzoek, hebben we ook onderzoek verricht met een maaltijdttest. Hierbij hebben we een willekeurige groep patiënten die 4 jaar eerder een gastric bypass hadden ondergaan getest (**Hoofdstuk 5**). Om de hypovolemische theorie te testen, hebben we hematocriet, bloeddruk en hartslag gemeten. Om de incretine-theorie te testen, hebben we actief en inactief GLP-1, VIP en Peptide YY (PYY) gemeten. De prevalentie van vroege dumping na deze gestandaardiseerde maaltijd (gemeten met een symptoomscore) was 26%. De meeste patiënten meldden de klachten 30 minuten na de inname van de vloeibare maaltijd. Er werden geen verschillen waargenomen in de objectieve parameters van dumping, zoals hartslag, bloeddruk en verandering in hematocriet tussen patiënten met of zonder symptomen van vroege dumping. Significante verschillen werden gezien in de postprandiale respons van de actieve GLP-1 en PYY na 20, 30 en 60 minuten, terwijl er geen verschillen in inactieve GLP-1 en VIP tussen de twee groepen werden gevonden. Er werden geen verschillen tussen de groepen waargenomen in glucose- of insulineconcentraties. We concludeerden uit deze studie dat PYY en GLP-1 (en dus intestinale L-cellen) waarschijnlijk een rol zullen spelen in de pathofysiologie van vroege dumping.

De behandeling van vroege dumping begint met veranderingen in het dieet: verlaging van de hoeveelheid voedsel die elke maaltijd wordt gegeten, het scheiden van eten en drinken, langzaam eten en goed kauwen en het consumeren van vezel- en eiwitrijk voedsel (**hoofdstuk 3**). Sommige van de behandelingen voor PHH hebben ook een effect op vroege dumping (somatostatine-analogen en acarbose) waardoor de gedachte wordt bevestigd dat de pathofysiologie van vroege dumping een relatie kan hebben met de pathofysiologie van PHH (**hoofdstuk 3**).^{8,9} Gezien onze bevindingen van intestinale L-cel betrokkenheid lijkt dit aannemelijk.

Postprandiale hyperinsulinemische hypoglycemie (PHH)

PHH wordt vrijwel uitsluitend waargenomen na operaties aan het bovenste deel van het maagdarmkanaal waarbij voedsel direct in de dunne darm komt en de twaalfvingerige darm wordt omzeild. Hypoglycemie wordt veroorzaakt door inname van voedsel dat rijk is aan koolhydraten en symptomen treden gewoonlijk op tussen 1 en 2 uur na de maaltijd. Het bewijs op PHH wordt geleverd door lage bloedglucose te documenteren waarbij patiënten ook tegelijkertijd symptomen hebben die passen bij hypoglycemie en dat de klachten verminderen op het moment dat de glucosewaarden weer normaal zijn (Whipple's triade). Artsen dienen zich ervan bewust te zijn dat sommige patiënten een verminderde gevoeligheid van hypoglycemie kunnen ontwikkelen en daarom symptomen missen. In **hoofdstuk 2** beschrijven we vijf aanbevelingen voor het diagnosticeren van PHH:

1. Voer diagnostische tests alleen uit bij patiënten met een hoge a priori kans op PHH.
2. Bevestig de diagnose van symptomatische PHH door een symptoomscore die gericht is op de identificatie van hypoglycemische klachten te combineren met een provocatietest, bij voorkeur de MMTT.
3. Gebruik een glucoseniveau lager dan 3,3 mmol / l als een gevoelige drempelwaarde voor postprandiale hypoglycemie tijdens oGTT of MMTT.
4. Gebruik geen capillaire glucosemetingen, continue subcutane glucosemeting (CGM) of nucleaire beeldvorming-modaliteiten voor de diagnose van PHH.
5. Voer aanvullende testen uit bij patiënten met een atypische aandoening, b.v. door 72 uur nuchter glucose onderzoek.

De pathofysiologie van PHH is grotendeels toe te schrijven aan de toename van hyperinsulinemie (**hoofdstuk 3**). Snelle toediening van onverteerde koolhydraten aan de dunne darm resulteert in hoge glucoseconcentraties die een hyperinsulinemische respons induceren, resulterend in een daaropvolgende hypoglycemie met gerelateerde symptomen. Intraveneuze glucosebelasting die leidt tot dezelfde glucoseconcentratie geeft een veel lagere insuline respons dan de orale inname van glucose, het zogenaamde incretine-effect.¹⁰ Twee gastro-intestinale hormonen lijken een cruciale rol spelen in dit incretine-effect: glucose-afhankelijk

insulinotroop polypeptide of gastrisch remmend polypeptide (GIP) en glucagon-achtig peptide (GLP-1).¹⁰

De rol van GLP-1 werd bevestigd in onze studie, waarbij 44 patiënten gemiddeld vier jaar na de primaire gastric bypass werden onderzocht met behulp van een maaltijd-test (**hoofdstuk 6**). Deze studie toont aan dat de ontwikkeling van PHH niet volledig kan worden toegeschreven aan de toename van deze hormonen. Patiënten met hypoglycemie na de maaltijd-test vertoonden een hogere insulinegevoeligheid (lagere HOMA-IR en geen voorgeschiedenis van type 2 diabetes) en een verbeterde bètacelfunctie in de postprandiale fase. De rol van GLP-1 in de ontwikkeling van PHH kan worden benadrukt door de bevinding dat met het blokkeren van de GLP-1-receptor door een GLP-1-receptorantagonist (Exendin 9-39) insulinereacties op enterale glucose worden verminderd en PHH wordt voorkomen.¹¹

De zelf-gerapporteerde, en dus subjectieve, prevalentie van PHH in een groep patiënten vier jaar na primaire gastric bypass is beschreven in **hoofdstuk 4** en bedroeg bijna 12%. In deze studie toonden we aan dat patiënten die frequente symptomen van PHH meldden een lagere kwaliteit van leven hadden (getest met de RAND-36) en een hogere incidentie van symptomen van angst en depressie (getest met de HADS), vergelijkbaar met patiënten met vroege dumping. Er werd geen verschil gezien in de prevalentie van vermoeidheid tussen patiënten met of zonder symptomen van PHH.

De objectieve prevalentie van hypoglycemie (glucose < 3,3 mmol / L) in een willekeurig geselecteerde populatie gemiddeld 4 jaar na primaire RYGB was 48% (**hoofdstuk 6**). Alle patiënten met hypoglycemie rapporteerden nauwelijks symptomen, getest met dezelfde vragenlijst als gebruikt in **hoofdstuk 3**. Deze bevinding suggereert een verminderde gevoeligheid voor (ernstige) hypoglycemie bij patiënten vier jaar na primaire gastric bypass, een bevinding die ook is gerapporteerd door anderen.¹²⁻¹⁴

Vroeger werd maagband-plaatsing beschouwd als een procedure met lage morbiditeit en mortaliteit met goede resultaten op het gebied van gewichtsverlies. Op de lange termijn heeft een groot deel van de patiënten met een maagband een revisie operatie nodig vanwege teleurstellende resultaten of in verband met complicaties. In **hoofdstuk 7** hebben we beschreven dat bij patiënten zonder redenen voor acute maagbandverwijdering, de geplande conversie van maagband naar Roux-Y gastric bypass veilig kan worden uitgevoerd in een éénstaps-procedure. Dit geeft geen toename van morbiditeit en laat geen verschil zien in postoperatief gewichtsverlies. In **hoofdstuk 8** hebben we de zelf-gerapporteerde prevalentie van PHH in deze populatie bestudeerd. De prevalentie was 30,2%, significant hoger in vergelijking met primaire gastric bypass ($p = 0,012$). We veronderstellen dat dit verschil te wijten zou kunnen zijn aan de beschadiging van de nervus vagus door de eerdere maagband-plaatsing. Verder zagen we in deze studie dat patiënten na gastric sleeve een prevalentie van zelfgerapporteerde hypoglycemie hadden van bijna 7%, enigszins maar niet significant lager dan de prevalentie na primaire gastric bypass, wat suggereert dat de veronderstelde beschermende functie van de pylorus laag is.

In **hoofdstuk 3** stellen we een step-up benadering voor voor de behandeling van PHH.

Patiënten die een slokdarm- of maagoperatie hebben gehad, moeten worden gecontroleerd op symptomen die duiden op dumping. Het eerstelijnsmanagement van PHH moet zich richten op dieetaanpassing gedurende 3 tot 4 weken, met toevoeging van acarbosebehandeling voor patiënten die PHH ervaren. Acarbose is een α -glycosidase hydrolase-remmer die de koolhydraatvertering in de dunne darm vertraagt, waardoor postprandiale hyperglycemie en daaropvolgende hypoglycemie verminderd.⁸ Wanneer dieetaanpassing en acarbosebehandeling niet succesvol zijn, dient behandeling met somatostatine-analogen worden overwogen bij patiënten met het PHH die arbeidsongeschiktheid zijn en/of een verminderde kwaliteit van leven ervaren. Kortwerkende en langwerkende somatostatine-analogen moet gedurende 2 weken en gedurende 2 maanden worden geprobeerd. Bij sommige patiënten die medicamenteus onvoldoende verbetering ervaren, kan een chirurgische re-interventie of continue gastrische / enterale voeding worden overwogen, maar de uitkomsten van deze interventies zijn wisselend en slecht bestudeerd.

BESPREKING VAN DE BELANGRIJKSTE BEVINDINGEN

Voor zowel vroege dumping als PHH toonden we aan dat patiënten die lijden aan dumping een lagere kwaliteit van leven hebben, meer angst- en depressiesymptomen en dat meer patiënten de operatie betreuren vergeleken met patiënten zonder dumping. Tot nu toe hebben geen andere studies dit onderwerp bestudeerd.

Vroege dumping

Voordat we aan dit onderzoeksproject begonnen, was de belangrijkste gedachte over de pathofysiologie van vroege dumping dat het werd veroorzaakt door hypovolemie, veroorzaakt door het snelle aanbod van een aanzienlijke hoeveelheid onverteerd vast voedsel aan de dunne darm. Hyperosmolaire voedingsstoffen in de dunne darm veroorzaken vermoedelijk een verschuiving van vloeistoffen uit het intravasculaire compartiment (dat wil zeggen plasma) naar het intestinale lumen, resulterend in een vermindering van plasmavolume met secundaire klachten, zoals tachycardie en - zelden-syncope. Deze hypovolemie kon worden waargenomen door een verandering in hematocriet en een verlaging van de bloeddruk en een hogere polsslag.^{3,4,15}

Onze belangrijkste bevinding na de MMTT was dat deze objectieve metingen voor de hypovolemische therapie, leidend tot een robuuste verandering in hematocriet, niet konden worden bevestigd. In onze studie toonden we aan dat met vroege dumping de L-cellen een belangrijke rol lijken te spelen in de pathofysiologie, zoals ook beschreven wordt door Ukleja.¹⁵ Alle symptomen die goed worden beschreven in de Sigstad-score kunnen worden verklaard door de overstimulatie van L-celproducten zoals GLP-1 en PYY. GLP-1 heeft meer-

dere effecten op verschillende paden, veroorzaakt verschillende symptomen (zoals misselijkheid, tachycardie, hypotensie) en beïnvloedt de insulinesecretie (veroorzaakt vaatverwijding en normalisatie van de hartfrequentie na 50-60 minuten.¹⁶⁻¹⁹ Ter ondersteuning van deze theorie is behandeling met somatostatine-analogen, waarvan bekend is dat ze de afgifte van GLP-1 uit L-cellen verminderen, succesvol geweest bij het verminderen van vroege dumpingklachten.^{20,21} Van PYY is bekend dat het vasoconstrictie veroorzaakt, de bloeddruk verhoogt, de darmmotiliteit vermindert en de opname van voedingsstoffen stimuleert.²²⁻²⁶ In onze studie is de piek van PYY veel later na de maaltijd, wat de theorie ondersteunt dat het optreedt als een negatieve feedback mediator. PYY is feitelijk het overheersende hormonale product van de meer distale L-cellen in het darmkanaal.²⁶

PHH

We hebben twee belangrijke bevindingen over PHH: de oorzaak van PHH is multifactorieel en de prevalentie van asymptomatische PHH is erg hoog.

Multifactoriële oorzaak van PHH

Toen we met dit onderzoeksproject begonnen, was de belangrijkste gedachte dat postprandiale hypoglycemie het gevolg is van hyperinsulinemie door een toename van GLP-1 door stimulatie van de L-cellen in het ileum en de dikke darm.^{6,27,28}

In onze MMTT-studie (**hoofdstuk 4**) zagen we dat de ontwikkeling van hypoglycemie vaker voorkwam bij patiënten met een lager gewicht bij operaties, met een hoger gewichtsverlies na een operatie, zonder eerdere diabetes en met een hogere insulinegevoeligheid, berekend met behulp van de Homeostasis Model Assessment-index en een verbeterde bèta-celfunctie. Al deze bevindingen suggereren een multifactoriële oorzaak van de hypoglycemie, die ook door anderen wordt gemeld.^{13,29} Het precieze mechanisme voor deze verschillen is niet bekend.

De andere belangrijke bevinding was de discrepantie tussen de zelfgerapporteerde prevalentie van hypoglycemie in onze vragenlijststudie en de prevalentie van (asymptomatische) hypoglycemie in onze MMTT. Deze hypogevoeligheid kan te wijten zijn aan een gestoorde autonome reactie op hypoglycemie na RYGB, wat indicatief is voor hypoglycemie-geassocieerd autonoom falen (HAAF). Niet herkennen van hypoglycemie is bekend van patiënten met type 1 diabetes die (te) strikt gereguleerd zijn en die gekenmerkt worden door een gebrek aan adrenerge waarschuwingssymptomen tijdens een hypoglycemie. Er wordt verondersteld dat terugkerende hypoglycemische episodes bij patiënten met diabetes afstomping van de adrenerge en hypothalamus-hypofyse-bijnier (HPA) -reacties op hypoglycemie veroorzaken en daardoor de tegenregulatie verminderen.^{14,30} Het niet herkennen van hypoglycemie werd ook door anderen gevonden, wat onze bevindingen bevestigt.^{12-14,31}

Er is een aanzienlijke interactie tussen de nervus vagus en de vrijlating van het darmhormoon.^{35,36} Een benadering om vroege dumping alleen als een endocriene stoornis te beschouwen, kan te simplistisch zijn. De rol van afferente en efferente vagale zenuwuiteinden pleit hier ook tegen.³⁷ Bovendien kunnen voedingsstoffen, galzuren en bijvoorbeeld darmmicrobiota allemaal een rol spelen bij vroege dumping en PHH.^{35,36}

In feite kan de toegepaste chirurgische procedure dus worden geoptimaliseerd, rekening houdend met het bovenstaande om optimale behandelingsresultaten mogelijk te maken.³⁷ Het combineren van behandelingen (bijvoorbeeld medische behandeling van obesitas toegevoegd aan gastric bypass) kan gunstige resultaten opleveren, niet alleen wat betreft gewichtsverlies, maar ook op PHH.³⁸

TOEKOMSTPERSPECTIEVEN

Vroege dumping

Uit onze onderzoeken bleek dat vroege dumping gepaard ging met verhoogde PYY- en GLP-1-concentraties onmiddellijk na inname van een maaltijd. De pathofysiologie is daarom niet zo verschillend als van PHH waarbij de productie van GLP-1 buitensporige hoeveelheden insuline stimuleert. Beide ziekten kunnen worden beschouwd als endocriene darmaandoeningen of meer in het bijzonder hyperstimulatiesyndromen van de L-cellen.

Het blijft echter onduidelijk waarom sommige mensen veel heftiger reageren op dezelfde voedselstimulus. Sommige studies tonen een belangrijke rol voor aminozuren bij het stimuleren van L-cellen via de calcium-sensing-receptor en het stimuleren van de productie van GLP-1 en PYY.³⁹⁻⁴¹ Meer onderzoek is nodig om te zien of dit fenomeen een rol speelt in de ontwikkeling van vroege dumping.

De galzuurconcentratie stijgt significant na RYGB. De meeste studies hebben aangetoond dat deze toename evenredig is voor alle galzure subtypes. Galzuren kunnen het glucose-metabolisme reguleren door de expressie van Takeda-G-eiwit-gekoppelde receptor (TGR) 5 in L-cellen, wat resulteert in een afgifte van glucagon-achtig peptide 1 (GLP-1) en speelt daarom mogelijk een belangrijke rol in de pathogenese van vroege dumping.⁴²⁻⁴⁴

Voor een juiste behandeling van ernstige vroege dumping met vermindering van de kwaliteit van leven, is het belangrijk om vroeg dumpen te onderscheiden van “normale” voedselintolerantie die het gevolg kan zijn van, bijvoorbeeld, te snel eten, niet goed kauwen, of niet scheiden van eten en drinken.

Een gevalideerde vragenlijst voor vroege dumping zou nuttig zijn om te gebruiken in de polikliniek. Deze vragenlijst moet niet alleen een opbouwende schaal bevatten voor het benoemen van de ernst van de symptomen, maar ook aspecten van de impact op de kwaliteit van leven en tevens na welk voedsel de symptomen optreden. Op basis van deze

vragenlijst kan advies worden gegeven aan patiënten, zoals verandering van eetgewoonten of vermijding van bepaalde voedingsmiddelen.

Bij patiënten met ernstige symptomen die een impact hebben op de kwaliteit van leven zijn objectieve metingen noodzakelijk om vroege dumping te onderscheiden van andere ziekten zoals PHH, maagzweren, obstipatie en gastro-intestinale problemen. Ons maaltijd-onderzoek toonde aan dat polsslag, bloeddruk en hematocriet geen discriminerende metingen waren. Toekomstig onderzoek moet betere objectieve maatregelen vinden voor het diagnosticeren van vroege dumping. Mogelijk kunnen beeldvorming van entero-endocriene celpopulaties, darmbiopten en markers van endocriene activiteit van de darm hieraan bijdragen.

Verandering in operatietechniek (langere pouch, banded bypass) kan een preventief effect hebben in de prevalentie van vroege dumping, maar kan enkele andere nadelen hebben, zoals variabel gewichtsverlies en migratie of wegglijden van de band.

Postprandiale hyperinsulinemische hypoglycemie (PHH)

De prevalentie van PHH vier jaar na de primaire maag-bypass was hoog in onze studie. Getest in een willekeurig cohort had bijna de helft van de patiënten een bloedglucose lager dan 3,3 mmol / L, hoewel geen van deze patiënten symptomen van hypoglycemie ervaarden. De prevalentie van zelfgerapporteerde PHH bedroeg slechts 11%. Beide uitkomsten samen suggereren een verminderd besef (unawareness), een fenomeen dat bekend is bij patiënten met diabetes mellitus type 1 als complicatie van frequente perioden van hypoglycemie.

Een gevalideerde vragenlijst gericht op symptomen van hypoglycemie en de timing van het hebben van deze symptomen en de impact op kwaliteit van leven is belangrijk om patiënten te selecteren die het risico lopen op ernstige hypoglycemie en die baat hebben bij de behandeling.

Zoals we hebben aangetoond, is de prevalentie van PHH anders na verschillende bariatrische procedures. Dit geeft ons inzicht in de verschillende factoren die van invloed zijn op de pathofysiologie. We hebben aangetoond dat GLP-1 een rol speelt in deze pathofysiologie, maar het bleek niet de enige factor te zijn die hierbij betrokken was: een hogere insulinegevoeligheid (lagere HOMA-IR en geen voorgeschiedenis van type 2 diabetes) en een verbeterde bètacelfunctie spelen ook een rol.

De prevalentie van PHH is hoger bij patiënten met eerdere maagband. Dit suggereert dat er een rol is weggelegd voor de nervus vagus. Bij het creëren van de pouch worden vezels van de nervus vagus doorgenomen. Maar bij eerdere maagbandplaatsing is meer littekenweefsel en lopen meer vezels van de nervus vagus het risico om beschadigd te worden.⁴⁵ Toekomstig onderzoek zou zich moeten concentreren op de rol van de nervus vagus in de pathofysiologie van PHH, zodat misschien strategieën kunnen worden ontwikkeld om deze vezels te sparen bij bariatrische chirurgie, waardoor de ontwikkeling van PHH wordt voorkomen. Na sleeve gastrectomie lijkt de prevalentie van PHH lager te zijn dan na primaire gastric bypass, maar deze is niet nul. Dit suggereert dat de pylorus PHH niet voorkomt. Aangezien

de vezels van de vaguszenuw tijdens deze operatie worden gespaard, kan het bestuderen van de prevalentie van PHH bij patiënten na de gastric sleeve en de rol van incretines ons meer inzicht geven in de pathofysiologie voor PHH voor de hele groep.

De studie met de maaltijd-test toont aan dat in bijna de helft van de patiënten na RYGB een hypoglycemie kan worden uitgelokt na een maaltijdstimulus. Dit is intrigerend omdat we in de klinische praktijk niet zien dat de helft van de mensen worstelt met deze klachten. Het zou mogelijk zijn dat bepaalde patiënten met ernstige neuroglycopenie zich niet aanpassen aan frequente hypoglycemie. In feite kan het verminderde herkennen van hypoglycemie worden gezien als een 'normale' reactie waardoor symptomen worden voorkomen.^{12,46} Toekomstige studies zouden deze neurologische aanpassing aan hypoglycemie moeten onderzoeken.

Een beschrijving in meer detail van de mogelijke gevolgen van herhaalde hypoglycemie is essentieel. Hebben patiënten met herhaalde hypoglykemische gebeurtenissen meer kleinere of grotere incidenten na hypoglycemie, problemen op het werk als gevolg van een gebrek aan concentratie of in andere domeinen?

In de klinische praktijk zien we dat een step-up benadering bij de behandeling van PHH een goed effect heeft. Een kleine groep patiënten heeft echter slechts een korte termijnvoordeel van medische behandeling en heeft om de paar maanden behoefte aan meer medicatie. Toekomstig onderzoek naar de behandeling moet zich richten op de vraag waarom deze patiënten geen voordeel meer hebben voor de behandeling. Nieuwe behandelingsmodaliteiten gebaseerd op de pathofysiologie moeten worden ontwikkeld. GLP-1-antagonisten zoals exendine 9-39 spelen bijvoorbeeld een gunstige rol bij de behandeling van PHH in kleine patiëntengroepen.¹¹

Net als bij vroege dumping moet ook de rol van galzuren en aminozuren verder worden onderzocht om meer van de pathofysiologie te begrijpen en nieuwe, en misschien betere en gemakkelijkere behandelingsmodaliteiten te vinden.³⁹⁻⁴¹

Voor die gevallen waarin medische behandeling faalt, moeten chirurgische opties meer in detail worden bestudeerd en moet een stapsgewijze benadering bij chirurgische behandelingen worden voorgesteld en geëvalueerd. Vanwege de kleine groep patiënten die een chirurgische therapie voor PHH nodig hebben, is het noodzakelijk dat bariatrische afdelingen van verschillende ziekenhuizen samenwerken bij het verrichten van wetenschappelijk onderzoek.

Voorkomen is beter dan genezen. Omdat bariatrische chirurgie nog steeds een jonge discipline is, is er nog veel ruimte voor verbetering. Verschillende chirurgische technieken worden uitgevoerd en ontwikkeld. Zoals in ons onderzoek blijkt, wordt sleeve gastrectomie geassocieerd met een verminderde kans op PHH bij veel mensen, maar deze ingreep heeft andere nadelen zoals reflux en verminderd gewichtsverlies in de loop van de tijd. In twee andere procedures (Duodenale switch en Sadi-S) wordt een maagpouch aangelegd en een enkele anastomose (Sadi-S) of een Roux-en-Y anastomose (duodenale switch) wordt aan het begin van de twaalfvingerige darm uitgevoerd.

Beide procedures zijn veelbelovend vanwege het gewichtsverlies en de resolutie van comorbiditeiten, echter de prevalentie van PHH is nog niet bekend. Het is noodzakelijk dat (nieuwe) chirurgische procedures ook worden beoordeeld op hun complicaties zoals vroege dumping en PHH, vanwege hun diepgaande invloed op de kwaliteit van leven.

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Appendices

List of publications

— Dankwoord

— Curriculum Vitae

List of publications

In this thesis

1. Emous M, van den Broek M, Wijma R, de Heide LJM, Laskewitz A, van Dijk G, Totté E, Wolffenbuttel BHR, van Beek AP. Prevalence of hypoglycaemia in a random population after Roux-en-Y gastric bypass after a meal test. *Endocr Connect*. 2019 Jun 1. [Epub ahead of print]
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- * both authors contributed equally
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Dankwoord

Het meest gelezen stuk van een proefschrift. Een promotie voelt toch een beetje als een bruiloft of een begrafenis: een gelegenheid om allerlei mensen te bedanken die je op je pad tegen bent gekomen en waarmee je samen opgelopen bent. Natuurlijk zijn er veel meer mensen in mijn leven waar ik van hou en ongelooflijk veel aan heb, dat je niet genoemd wordt maakt dat niets minder.

Als eerste wil ik alle patiënten bedanken die hebben meegewerkt aan het onderzoek.

Dr. A.P. van Beek, beste **André**, wat leuk om jouw eerste promovendus te zijn.

Nu alweer 8 jaar geleden begonnen de eerste gesprekken, jij was al langer bezig om de samenwerking tussen het CON en UMCG van de grond te krijgen. Deze promotie is daar de vrucht van.

Dank voor het vertrouwen in mij en dat je altijd in het project hebt geloofd. Dank voor al je hulp bij de studies en je motivatie op de lange weg.

Een promotie is pas het begin van mijn wetenschappelijke carrière en ik denk dat we in de toekomst nog goed kunnen samenwerken en nog mooie dingen kunnen maken!

Prof. Dr. B.H.C. Wolffenbuttel, beste **Bruce**, het is me gelukt! Ik weet nog goed de eerste keer dat we over een promotietraject praatten. Je waarschuwde me dat het vaak niet lukt om te promoveren naast een fulltime baan. Het heeft een poos geduurd en makkelijk was het niet, maar hier ligt het dan.

Dank dat je er voldoende vertrouwen in had om mijn promotor te worden en dank dat je nu op de eindstreep André de mogelijkheid hebt gegeven om mijn promotor te zijn.

Dr. E. Totté, lieve **Erik**, ik weet nog goed de eerste dag dat ik mee kwam lopen en bij jou werd gestald op de OK. Er was een directe klik. Enkele maanden later begon ik al bij jullie als fellow.

Jouw optimisme over de kansen en snelheid van het onderzoek doen en promoveren was grenzeloos, maar het is me toch gelukt. Jouw brein borrelt van ideeën, dank dat ik daar van mee heb mogen genieten, al ben je soms onnavolgbaar.

Dank voor je vertrouwen in mij als dokter, chirurg, onderzoeker en manager.

Ongelooflijk zonde dat je chirurgische carrière zo heeft moeten stoppen en ik hoop dat je iets (en ook iemand) tegen komt waarbij je gelukkig wordt.

Prof. dr. J.W. Eriksson, dear **Jan**, I like to thank you for being one of the members of the Reading committee. I really appreciate that you can come to the defense and that you be one of the speakers during the symposium.

Prof. dr. H. Pijl, beste **Hanno**, bedankt voor het lezen en goedkeuren van mijn proefschrift. Heel jammer dat je niet aanwezig kan zijn op de verdediging maar ik wilde het echt niet verder uitstellen. Dank voor je begrip. Hopelijk kunnen we in de toekomst wel een samenwerking opzetten over dit ongelooflijk interessante onderwerp.

Prof. dr. J.M. Klaase, beste **Joost**, zoekend naar nog iemand voor de leescommissie kwam ik al snel op jouw naam. Met je betrokkenheid bij de HPB en als chirurg zag ik voldoende raakvlakken met dit proefschrift. Dank dat je hieraan mee wilde werken. Ik verwacht dat we nog heel wat gezellige uren zullen doorbrengen binnen de ROC in het selecteren van geschikte kandidaten om ons vak te versterken!

Beste leden van de corona

Wat spannend dat jullie straks het vuur aan mijn schenen gaan leggen, ik hoop dat het niet te warm wordt. Bedankt dat jullie dit voor me willen doen.

Lieve paranimfen, ook jullie wil ik bedanken.

Lieve **Lieke**, wat fijn dat jij mijn vriendin bent. We gaan al lang mee. Super dat je nu mijn paranimf kan zijn, terwijl ik eens jouw getuige was. Ik hoop dat ik deze datum niet vergeet. Ik hoop dat we samen nog vele wandelingen zullen maken tot we oude besjes zijn en we al blij zijn met een blokje om.

Lieve **Marjanne**, ik blijf het fascinerend vinden hoe onze levens met elkaar verweven zijn geraakt, als start bij de chirurgie maar daarna met het wonen en werken in dezelfde regio en dorpen. Ongelooflijk leuk om te zien hoe onze kinderen bij elkaar komen. Ik hoop dat we daar nog lang van kunnen genieten.

Lieve **Jan**, **Ewoud**, **Mirjam** en **Stefan**, mijn maten van de bariatrie. **Jan** dank voor je grenze-loze optimisme en positivisme in het algemeen en je collegialiteit in het bijzonder. Jammer dat je nu ergens anders zit maar we hebben ook op die manier al leuke samenwerkingen gehad en er zullen er nog vele volgen! **Ewoud**, je kwam in een lastige periode als een enorme versterking. Zo anders dan ik, maar juist dat maakt ons beide een beetje beter. Ik hoop dat we nog jaren van elkaar kunnen genieten. Lieve **Mirjam**, paranimfen en een kind krijgen in 1 week is misschien wat veel. Wat fijn dat je toch kon komen naar het MCL en wat een aanwinst om je te hebben. Ik hoop ergens in de aankomende jaren ook bij jou op je promotie te komen! Ik hoop dat we nog lang samen alle “moeilijke “ patiënten kunnen delen. **Stefan**, dat was even een hobbel in de start van onze professionele relatie maar wat goed dat we dat nog even over konden doen. Jouw flexibiliteit en werkethos is een voorbeeld voor een ieder! We komen zeker nog een keer uit het ei eten!

Lieve HFG,

Wat een leuke dynamische groep hebben we toch, nooit een saai moment en altijd wel een brand te blussen. Gelukkig gebeuren er ook een heleboel leuke en mooie dingen in zo'n grote groep, dit is daar een van.

Lieve mannen van het eerste uur: **Christiaan, Sietze, Eric, Pier, Joost, Rein, Omid, Ties, Rob, Diderick, Floris, Erik en Jan**; dank voor het vertrouwen in deze GE-vrouw en dat ik zo helemaal als one-of-the-guys in jullie midden ben opgenomen.

Lieve CON,

Lieve secretaresses, poli-assistentes, verpleegkundigen van afdeling en polikliniek.

Ik durf gewoon niet iedereen op te noemen, veel te bang dat ik iemand vergeet.

Wat een fantastisch team zijn jullie. Mede door jullie is het zo fijn om bij de bariatric te werken. Patiënten voelen zich welkom en gehoord, en dat is voor deze groep patiënten een nieuwe ervaring. Ik vind het heel leuk om jullie een beetje te managen, al doen jullie het meeste werk natuurlijk gewoon zelf! Ik hoop dat we de aankomende jaren naar nog grotere hoogten kunnen groeien zonder uit het oog te verliezen dat het gaat om de individuele patiënt en het werkplezier van de medewerker! Ik vermoed dat met dit proefschrift er meer onderzoek gedaan zal gaan worden op de afdeling en ik ga proberen jullie daar zoveel mogelijk in te betrekken!

Lieve verpleegkundig specialisten en physician assistants: **Willy, Sanne, Willeke, Anna en Gaatsche** jullie zijn natuurlijk een speciale categorie. Jullie nuchtere kijk naar de patiënt, kritische blik naar het traject en onszelf helpen het CON elke keer weer verder. Het is een plezier om met jullie samen te werken. En ik hoop dat het wetenschappelijk onderzoek samen met jullie nog verder van de grond gaat komen!

Lieve **Loek**, wat een ongelooflijke plezierige samenwerking hebben we. Dank voor je humor, je vertrouwen en alles wat je in klinisch werk en onderzoek voor ons en in het bijzonder voor mij doet.

Lieve arts-assistenten,

Sinds twee jaar jullie opperhoofd. Wat een plezier heb ik bij het coachen van jullie door het leven als anios en aios, in leuke en ook in minder leuke dingen. Elke keer leer ik weer zo veel van jullie. Ik hoop dat ik met dit proefschrift een verdere aanzet zal geven voor de ontwikkeling van wetenschap binnen de chirurgie en bariatrische chirurgie in het bijzonder, zodat ook jullie daarvan kunnen profiteren. Dank voor alle tips van degenen die al eerder gepromoveerd zijn en zorgden dat ik niet in dezelfde valkuilen liep.

Lieve verpleegkundigen, poli-assistentes, verpleegkundig specialisten van de chirurgie

Ook dankzij jullie heb ik het zo naar mijn zin. Dank voor al het werk dat jullie mij uit handen nemen en dat ik naar jullie mag delegeren.

Lieve **Merel** en **Ragnhild**, dank voor al jullie hulp in de praktische uitvoering en in het helpen met de statistiek. Voor jullie beiden geldt dat ik heel benieuwd ben waar jullie gaan landen. Merel, jouw boekje verwacht ik in 2020, maken we ook een mooi feestje van. Ragnhild, met jouw ambitie zal dat ook nog wel een keer gebeuren, denk ik!

Lief management en oud-management en bureau heelkunde, met name: **Eline, Alie, Koert, Hans, Marjoke, Louise, Inge, Piet** en **Iris**.

Dank voor het vertrouwen dat jullie elke keer weer in mij stellen, dank voor de complimenten die jullie me geven. Wat een fijne samenwerking. De afgelopen jaren waren niet altijd makkelijk met manager en unithoofd die vertrokken. De boel gaat weer veranderen in het ziekenhuis, maar ik denk dat voor ons stukje we doorgaan met naar buiten treden en de patiënt opzoeken. Dank voor het helpen met het reilen en zeilen en jullie enthousiasme over “ons product”, die super goede patiëntenzorg die we elke dag weer voor elkaar weten te boksen!

Lieve pinksterweekend skutsje-zeilers (of SK6, LCGJ, Ôlepanne, of weet ik welke term erbij hoort)

Al hebben jullie echt helemaal niets voor dit proefschrift gedaan, ik wil jullie toch bedanken voor jullie vriendschap. Ik heb het altijd een beetje druk maar Pinkster-weekend is heilig, alleen als Hugo jarig is mag ik echt niet mee. Maar ik krijg zoveel energie en blijheid van jullie dat ik hoop dat we hier nog mee door kunnen gaan tot ons 80^{ste}!

Lieve schoonfamilie,

Wat is het toch jammer dat we zo ver weg zijn gaan wonen. Gelukkig krijgen we het toch steeds weer voor elkaar om bij elkaar te buurten. De familieweekenden vind ik grandioos en het eindeloos spelletjes doen is heerlijk. Ik hoop dat **Jan** en **Akkelies** de komende jaren iets minder ziekenhuizen van binnen hoeven te zien dan afgelopen jaar (ziekenhuis is om er te werken, niet om er te liggen!) Ik ben ontzettend benieuwd waar al onze kinderen terecht gaan komen en wat voor leuke dingen ze gaan doen!

Lieve **David, Papatya, Izan** en **Dünya**

Wat fijn dat jullie maar een beetje ver weg wonen maar nog goed bereikbaar. Het is altijd gezellig als we bij elkaar zijn. Jullie zijn goed in het vieren van feestjes en het vieren van het leven. Ik moet en ga dat ook meer doen en dit feestje is er een voorbeeld van. Ik hoop dat er nog vele zullen volgen samen met jullie.

Dear **Mattias, Rachael, Isla** and **Nils**,

To bad that you are living in England. We love to see you and just relax, talk, drinking tea (o no, not for Mattias) and having fun. It is my wish that we will visit you more than we did. I hope you will practice speaking English with us, me and the kids, we need it!

Lieve **Rob en Ina**,

Tja wat moet je zeggen tegen zulke geweldige ouders. Dank voor jullie rotsvaste vertrouwen in ons allemaal. Wat knap dat het jullie lukt om geen oordeel te laten zien over hoe wij ons leven leven (natuurlijk hebben jullie wel een oordeel, maar die komt naar voren in support en niet in veroordeling). Dank voor al jullie steun, oppas-dagen en weekenden als ik weer iets moet doen. Ik heb het niet van een vreemde, geen nee kunnen zeggen, work-aholic zijn, niet zo goed in delegeren en mijn eigen tijd afbakenen, maar ik leer, mede dankzij jullie spiegel.

Ik hoop dat we nog heel lang van elkaar kunnen genieten.

Lieve **Hugo en Ilse**

Ik hoop dat het redelijk is gelukt wat ik de afgelopen jaren hebt geprobeerd; werken aan dit proefschrift als jullie er niet zijn, of in de randen van de dag als jullie toch bezig waren op de "ipad". En dat ik er zoveel mogelijk voor jullie ben geweest en zal zijn. Ik kan niet beloven dat ik nu opeens altijd thuis zal zijn, want dat zit niet in mijn aard. Maar ik hoop wel dat ik jullie kan helpen door de aankomende jaren heen en ik ben ontzettend benieuwd wat jullie in het leven gaan kiezen. Ik hou van jullie voor eeuwig.

Lieve **Jeroen**,

Mijn moter en mijn rem. Mijn externe geweten. Mijn theoretisch basis van het leven. Je humor verrast me altijd weer en ik kan er zo om lachen. Door de druk van alles wat ik op me neem in de afgelopen jaren, ben ik wel eens zelf wat in de knoop gekomen. Wat ongelooflijk dat je me altijd blijft steunen en zo weinig moeilijk doet en me mijn eigen keuzes laat maken. Dank dat je met me mee bent gereisd naar Friesland, terwijl dat helemaal niet was wat je wilde.

Ik kijk uit naar alles wat we samen gaan doen.

Curriculum Vitea

Marloes Emous werd geboren op 26 juni 1975 in De Bilt als jongste kind van Rob Emous en Ina Emous-van der Kooij en zus van twee oudere broers, David en Mattias. Na de Vrije School in Leiden en Zeist afgemaakt te hebben, deed zij eindexamen VWO.

Marloes werd ingeloot voor de studie Geneeskunde en zij besloot te gaan studeren aan de Universiteit van Maastricht (1994–2000). Tijdens haar studie werd ze lid van de Studenten Zeilvereniging Lagakari in Maastricht en was daardoor bijna elk weekend op het water in Friesland of bij de andere studentenzeilverenigingen te vinden. Tijdens haar coschap en wetenschapsstage bij de Heelkunde Ziekenhuis Sittard onder leiding van dr. A. Hoofwijk, werd de liefde voor en de affiniteit met de chirurgie duidelijk.

Na het afronden van de Geneeskunde studie ging Marloes werken als ANIOS bij de afdeling Heelkunde, eerst in de Gelderse Vallei te Ede, onder de bezielende leiding van drs. P.M. Kruyt en dr. W.K. de Roos (2001), daarna in het Academisch Medisch Centrum, onder leiding van hoofd van de afdeling en toenmalig opleider Prof. dr. H. Obertop (2002). Hier werd duidelijk dat Marloes zich als een vis in het chirurgische water voelde en werd de bijnaam Supermouse geïntroduceerd door Obertop.

In 2002 werd zij door Prof. dr. D.A. Legemate betrokken bij een kwaliteitsverbetering project rond de beoordeling van post-chirurgische complicaties. Hoewel dit niet tot een publicatie leidde, legde het hieruit ontwikkelde model een basis voor een kritische evaluatie van de voor- en nadelen van operatief ingrijpen bij de individuele patiënt.

Zij werd in 2004 aangenomen voor de opleiding onder Prof. dr. D.J. Gouma, later opgevolgd door Prof. dr. J.J.B. van Lanschot (2004-2005). Na 2 jaar academische opleiding en een korte episode in het Antoni van Leeuwenhoek Ziekenhuis onder leiding van Prof. dr. B.B.R. Kroon, vervolgde Marloes haar opleiding in Tergooiziekenhuizen, locatie Hilversum, onder leiding van dr J.W. Juttmann en dr. J.P. Eerenberg (2006-2011).

Op 26 mei 2011 werd Marloes chirurg. Na een korte periode als Chef de Clinique gewerkt te hebben bij de Tergooiziekenhuizen, startte Supermouse op 1 augustus 2011 als fellow Bariatrie in het Medisch Centrum Leeuwarden (MCL) onder leiding van dr. E. Totté (2011-2013). Sindsdien werkt zij als bariatrisch, oncologisch en gastrointestinaal chirurg in het MCL.

Tijdens haar fellowship begon zij aan het wetenschappelijk onderzoek wat uiteindelijk geresulteerd heeft in dit proefschrift, mede dankzij de uitstekende samenwerking met de af-

deling Interne Geneeskunde van het MCL en de afdeling Endocrinologie van het Universitair Medisch Centrum Groningen.

Sinds 2015 is zij medisch manager van het Centrum Obesitas Noord-Nederland. Sinds 2017 is zij opleider Heelkunde in het MCL voor regio VI.

Marloes woont met Jeroen van Driel en hun twee kinderen Hugo en Ilse in Grou, Friesland.