Roux-en-Y gastric bypass

- clinical outcome and mechanisms of action

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ABSTRACT

Roux-en-Y gastric bypass (gastric bypass) is an effective surgical technique for treating morbid obesity. The objective of this thesis is to increase knowledge of long-term outcomes of gastric bypass surgery and to elucidate some of the associated mechanisms of action. Changes in BMI, needs for revisional surgery and influences on body composition as a result of a gastric bypass are compared with the results of the restrictive vertical banded gastroplasty (VBG) technique. This thesis further explores the role of gastrointestinal hormonal signalling by GLP-1, PYY and ghrelin as well as postoperative energy expenditure as representing potential weight-reducing mechanisms of action after gastric bypass surgery.

A long-term follow up of a clinical randomized study demonstrated that gastric bypass patients had lower BMI, better preservation of muscle mass and greater loss of fat mass compared to VBG patients six years after surgery. Nine years after primary surgery 90% of VBG patients required revisional surgery to gastric bypass due to severe discomfort in relation to food intake. Two days after gastric bypass surgery postprandial levels of GLP-1 and PYY were significantly higher and this pattern was maintained over time. Furthermore, the magnitude of weight loss was directly related to the magnitude of hormonal response. After gastric bypass levels of GLP-1 and PYY in patients correlated to energy intake as well as to satiety sensations, in contrast to patients after gastric banding procedures. No changes in ghrelin levels were noted as a consequence of either surgical technique. Nine years after surgery 24-hour indirect calorimetry revealed that meal-induced thermogenesis was significantly higher in gastric bypass patients than in weight-matched VBG patients.

The results of this thesis project show that the gastric bypass technique has a favourable long-term clinical outcome in comparison to VBG in terms of superior weight control, less need for revisional surgery and advantageous body composition. The better weight-reducing effect of gastric bypass can be partly explained by the augmented postprandial response of GLP-1 and PYY, both known to mediate satiety and decrease food intake, and which could be observed only days after surgery. These positive post-operative results remained for over nine years. Gastric bypass surgery is also associated with both higher postprandial energy expenditure and with generally increased energy expenditure throughout the day. These mechanisms may account for the maintenance of lower body weight.

Keywords: Roux-en-Y gastric bypass, gastric bypass, Vertical banded gastroplasty, VBG, Bariatric surgery, weight loss, clinical outcome, mechanisms of action, body composition, DEXA, GLP-1, PYY, ghrelin, predictive tool for weight loss, energy expenditure, indirect

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SAMMANFATTNING PÅ SVENSKA

Roux-en-Y gastric bypass (gastric bypass) är en effektiv kirurgisk behandlingsmetod mot sjuklig fetma, obesitas. Syftet med denna avhandling var att öka kunskapen om de långsiktiga kliniska effekterna och några av verkningsmekanismerna bakom gastric bypass-teknikens effekt.

Kliniska resultat som viktutveckling, behov av om-operationer och inverkan på kroppssammansättning, dvs fett-, muskel och benmassa, bedömdes i jämförelse med en annan kirurgisk teknik mot obesitas; den restriktiva kirurgiska tekniken vertikal bandad gastroplastik (VBG). Som exempel på möjliga verkningsmekanismer hos gastric bypass tekniken undersöktes aptitreglerande signalering från mage och tarm via frisättning av hormonerna GLP-1, PYY och ghrelin, samt om kroppens energiförbrukning påverkades av det operativa ingreppet.

En uppföljning 6 år efter operation, i en randomiserad klinisk studie, visade att gastric bypass patienter hade lägre BMI, förlorade mindre muskelmassa samt hade större förlust av fettmassa jämfört med VBG patienter 6 år efter operation. Vid uppföljning 10 år efter operation hade 90 % av VBG patienterna behov av om-operation till gastric bypass på grund av dagliga negativa symtom i samband med matintag, tex smärta, kräkningar och svårigheter att svälja.

Via andra studier kring gastric bypass tekniken och hormonerna GLP-1 och PYY, som signallerar mättnad efter födointag, visade det sig att hormonnivåerna och mättnadskänslan ökade avsevärt och sedan kvarstod höga från så tidigt som 2 dagar efter operationen. Denna effekt visade sig kvarstå 1 år efter operationen och var då dessutom större än hos patienter opererade med restriktiv kirurgisk teknik, gastric banding. 2 år efter gastric bypass operation kunde man se att de patienter som hade gått ner bättre i vikt hade en starkare signalering av hormonerna GLP-1 och PYY än de patienter som hade gått ner sämre i vikt. Ytterligare undersökningar, 6 och 9 år efter operation, visade att nivåerna av GLP-1 och PYY fortfarande var förstärkta hos gastric bypass patienter, nu i jämförelse med VBG patienter. Vid inget av undersökningstillfällena kunde man se någon skillnad avseende ghrelin-nivåerna, ett hormon signallerande för hunger, efter de olika kirurgiska teknikerna jämfört med innan operation.

Nio år efter operation, med gastric bypass och VBG, jämfördes energiförbrukningen under ett dygn i en sk energikammare vilket är ett specialutrustat mindre rum där patienten bor under hela undersökningen. Kroppens ämnesomsättning mättes genom ”indirekt kalorimetri”, dvs via beräkningar genom rummets ventilationssystem av gasinnehållet i in- och utandningsluften. Gastric bypass patienterna visade sig ha högre energiförbrukning både efter födointag samt under hela dygnet jämfört med VBG patienterna.

Sammanfattningsvis visar denna avhandling att gastric bypass ger mer gynnsamma långsiktiga effekter än VBG tekniken genom bättre viktkontroll, mindre behov av om-operationer samt mer fördelaktig effekt på mängden fett och muskelmassa. Gastric bypass goda effekt på vikten kan troligen delvis förklaras av de förhöjda nivåerna av mättnadshormonerna GLP-1 och PYY, som kunde ses från 2 dagar upp till över 9 år efter operationen. Ytterligare en orsak till gastric bypass teknikens långsiktiga goda resultat kan vara den ökade energiförbrukningen både under ett helt dygn och efter födointag, som uppmätts så långt som 9 år efter operationen.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Long-term results of a randomized clinical trial comparing Roux-en-Y gastric bypass with vertical banded gastroplasty. Werling M, Fändriks L, Björklund P, Maleckas A, Brandberg J, Lönroth H, le Roux CW, Olbers T.
Br J Surg. 2013 Jan;100(2):222-30.

II. Gut hormones as mediators of appetite and weight loss after Roux-en-Y gastric bypass. le Roux CW, Welbourn R, Werling M, Osborne A, Kokkinos A, Laurenius A, Lönroth H, Fändriks L, Ghatei MA, Bloom SR, Olbers T.
Ann Surg. 2007 Nov;246(5):780-5.

III. Preoperative assessment of gut hormones does not predict weight loss after Roux-en-Y gastric bypass surgery. Werling M, Fändriks L, Vincent RP, le Roux CW, Olbers T
In manuscript

IV. Increased postprandial energy expenditure may explain superior long term weight loss after Roux-en-Y Gastric Bypass compared to Vertical Banded Gastroplasty. Werling M, Olbers T, Fändriks L, Bueter M, Lönroth H, Stenlöf K, le Roux CW.
PLoS One. 2013;8(4):e60280. doi: 10.1371/journal.pone.0060280. Epub 2013 Apr 3.

CONTENT

ABBREVIATIONS

BMI	Body mass index (kg/m^2)
VBG	Vertical Banded Gastroplasty
GLP-1	Glucagon-like Peptide 1
PYY	Peptide YY
EE	Energy Expenditure
DIT	Diet Induced Thermogenesis
Ad lib	Ad libitum
CNS	Central Nervous System
BPD	BilioPancreatic Diversion
DS	Duodenal Switch with biliopancreatic diversion
Kcal	Kilocalorie (1000 calories)
VAS	Visual Analogue Scale
DEXA	Dual Energy X-ray Absorptiometry

DEFINITIONS IN SHORT

BMI	The relationship between height and weight is normally described as body mass index (BMI); Body weight in kilos divided by the square of height in meters; kg/m^2.
Excess BMI	BMI units exceeding 25.
Excess BMI loss	BMI units lost in relation to BMI units above 25 before intervention.
Mechanism of action	Mechanism of action refers to the process through which some type of treatment or intervention (for example gastric bypass surgery) has an effect on the condition in question (for example obesity).
DIT	Diet induced thermogenesis; the rise in energy expenditure after food intake, assessed in relation to the amount of energy ingested. The value is expressed as a percentage.

1 INTRODUCTION

Mankind has been shaped throughout the ages by the varying availability of food. Strong urges driving us to seek nutrients, prevent weight loss and store energy have historically been survival features in the physiology of humans. Lately we have created new and more secure living conditions and in this environment the basic metabolic advantages that kept us alive during less favourable times have instead created environments resulting in health problems due to excessive weight and obesity. Overweight and obesity have developed into a major threat to public health despite the best efforts of healthcare services to tackle them.

It is clear that while we are trying to find strategies to bring about weight loss, our physiology is striving for high energy intake and energy storage, counteracting the desire to overcome obesity. Therefore, it is of great interest to explore active mechanisms both in natural physiology and in different weight loss methods. Learning more about the mechanisms causing obesity-associated morbidity is equally interesting as it may define groups at risk who need early and effective intervention.

The dietary composition (carbohydrates, fat and protein) of food is another area of interest in trying to find a solution to the obesity problem. Different kinds of physical activities for weight loss and health improvement have been suggested and evaluated. The role of intestinal microbiota is of current interest, both for general health implications and in the context of overweight and obesity treatment. The mechanisms behind the effects of obesity surgery are well understood in the cases of some surgical techniques, but less explored in others.

Different treatments for obesity have been used during the last decades, with great variation in efficacy. Attempts to lower energy intake and increase energy expenditure have given rise to more or less effective, and in some instances even absurd, weight-loss strategies. The search for pharmaceutical therapy has generally been disappointing resulting in few, and only modestly effective, drugs. Bariatric surgery is currently the most effective method for achieving long-standing weight loss and health improvements. There are nevertheless several different surgical techniques giving different results both in regard to efficacy and side effects.

Roux-en-Y gastric bypass is one of the most effective surgical techniques, both regarding health improvements and weight loss. The gastric bypass works through complex mechanisms of action, which are not fully understood. This thesis aims at expanding knowledge of the gastric bypass technique, both as regards long-term clinical outcome and mechanism of action.

2 BACKGROUND

2.1 Overweight and obesity

2.1.1 History

Nutritional deficiency and underweight have been a major problem in the daily lives of men and women through the ages. Genetic development favoured individuals with a capacity to store large amounts of energy whenever possible. (1-4) After the historic transition around 80 000 years ago, when humans changed from being hunters and gatherers to being growers in an agricultural society, food intake changed to a more carbohydrate-based diet, although food shortages could still be frequent . (1-4) From the first half of the 20th century access to food increased as industrialization developed. During the last few decades food has become increasingly available in every conceivable form. For a large proportion of the world population today, fulfilling the daily need of nutrients is easily achieved. Nutritional deficiency and underweight are still current problems for some, but overweight and impaired health as a result of excess calorie intake and the absence of physical activity are undeniably serious problems in many regions, and not only in developed countries. (1-6)

Until the beginning of the 20th century overweight was considered healthy and represented high status and power. It was also presented positively in literature and art. (2, 4) As late as at the end of the 19th century medical literature gave advice on how to gain weight so as to have some extra kilos to benefit general health. (2) However, as early as in the 5th century BC Hippocrates indicated overweight was a health problem in *Corpus Hippocraticum*. From the 18th century medical literature included overweight as a serious health problem. (2, 4) Research into subjects' gastric physiology, sensations of hunger and energy expenditure started during the 19th century largely due to the insight of medical professionals that many health problems resulted from overweight. (2)

2.1.2 Definitions

Overweight and obesity are defined as excessive fat accumulation. The most common way to assess overweight and obesity is BMI, a measurement where weight is related to height. The WHO's definitions are as follows: Normal weight is BMI 20 to 25 kg/m^2. Overweight is BMI >25 to <30. Obesity is defined as BMI >30 and is divided into three classes: Obesity class I: BMI 30-35 Obesity class II: BMI 35-40, Obesity class III BMI>40. (6)

Body weight and the calculation of body mass index does not, however, give detailed information about the proportion of muscle mass, fat mass and bone mass in the body. Genetics, gender, age, various diseases and level of fitness are examples of factors causing variations in the proportions of muscle, fat and bone. In most cases weight loss gives not only a reduced proportion of fat mass, which of course is desirable, but results also in loss of muscle mass. This makes it interesting to explore different weight-loss methods in regard to their impact on body composition.

2.1.3 Prevalence

During the 20th century the prevalence of overweight and obesity increased dramatically. From a slow rise in the beginning of the 20th century the prevalence of obesity has almost doubled since 1980. According to data from 2008 from the World Health Organization (WHO), over 1.4 billion adults over 20 years of age are overweight and 500 million are obese. Expressed as percentages, this applies to 35 % and 11 % respectively of the world's population. (6) Currently, overweight and obesity are a greater contributor to mortality worldwide than underweight. (6) It is estimated that over 2.8 million adults die every year due to excessive weight. (6)

2.1.4 Associated morbidity

Overweight and obesity are associated with impaired health through a complex pathophysiology. (7-9) The increased amount and size of adipocytes distributed as subcutaneous or visceral excess fat tissue generates an inflammatory condition followed by increased disposition for further morbidity, especially metabolic syndrome with its increased risk of cardiovascular disease. (7-9) The syndrome correlates to an overall increased risk of mortality. (10) The prevalence of diabetes is several times higher in obese subjects compared to individuals of normal weight. (8, 11-15) Hypertension (11, 13-15), dyslipidemia (11, 13-15), stroke (13-15) are significantly more frequent in the overweight and obese populations. The life risk of cancer is also elevated in obese persons, (13-15) possibly due to increased inflammation. The increased mechanical load on joints is associated with an increased incidence of osteoarthritis. (16, 17) The quality of life is reduced in proportion to the level of obesity, and in severely obese subjects their quality of life corresponds to that of cancer patients with a recurrence. (18, 19)

2.2 Regulation of food intake

Knowledge of the complex appetite signalling system is profound and based on long-standing research. (Figure 1) The more detailed relation between hunger/satiety sensations, food intake, weight regulation and gut signalling has a shorter history in the context of research. Gut signalling involves both humoral and neural mediation, influencing all types of gastrointestinal functions such as motility, secretion and absorption, but it also plays a role in regulating appetite. (20-24)

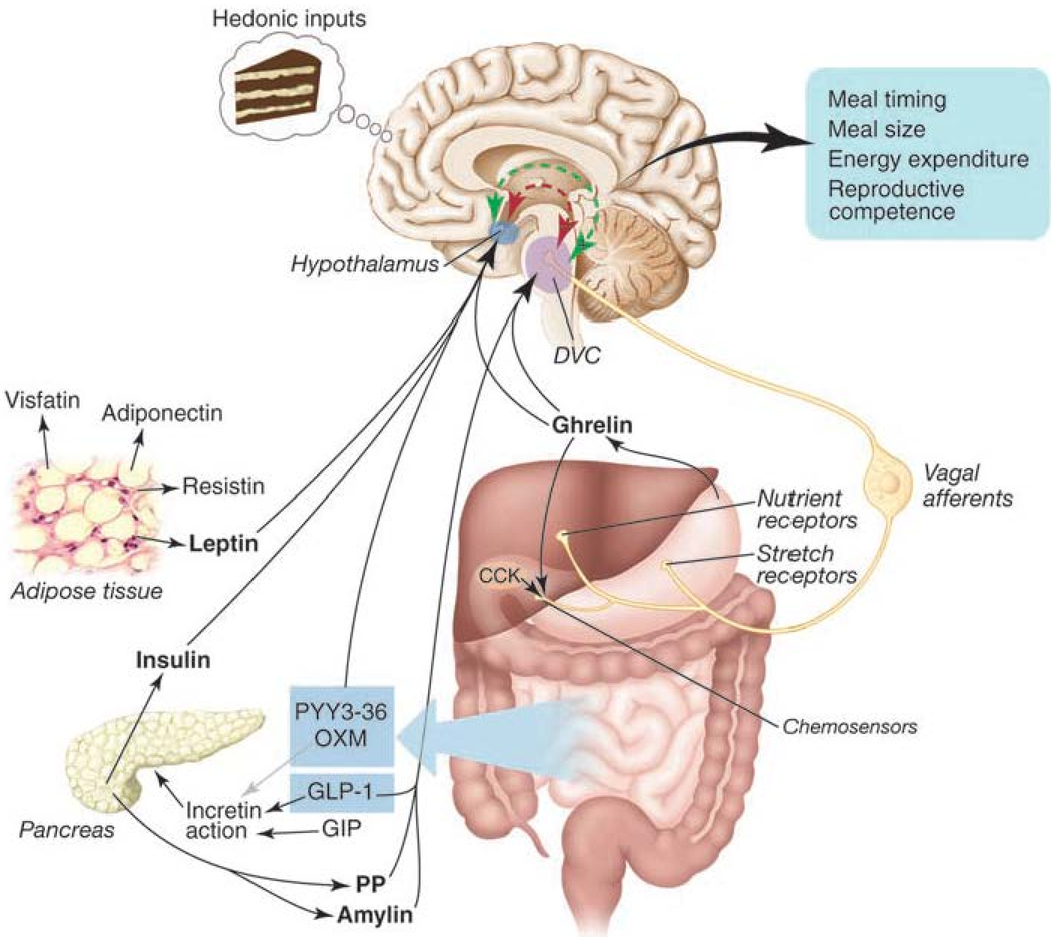

Figure 1. The gut and energy balance: visceral allies in the obesity wars. Badman MK, Flier JS. Science. 2005 Mar 25;307(5717):1909-14.Reproduced with permission from the publisher.

More specific studies regarding how gastrointestinal hormones affect our dietary habits and weight regulation have been performed since the 1990’s. (Table 1) (24, 25) Several signalling peptides and hormones have been investigated in regard to their roles in obesity and weight regulation. However, results have been inconclusive or widely different. Further studies are required regarding the possible involvement of gastrointestinal hormonal signalling in different weight loss methods. As surgical treatment options for morbid obesity have developed, attention has been directed to a possible mechanistic connection to the gastrointestinal signalling system. Previous studies have suggested changes in release patterns for GLP-1, PYY and ghrelin, indicating a possible correlation with food intake and weight control. This thesis will present a more detailed exploration of the behaviour of these gastrointestinal hormones.

Table 1. Examples of gastrointestinal hormones involved in the physiological response to food intake and their effects in brief

Hormone; abbreviation	Secretion from	Stimulus	Effect
Glucose-dependent insulinotropic polypeptide; GIP	K cells in the duodenum and jejunum	Food intake	Stimulates insulin secretion, is involved in fat metablism
Cholecystokinin; CCK	I cells in the small intestine	Gastric distention, food intake mainly fat and proteins	Inhibits gastric emptying and intestinal motility
Leptin	White fat cells	Circulatin levels In relation to adipose tissue	Reduce hunger
Oxyntomodulin; OXM	L cells in the small intestine, colon and pancreas	Caloric intake, Fat intake	Inhibits gastric emptying and gastric acid secretion
Pancreatic polypeptide; PP	F cells in pancreas	Caloric intake, exercise, hypoglycemia	Inhibits gastric emprtying, intestinal motility, excretion of bile acid and pancreatic enzymes

2.2.1 Glucagon-like peptide 1 (GLP-1)

GLP-1 is a polypeptide derived from the transcription product of the proglucagon gene. The active form of the peptide, GLP-1 (7-36), is secreted from the L cells, located mainly in the colon and small intestine. GLP-1 has a half-life of less than two minutes when in the circulation, due to degradation by dipeptidyl peptidase 4. Receptors for GLP-1 are found in the brainstem and the hypothalamus. (22, 24, 25) Plasma levels increase within minutes after food intake. (22, 24-27) GLP-1 has a stimulating effect on the beta cells in the pancreas, inducing insulin secretion. (28, 29) The peptide also slows gastric emptying and suppresses meal-induced secretion of gastric acid and pancreatic enzymes. (22, 30) Food intake decreases and satiety increases after peripheral infusions of GLP-1 in both humans and rodents. (22, 24-27, 31) Previous research strongly suggests that GLP-1 levels are lower in obese subjects when they are compared to lean subjects, but possible changes following weight loss are unclear. (31, 32)

2.2.2 Peptide YY (PYY)

PYY is a polypeptide present as PYY 3-36 and PYY 1-36. (22, 24, 30) Because of structural similarities, PYY is included in the pancreatic peptide family. PYY is released from the L cells in the small intestine, colon and rectum. (22, 24, 30) PYY receptors are found in the hypothalamus. (30, 33) Levels increase shortly after food intake. (22, 24, 30) PYY delays gastric emptying and increases absorption of fluids from the ileum and colon. (22, 24, 30) Injections of PYY can reduce food intake in short-term experiments, both in humans and in rats. (34-36) Levels after food intake are shown to be significantly lower in obese subjects compared to those of normal weight. (35, 37)

2.2.3 Ghrelin

Ghrelin is an oligopeptide produced mainly in the gastric mucosa but also in the mucosa of the duodenum, ileum and colon. (24, 25, 38-40) Ghrelin has a potent stimulating effect on growth hormone release from the pituitary gland. (24, 25, 38-40) The level of ghrelin in the blood is low in the fasting state, but increases distinctly before food intake and decreases shortly after ingestion. (22, 24, 25, 41) Peripheral administration induces increased food intake in both rodents and in humans. (22, 24, 25, 42, 43) The same variations in ghrelin levels are not seen in obese individuals. For example, the response to food intake is diminished in overweight subjects. (22, 24, 33, 44, 45) Conventional weight loss intervention is associated with increased levels of ghrelin for a 24 hour period, possibly as a physiological defence against starvation and weight loss. (22, 41, 46)

2.3 Energy expenditure

2.3.1 Definition

Total daily energy expenditure can be divided into resting energy expenditure (= basic metabolic rate), physical activity energy expenditure and postprandial energy expenditure or diet-induced thermogenesis (DIT). Total daily energy expenditure is the sum of the energy produced by the body regardless of its origin. Resting energy expenditure is the energy produced during rest, yet while awake, a long time after food intake. It represents about 60-70 % of the total daily energy expenditure. The postprandial energy expenditure is defined as the increase in energy production that occurs after food intake. Depending on the amount of food ingested, the postprandial energy expenditure represents about 10-15 % of the total energy expenditure. When the rise in energy expenditure (EE) after food intake is assessed in relation to the amount of energy ingested, the term “diet induced thermogenesis” (DIT) is normally used and the value is expressed as a percentage. DIT increases by the amount of energy ingested and is also shown to increase with body weight. Physical activity energy expenditure is defined as the extra energy produced by the body due to muscle activation. Physical activity energy expenditure can be divided into “exercise activity energy expenditure” which consists of the physical activity expended in our daily lives during work and training for example, and the “non-exercise activity energy expenditure” which depends on individual patterns of movements. These include the small, extra, unnecessary movements we make throughout the day.

2.3.2 Influencing factors

Energy expenditure (EE) is determined primarily by body mass, the proportions of fat and muscle mass, physical activity and food intake. (47, 48) A greater body mass produces more energy. Muscle mass consumes more energy than fat mass whilst EE decreases with increasing age. (49) In comparison to lean subjects obese subjects have higher total EE during a 24-hour period but a lower rise in EE as a response to food intake. (47-53) EE is associated with a variation in body mass where weight gain increases and weight loss decreases EE. (47, 48, 50, 51, 53) The decrease in EE after weight loss is even greater than would be expected in relation to the new body weight, indicating a decrease in EE solely due to the weight loss per se. The decrease in EE in response to weight loss is interpreted as an adaptive physiological mechanism to counteract and protect the body from losing weight during starvation. (48-51, 53-56) The change in EE after weight loss remains for a long time after the change in weight, at the new, stable, body weight but also after weight has been regained. (48-51, 53-56) A repeated cycle of weight loss and weight gain, as experienced by many obese individuals, can thus make it increasingly difficult to achieve a stable, low, healthy weight.

2.3.3 Measuring methods

Measurements of EE (energy expenditure) can be made using various methods and there is a great diversity in the accuracy of different methods. The term *calorimetry* (from the Latin word *calor*) refers to measuring EE.

In direct calorimetry, heat radiating from the body is measured with devices placed on the skin. However, variation in the temperature of different parts of the body, external temperature etc. can easily influence the results.

Indirect calorimetry is based on exact measurements of oxygen consumed and carbon dioxide produced, reflecting the caloric effect of oxidation during metabolic and physiological processes. The "gold standard" method for indirect calorimetry is a 24-hour measurement process, conducted in a small sealed room called an energy chamber. (57, 58) Indirect calorimetry can be assessed over shorter times using a device, called a hood, placed over the head. The principle of analysis is the same as in the energy chamber but measurements are made only during shorter periods of time and not during food intake and when the subject is moving.

The "doubly labelled water" (DLW) method is considered to be the most exact method for determining energy expenditure and is considered the reference method for validation of other techniques. The DLW method uses isotopes of hydrogen and oxygen to measure the exact metabolism for longer periods of time. The technique is seldom used due to the high costs of the isotopes. (58)

2.4 Non-surgical obesity treatment

Ever since overweight and obesity were recognized as health hazards there have been publications suggesting ways to lose weight in the best and most efficient manner. (2, 4) Water fasting or total fasting, warm and cold baths, increased physical activity and ad lib eating in combination with vomiting are the main components of historical weight loss methods. (2, 4) Modern obesity treatments are based on the fact that weight balance depends on equilibrium between energy intake and energy expenditure. Hence different methods aim at decreasing energy intake and increasing energy expenditure, or a combination of the two. (1, 59-61) The number of weight-loss methods, both in health care systems and promoted by the industry, increase steadily to keep pace with the current obesity epidemic. This clearly illustrates the unsuccessful battle between weight control ambitions and our constitutional preference for a more indulgent life in an environment of readily available, energy-rich food. (1, 2, 4)

Several pharmaceutical treatments have been used but many of them have been withdrawn from the market due to severe side effects. Some drugs, including amphetamine, were shown to be effective but were associated with abuse and addiction. (62, 63) Other drugs, like Rimonabant, a cannabinoid receptor antagonist, addressed the reward system in the central nervous system (CNS) and suppressed appetite. However, Rimonabant was withdrawn due to side effects such as depression and suicide. (62, 63) Sibutramin was a drug initially developed for other conditions but was also found to cause weight loss. The drug reduced the sensation of hunger and it mimicked the effects of antidepressant medication, lowering the reuptake of serotonin, noradrenalin and dopamine. The drug was withdrawn due to cardiovascular side effects, with increases in blood pressure and heart rate resulting in an increased frequency of cardiovascular events. (62, 63) Orlistat is an example of a drug reducing intestinal fat absorption, resulting in modest weight reduction. However, a large number of subjects report substantial gastrointestinal side effects. (62) Other pharmacological substances are in clinical trials both as single and combination treatments. (63) Many of them address the CNS and aim at lowering the sensation of hunger. (63)

Short-term results up to one year after comprehensive interventions show that patients, at best, can obtain a total weight loss of 15% (60, 62-66). However, long-term results of conventional therapies, over 10 to 15 years, are in general discouraging, showing a total weight loss of 0 to 5 %. (60, 62-66) Weight loss is greater when combining decreased energy intake, increased physical activity, behavioural therapy, frequent monitoring and extensive personal support. (59-61, 64, 66-70) Cognitive behavioural therapy also improves long-term weight-loss maintenance (67, 70) The best results are seen in patients with good initial weight loss, overall better behavioural self-control, better coping strategies and good social support. (70) Data confirms that it remains difficult to fight the strong physiological urge to over-eat. Weight maintenance is difficult and many people regain weight after perceived starvation during weight loss.

2.5 Bariatric surgery

Surgical treatment is currently the most effective treatment option for severe obesity. (19, 71-75) It is claimed that the first surgical treatment procedure for obesity was performed during the 1950s by Viktor Henrikson in Gothenburg. It involved a resection of a large part of the small bowel, creating weight loss through nutrient malabsorption. Surgeons following in the footsteps of Viktor Henrikson developed new surgical techniques searching for effective weight loss effect in combination with a low complication rate. Not surprisingly, there was a high frequency of adverse events during the first decades of development. (76)

Bariatric surgery was initially performed with open surgery but for several years most bariatric procedures are performed using laparoscopic surgery, making for shorter hospital stays and quicker recovery. Hans Christian Jacobaeus from Sweden was one of the pioneers of laparoscopic surgery in the early years of the 20th century.

Weight loss after bariatric surgery is a result of many mechanisms, all of which we have not been able to explain. Some techniques work through restricting food intake by reducing the volume of the stomach. Such a restriction is meant to decrease the volume of the meals ingested, resulting in lower energy intake. Other techniques reduce intestinal caloric uptake by changing the anatomy of the gut and reducing contact between the absorptive part of the intestine and the nutrients. Some older, as well as currently- used, bariatric techniques are described below.

2.5.1 Restrictive techniques

VBG

The vertical banded gastroplasty (VBG) was developed in the 1980s. The technique includes the creation of a stomach pouch by stapling. The outflow of the pouch is limited to a narrow channel reinforced with a band. The primary mechanism of action is considered to be the mechanical restriction of food intake, causing reduced meal size. Despite compensatory decreased energy expenditure, there is evidence of weight loss after VBG surgery. (77) Retrospective studies show weight loss of up to 57 % over 5 years, 38 % over 6 years and 16 % over 10 years. (71, 74, 75, 78) However, other studies show lower weight loss, and weight regain, at follow ups from one to approximately 15 years after surgery. (74, 79-82) There is also data indicating a substantial need for revisional surgery after this technique, due to food intolerance and vomiting or weight regain. (71, 74, 75, 81-83) Less than 1 % of the bariatric procedures performed in the world are currently VBG. (84) Figure 2.

Gastric banding

Gastric banding surgical techniques evolved during the 1970's with the aim of providing a less invasive approach to restricting food intake. The band is placed round the upper part of the stomach, forcing the patient to eat smaller portions. Initially, bands with a fixed diameter were used. The bands used today are usually adjustable, enabling an optimal tightening of the stomach passage without causing dysphagia. Long-term data indicates a 40 % excess weight loss. Gastric banding is followed by improvement in co-morbidities of up to 50 % resolution and 30% amelioration of type-2 diabetes, as well as improved blood lipid levels. (71, 85) In 2011 around 20 % of all bariatric procedures were gastric banding, but recently numbers have declined. (84) Figure 3.

Sleeve gastrectomy

In a sleeve gastrectomy a major part of the greater curvature of the stomach is removed, leaving only a narrow tube or sleeve along the lesser curvature. The mechanism of action is the restriction of food intake through a decrease in gastric volume. The pylorus function is left intact, enabling a normal outflow of gastric content. Weight loss is shown to be up to 60 % of excess weight, diabetes resolution occurs in up to 80 % of diabetic patients and amelioration in sleep apnea is found in 80 % of the affected patients. (86-88) Thirty per cent of all bariatric procedures worldwide are sleeve gastrectomy. (84) Figure 4.

2.5.2 Malabsorptive techniques

The mechanism of action of these techniques includes malabsorbtion of calories and nutrients. Initially, the most commonly used technique was the jejuno-ileal shunt where nutrients were in contact with only 75 cm of intestine.

Biliopancreatic diversion (BPD) and Duodenal Switch with biliopancreatic diversion (DS)

The BPD surgical technique developed by Nichola Scopinaro comprises a resection of the lower part of the stomach and a rearrangement of the flow of nutrients and digestive juices in the gut. The duodenum and the inflow of pancreatic juice and bile acid are left intact. The digestive enzymes and digested food merge further down the gut in a 50-100 cm small common limb. DS evolved during the 1990's as a variation of the original BPD technique, aimed at reducing the number of stomal ulcers. In this technique the stomach is reduced in size with a vertical resection, and parts of the antrum and the pylorus are preserved. The food is bypassed through a bowel loop, an alimentary limb, from the proximal duodenum, above the papilla of Vateri, to the distal small bowel. The food and the digestive enzymes, from the liver and the pancreas, thus mix in a short distal common limb.

Both DSBD and DS are very effective, with general results of 70 % excess weight loss and 40 % total weight loss. Amelioration in co-morbidities is high. There is over 90 % resolution of diabetes and 90 % clear improvement of sleep apnea. Cardio-vascular risk factors are further lowered by the amelioration of blood-lipid levels in almost all patients. (71, 89, 90) Only a few per cent of all bariatric procedures in the world are DSBD or DS. (84) Figure 5.

Figure 2. Vertical banded gastroplasty; VBG.

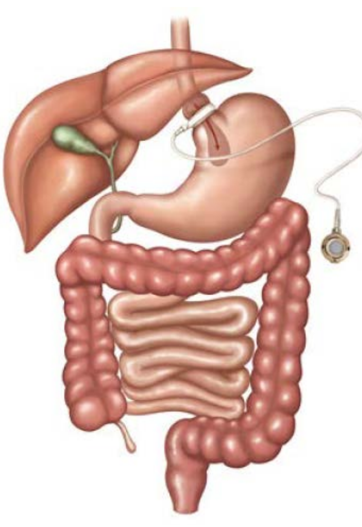

Figure 3. Gastric banding; GB.

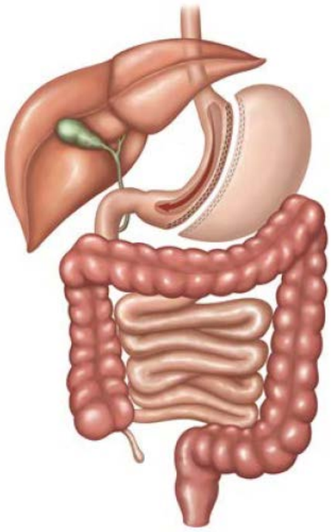

Figure 4. Sleeve gastrectomy.

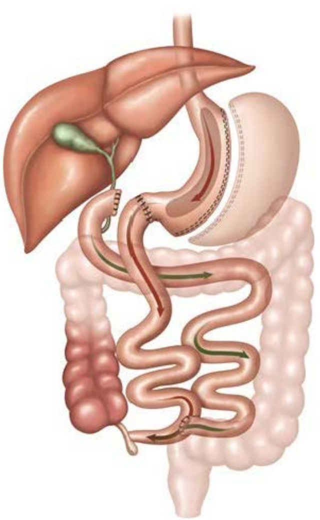

Figure 5. Duodenal switch with biliopancreatic diversion; DS.

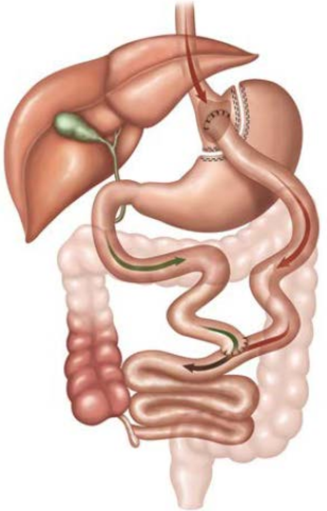

Figure 6. Gastric bypass.

2.5.3 Techniques with mixed mechanisms of action

Gastric bypass

The gastric bypass technique was developed during the 1960's when Iowa-based surgeon Edward Mason observed that patients lost weight after the Bilroth II operation for ulcer disease. He used a similar surgical technique but did not resect the excluded stomach, and he could demonstrate a substantial postoperative weight loss. However, as this was a major surgical procedure and intensive care was not very well developed, the procedure was associated with substantial postoperative mortality.

The surgical technique for gastric bypass has evolved over decades and today it is normally performed laparoscopically. The major part of the stomach is separated from a small stomach pouch of approximately 10–25 mL, just below the cardia. The small intestine is divided some 50–60 cm from the duodeno-jejunal junction and the distal part of the jejunum is brought up and is connected to the small gastric pouch. This alimentary limb, or "Roux limb", includes the small gastric pouch receiving food from the oesophagus and the first 100–150 cm of jejunum. The biliopancreatic limb from the disconnected remnant of the stomach is connected to the jejunum 100-150 cm down, in order to allow gastric juice, bile- and pancreatic fluid to mix with the ingested nutrients. In summary, the food passes almost directly from the oesophagus down into the small intestine and meets the digestive enzymes further down in the gastrointestinal system, in the common limb. (76, 91) Figure 6.

Gastric bypass is one of the most effective bariatric techniques. Clinical studies demonstrate between 30 and 40 % total weight loss one to two years after surgery and 20 to 30 % total weight loss up to ten years postoperatively. (71, 73, 74, 80) The gastric bypass technique has a favourable outcome regarding resolution of comorbidities with 90 % improvement or total resolution of type 2 diabetes, over 90% improvement rate of blood lipid levels, almost 90 % amelioration rate of hypertension as well as a reduced long-term risk of cancer in females. It is also associated with a lower rate of cardiovascular events. (71, 72, 74, 75) There is converging data on changed eating patterns after gastric bypass surgery, with reduced fat and higher fruit intake. (92, 93) Close to 50 % of all bariatric procedures in the world are gastric bypass procedures. (84)

It was initially believed that the gastric bypass worked through malabsorption because of the shortened food passage through the small intestine, in combination with food restriction caused by a smaller stomach and a narrow passage through the gastroentero-anastomoses. However, recent studies reveal that there might be other reasons underlying the effective weight loss and amelioration of co-morbidities associated with this technique. Some studies have indicated that the gastric bypass reduces weight effectively without the gastric pouch or the gastroentero-anastomosis. (94) It is possible that the gastric bypass technique work through changing hunger and satiety signalling and through affecting the energy expenditure. (22, 24, 30, 82, 95, 96)

2.6 Body composition, neuro-hormonal modulation of behaviour and energy expenditure after bariatric surgery

2.6.1 Lack of long-term studies of bariatric surgery

Bariatric surgery is considered to be very effective yet there are few long-term (over 5 years) controlled or randomized studies comparing different surgical techniques regarding weight loss outcome and mechanisms of action. (71, 72, 75) The gastric bypass, one of the most frequently used and most effective procedures for weight loss and health improvement, is probably the bariatric technique with the least clear mechanisms of action. To explore the physiological changes involved in gastric bypass it would be valuable to compare it with techniques with other mechanisms of action. VBG and gastric banding are known to have positive effects on the restriction of food intake, causing weight loss mainly through decreased energy intake.

2.6.2 Body composition after bariatric surgery

High-quality investigations into the impact of bariatric surgery on body composition are sparse. Moreover, there are very few long-term studies after surgery, i.e. more than three years, comparing the impact of different surgical techniques on body composition. (97) Some studies show less loss of muscle mass after gastric banding compared to gastric bypass technique (97) and others show a better preservation of muscle mass in the gastric bypass technique compared to restrictive techniques. (92)

2.6.3 Gastrointestinal signalling after bariatric surgery

GLP-1 after gastric bypass and VBG surgery

Gastric bypass surgery has been shown to increase postprandial levels of GLP-1 in comparison both to obese subjects and lean subjects. (27, 98, 99) No such effect on GLP-1 levels has been shown after restrictive bariatric surgery, such as VBG and gastric banding. (27)

PYY after gastric bypass and VBG surgery

Gastric bypass surgery has been proven to increase postprandial levels of PYY. A short time after surgery, studies show an increase in the postprandial levels to levels exceeding those seen in subjects of normal weight. (27, 28, 100) No changes have been demonstrated after VBG or gastric banding surgery.

Ghrelin after gastric bypass and VBG surgery

Studies of ghrelin levels after gastric bypass surgery show widely differing results - decreased levels, increased levels and unchanged levels. (22, 41, 46, 101-106) No changes in ghrelin in response to food intake after restrictive surgery have been observed. (106)

2.5.4 Energy expenditure after bariatric surgery

Only a few studies have addressed the impact of gastric bypass surgery on human energy expenditure and the results vary. (96, 107, 108) These studies have assessed energy expenditure a short time after surgery and while resting, using respiratory hoods. In studies using state-of-the-art energy chambers rats reveal a convincing increase in energy expenditure after gastric bypass surgery both over a 24-hour period and after food intake. (109, 110) There have been few investigations into energy expenditure in patients after VBG surgery but it has been reported to increase a short time after the operation. (77, 92)

3. AIMS

General aim

The objectives of this thesis are to increase knowledge of long-term outcomes of gastric bypass surgery and to elucidate some of the associated mechanisms of action.

Specific aims

1. To evaluate long-term clinical outcomes after gastric bypass surgery in terms of weight control and the need for remedial surgery

2. To investigate long-term effects of gastric bypass surgery on body composition

3. To characterise meal-induced changes in the appetite-regulating hormones GLP-1, PYY and ghrelin after gastric bypass surgery

4. To assess whether preoperative levels of GLP-1 and PYY in fasting and as a response to a standard meal, predict weight outcome after gastric bypass surgery

5. To describe long-term effects of gastric bypass surgery on energy expenditure compared to the restrictive VBG technique

4. METHODOLOGICAL CONSIDERATIONS

4.1 Ethics

All studies were performed according to the principles of the Declaration of Helsinki. Ethical approvals were obtained from the local Ethics Committee of the University of Gothenburg, Sweden (I, parts of II & III), the Regional Ethical Board in Gothenburg (IV) and The Research and Ethics Committee at Musgrove Park Hospital, Taunton, England (parts of II). All patients signed an informed consent form after receiving oral and written study information.

4.2 Study design

4.2.1 Paper I

Paper I describes a follow up of a prospective clinical trial, randomized between gastric bypass and VBG surgery. The paper describes an intention-to-treat-analysis performed six years after randomization and a per protocol analysis after another 3 to 4 years.

Initially 100 patients were enrolled for randomization but 18 patients declined. The remaining 82 were randomized and included in the trial. (92) Six years after inclusion in the study 66 patients (80.5 %) of the 82 randomized patients were investigated; 30 gastric bypass and 36 VBG patients. Five patients (6 % of 82 patients) were lost to follow-up, one in the gastric bypass group and four in the VBG group. Nine patients declined participation (gastric bypass n=4 and VGB n=5). Two patients from the gastric bypass group had died.

At the follow-up six years after surgery the primary endpoint (BMI) was analysed according to the intention-to-treat model. Furthermore, the patients having their original surgical construction (VBG and gastric bypass, no re-operations allowed) were invited to assessment of body composition with DEXA, meal-induced GLP-1, PYY and ghrelin liberation and dietary habits, by questionnaire. The six-year follow-up also included a survey of the frequency of conversion surgery with an additional follow-up conducted in mean 10.2 years after randomization. This was based on hospital records (the latter with follow up rate of 95 %).

<u>Comment:</u> The follow-up rates, both at six years (68/82 patients = 83 %) and 10.2 years (78/82 patients = 95 %) after surgery, can be considered high in comparison to most long-term follow-up studies. The assessments of body composition, gastrointestinal hormones and dietary intake at six years after randomization were performed in order to analyse the long-term physiological effects of the two surgical methods. Only patients with their original surgical construction were therefore invited to join the study. Not all patients participated in the subgroup analyses and for this reason the results have to be considered in the context of being obtained from a selection of the original study population.

4.2.2 Paper II

Paper II presents three sub-studies describing the hormonal gastrointestinal signalling as represented by GLP-1 and PYY before and after gastric bypass surgery. Sixteen patients were assessed preoperatively regarding the hormonal response to a standard meal, and then 2, 4, 7, and 42 days after surgery. A cross-sectional cohort analysis was made in another group of gastric bypass patients

25 months after surgery, comparing hormonal signalling in patients having good (n=13) and poor (n=7) weight loss. The third study in paper II is a cohort study comparing satiety, food intake and response of GLP-1 and PYY in patients having undergone gastric bypass or gastric banding surgery. Patients were assessed on two occasions in a double-blind trial using saline or octreotide injections as pre-treatment before meal provocation and gut hormone assessments. Octreotide is a peptide that mimics the natural hormone somatostatin. The rationale was to inhibit the release of GLP-1 and PYY and analyse potential principal differences in dietary intake of subjects who had experienced the two different surgical techniques; gastric bypass and gastric banding surgery

Comment: The three sub-studies utilized similar surgical procedures. Standard meals were the same and the collection of samples was performed and handled according to the same protocols. Moreover, all analyses of GLP-1 and PYY were performed at the same laboratory and by well-validated methods. Food intake, levels of satiety and levels of GLP-1 and PYY during placebo conditions and after octreotide injections were investigated. Somatostatin is an inhibitory hormone with multiple effects on gastrointestinal functionality. It cannot be ruled out that other physiological changes had some effect on the results seen in the study.

4.2.3 Paper III

Paper III is a prospective cohort study examining whether hormonal satiety-signalling, as represented by release of GLP-1 and PYY, can predict weight loss after gastric bypass surgery. Patients on the waiting list for gastric bypass surgery at Sahlgrenska University Hospital, Gothenburg, were asked to participate. Forty-three subjects agreed to participate and were invited to a study visit involving an assessment of BMI. Plasma levels of GLP-1 and PYY were also measured both in fasting and postprandially over 180 minutes after a 400 kcal standard meal. The visit was conducted before the mandatory preoperative weight reduction. At the second study visit, in mean 16.2 months after surgery, at a period of individual weight stability, the patients' BMI was measured. Data were analysed for correlations between preoperative hormone levels and postoperative BMI changes.

Comment: The study group was representative in regard to age, gender distribution and preoperative BMI both in comparison to the patient population of the clinic as a whole, and to the international gastric bypass population. Exclusion criteria were diabetes type 2 and other severe co-morbidities in order to avoid factors which might complicate the main purpose of the study; namely, to correlate hormonal levels to weight development. The exclusion criteria caused our study group to be healthier than the general gastric bypass population.

4.2.4 Paper IV

Paper IV is a cohort study comparing energy expenditure 9.4 years (mean value) after surgery using a subset of gastric bypass and VBG patients from the randomized clinical trial described in paper I. The last available (not re-operated) female VBG patients (n=7) were matched with gastric bypass patients from the same study population regarding gender, preoperative and postoperative BMI as well as for resting energy expenditure before surgery (n=7). To be eligible, patients had to be weight-stable and to have taken standard vitamin and mineral supplements for at least three months before the study visit. They were carefully instructed to keep to their regular, individual, stable diets the week before and to eat a standardized meal the evening before the visit.

The study visit procedure included a 24hour stay in an "energy chamber". This was a small room resembling a hotel room. There, energy expenditure was measured in near-normal living conditions, using indirect calorimetry based on oxygen consumed and carbon dioxide produced. In the morning following an overnight fast, and before entering the chamber, the weight and height of each subject was assessed. Body composition was measured using DEXA (dual energy X-ray absorptiometry) Blood samples were collected for free fatty acids, HDL, LDL, TSH, free T4, FSH, HbA1c, iron and creatinin. In addition, meal-induced GLP-1 and PYY liberation was assessed and the patients filled in a three-month recall questionnaire regarding their eating habits.

During the chamber visit patients received standardised meals and performed activities according to a predefined protocol. Figure 7, for details see IV.

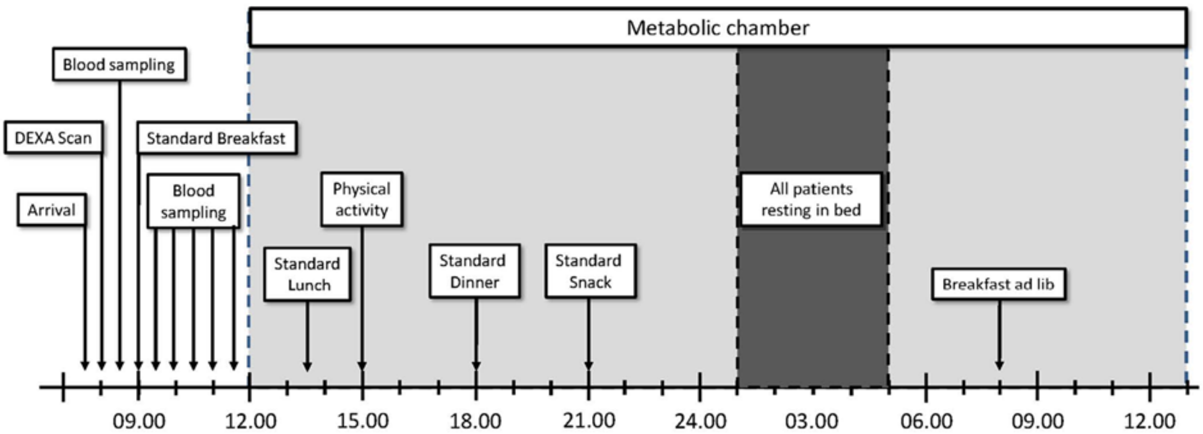

Figure 7. Protocol during study visit for assessment of body composition, gastrointestinal hormones, other biochemistry and energy expenditure.

Comment: Analysing 24- hour energy expenditure by indirect calorimetry in a whole body chamber is considered the "gold standard" method. The only method considered superior is the direct measurement of the metabolism using "doubly labelled water" in free living conditions,, but that type of measurement is very costly and with limited availability. (57, 58, 111) The energy chamber used in the present thesis project is considered to be of very high quality and with high measurement sensitivity. Due to the algorithms developed during the construction of the chamber (including data noise suppression, gas flow stability, constant humidity and temperature, and high sensitive gas sensors with trend identification) the data extracted is very reliable both during 24-hour measurements and over shorter periods of time. (57)

The two groups of study subjects were included in a randomized clinical study comparing gastric bypass with VBG surgery (I). The VBG-study patients available after nine years were very few (n=7) and therefore carefully matched with patients in the gastric bypass treatment group with regard to BMI, body composition and preoperative resting energy expenditure.

4.3 Surgical interventions

Gastric bypass and VBG were performed laparoscopically as previously described. (91) The gastric bypass technique included a small gastric pouch (10-20 mL) connected to the jejunum in an antecolic-antegastric Roux-en-Y construction. (112) In paper I, III and IV the length of the Roux-limb was 75 cm and the entero-entero anastomosis was created 30 cm distal from the ligament of Treitz. (91) In paper II the length of the Roux-limb was 100 or 150 cm (for patients with BMI below 50 kg/m^2 and above 50 kg/m^2 respectively) and the entero-entero anastomosis was created 50 cm distal from the ligament of Treitz. The VBG technique included a small gastric pouch (10-20 mL) and a separated vertical staple line. The gastric pouch outlet was reinforced with a 5.0 cm pre-stretched Gore-Tex band. (83) (I, IV)

Comment: The surgical methods used in the studies can be considered representative of the routine procedures performed in surgical departments during the time period. Weight loss after both gastric bypass and VBG surgery resembles published results from other cohorts. (71, 73, 113)

4.4 Assessments

4.4.1 Body composition and overweight

Weight measurements to the nearest 0.1 kg were performed according to a calibrated scale with patients in light clothing after an overnight fast. Height was measured to the closest 0.5 cm by a wall-mounted standard stadiometer. (I, II, III, IV) Body composition was recorded using dual energy X-ray absorptiometry (DEXA), analysing muscle mass, fat mass and bone mass as well as bone density. The technique uses X-ray in low doses. The radiation dose from a DEXA examination is less than 0.002 msV which falls far below annual background radiation of approximately 1 msV, as well as the dose from a normal chest X-ray of around 0.1 msV.

Comment: Different techniques exist for measuring body composition and they have various degrees of accuracy. Impedance measurements by bioelectrical impedance analysis (BIA), bio impedance spectroscopy (BIS) or multi-frequency BIA, are all based on analysing the electrical conductivity of the body which varies depending on the proportions of muscle and fat mass. The advantages of the BIA technique are the price and portability of the equipment and also that the analysis takes a short time and is easy to perform. (114) However, measurement quality is generally bad with low precision and reproducibility. DEXA, on the other hand, is considered the best possible method, both as a clinical tool and for research purposes. Because of it relatively high degree of accuracy this applies both to the measurement of muscle and fat mass as well as to evaluations of bone mass and density. Examinations are more expensive in comparison to impedance measurements and are dependent on skilled personnel performing the examination. (114, 115)

4.4.2 Blood sample analysis

GLP-1, PYY and ghrelin analysis

Blood samples for the gastrointestinal hormone analysis of GLP-1, PYY and ghrelin were collected in tubes containing EDTA and aprotinin; 200 kallikrein inhibition units per mL blood. After ten minutes centrifugation at 3100 rpm serum samples were stored in minus 80 degrees Celsius until analysis. The samples were thawed immediately before the assay. (Paper I, II, III and IV)

GLP-1 was analysed by RIA, using an antibody produced by a rabbit, which cross-reacts fully to GLP-1 peptide. A ^{125}I-labeled GLP-1 was used as the antigen. The assay was left for incubation for five days. After separation, concentration differences of 0.75 pmol per litre plasma could be detected with 95 % confidence. The inter and intra assay coefficients of variation were under 10 %. (29)

A PYY analysis of both PYY3-36 and PYY1-36 was performed with a RIA developed in-house. The antibody, produced in a rabbit as a reaction to synthetic porcine PYY, was allowed to react with a ^{125}I-labeled PYY. The assay detected changes of 2 pmol per litre plasma with 95% confidence, and with an intra-assay coefficient with a variation of 5.8 %. (35)

Ghrelin analysis was performed in duplicate using a RIA developed in-house, and with a commercial antibody (SC-10368, from Santa Cruz Biotechnology, Inc., Santa Cruz). This is a goat polyclonal antibody to an internal region of the human ghrelin. The antibody cross-reacts fully with human acylated (active) and des-acylated (inactive) ghrelin. The antigen used for the assay was ^{125}I-labeled ghrelin. After three days of incubation the assay was analysed. The assay detected changes of 25 pmol/litre plasma with 95% confidence, and inter and intra assay coefficients with variations of 5.5 and 10.1%, respectively. (116)

Biochemistry

Samples, other than gastrointestinal hormones in paper IV, were all analysed by the Central Laboratory at Sahlgrenska University Hospital, Gothenburg. The methods of analysis are accredited according to international standards (ISO) 15189.

4.4.3 Dietary intake

A questionnaire was used to assess dietary intake (I & III). The questionnaire was originally developed for the "Swedish subjects study" (SOS-study) and was validated in a larger group of patients. (117) The questionnaire was designed to collect information on eating habits regarding food choice and meal patterns during the previous three months. The data was transferred to a computer program for analysis. Data output consisted of the energy, protein, carbohydrates, fat, mineral and vitamin content of the total amount of food ingested, as well as for food subgroups such as cooked meals, sandwiches, cookies, dairy products etc.

Comment: Assessing dietary intake is complicated. Several questionnaires have been developed for this purpose but the accuracy of the results depends on the quality of the instrument and the compliance of study subjects. The questionnaire used in paper I and III is considered a high-quality tool with high validity and reliability. Nevertheless, while interpreting the results, it is important to take into consideration that the questionnaire is validated only for larger groups of patients (n> ≈50) and that results can include both over- and underestimations. Due to the fact that the questionnaire is validated only for larger groups than our study groups, there is a risk of type 2 errors in our application.

4.5 Statistics

In all studies the conventional $p<0.05$ was used as the statistical rejection criterion. If nothing else is stated, data is presented as mean values and confidence intervals.

Data in papers I, II and VI was considered to be normally distributed and therefore parametrical analysis was used. Comparison of data between groups was made using two-sample students´ t-test. In paper III, data was examined for normal distribution by Shapiro-Wilk's and Kolmogorovs-Smirnov's tests, and was also assessed for skewness and kurtosis. Non-parametric tests were used as data was not normally distributed. Wilcoxon signed-rank test was used to compare BMI before and after surgery and correlations were calculated by Spearman's rank correlation test.

5 RESULTS

5.1 Long-term clinical outcomes after gastric bypass surgery (I)

5.1.1 Primary outcome variables: weight loss and remedial surgery

Out of the 82 patients enrolled in the clinical study 37 were randomized to gastric bypass and 45 to VBG surgery. (Fig 8) There were no significant differences between groups regarding age, gender or body composition at inclusion. (92, 112, 118)

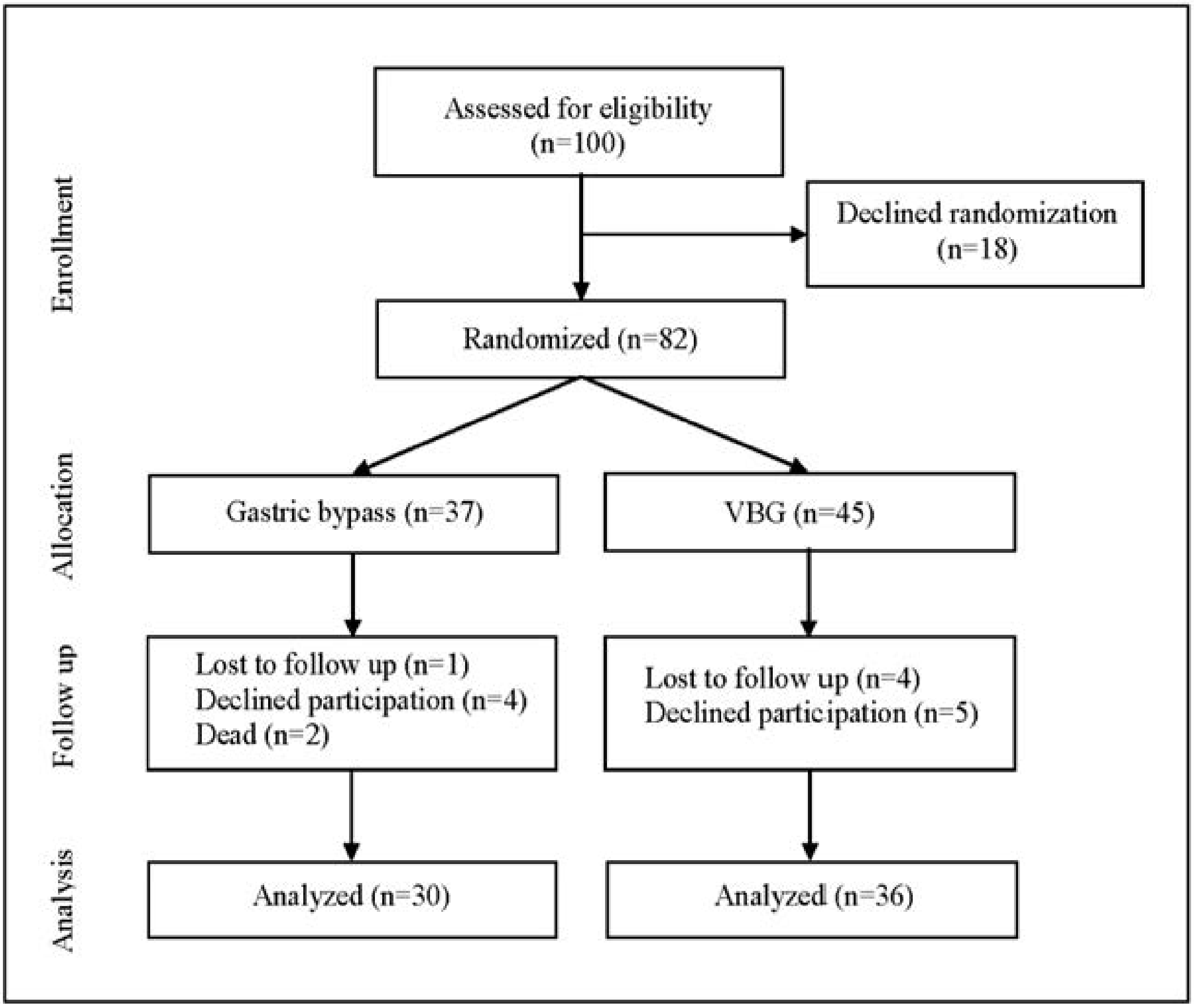

Figure 8. Consort flow diagram; paper I.

The BMIs of 66 patients (80 % of the originally randomized study population) recorded during a study visit at six years after surgery were used in an intention-to-treat analysis. (Fig 8) The gastric bypass group (n=30) had a significantly (p=0.036) lower BMI compared to the VBG group; in mean (CI) 30.3 kg/m^2 (28.6 to 32.0) versus 32.9 kg/m^2 (31.3 to 34.5). Fourteen of the VBG patients (31 %) had undergone conversion to gastric bypass due to negative symptoms related to food intake, namely dysphagia, pain and vomiting. Conversion surgery had been performed in mean 2.8 years (1.9 to 3.8) after primary surgery.

A per protocol analysis with a mean follow-up time of 10.2 years and based on hospital records, included 95 % of the initially-enrolled patients. Twenty-seven of the 45 VBG patients had by this time been converted to gastric bypass due to food-intake related discomfort. The conversions had been performed in mean 5.7 years (range 0.2 to 10y) after the primary operation. A further 13 patients (19 %) were planned for conversion surgery for the same reason. At this follow-up there was no significant difference between groups regarding BMI: the gastric bypass patients had a BMI of in mean (CI) 30.9 kg/m^2 (28.8 to 33) and the VBG patients of 34.1 kg/m^2 (31.6 to 36.5). The converted patients (from VBG to gastric bypass) had a BMI of 32.3 kg/m^2 (30.3 to 34.3). None of the differences was significant. For total weight loss and excess weight loss, please see Table 2.

Table 2. Total weight loss and excess weight loss in percentage for gastric bypass, VBG and converted patients from intention to treat analysis 6 years and per protocol analysis 10.2 years after primary surgery.

	6 years intention to treat analysis			10.2 years per protocol analysis		
	n	Total weight loss	Excess Weight loss	n	Total weight loss	Excess Weight loss
Gastric bypass	30	27.5 (23.3-31.7)	68.7 (58.8-78.5)	31	25.8 (21-30.5)	65.4 (54.1-76.7)
VBG	36	22.1 (18.5-25.8)	55.3 (46-64.6)	16	20.7 (16.2-25.2)	50.9 (39.2-62.6)
Converted				24	23.7 (19.9-27.5)	59.9 (49.9-69.9)

Values are mean percentage and confidence intervals within brackets.
There are no significant differences between values for any of the groups

There are plenty of studies in the literature demonstrating weight loss following bariatric surgery over the short term, usually with follow ups of between one and three years. However, prospective randomized trials targeting weight development over the longer term (more than five years) are rare. It should be noted that the weight loss after gastric bypass in the present randomized study was of the same order of magnitude as previously reported from non-randomized studies (69, 71-74, 80, 82, 119, 120) Furthermore, there are several studies showing good weight reduction after VBG, but generally these studies have a short follow-up period (71, 80).When studied over longer periods the effect of VBG appears to be less pronounced. (71, 73, 74, 78-80, 82, 119, 120) Six years after surgery, the VBG patients in the present study had a greater weight loss than those in other studies with long follow-up periods. The reason for this is probably related to the currently used intention-to-treat design, where several patients in the VBG group had been converted to the apparently more effective gastric bypass.

The patients converted from VBG to gastric bypass deserve some extra attention. In findings published elsewhere, final weight after conversion from VBG to gastric bypass due to weight regain resembles the results in the present study. (81, 121-125) However, the reason for conversion in the present study was not weight regain, but rather discomfort symptoms in association with food intake. Other studies have also demonstrated negative eating symptomatology before conversion, thus resembling what was reported in the present study. Other studies also demonstrate similar amelioration after conversion to gastric bypass. (81, 122, 124)

5.1.2 Secondary outcome variables: mortality, complications, dietary intake

Follow up at ten years showed that five patients who had had a primary gastric bypass operation had died. Reasons were heart failure, suicide, gynaecological cancer, malignant melanoma with complications, multi-organ failure after revisional surgery for a gastro-gastric fistula. One primary VBG patient who was converted to gastric bypass died from endocrine cancer.

The short-term complication rate was 5.7 % in the whole group after primary surgery, including three conservatively-treated minor bleedings and one case of pneumonia. Long-term complications after gastric bypass and primary VBG were absent except for internal hernias after gastric bypass operations and endoscopies for impacted food in the pouch after VBG. Three patients in the primary gastric bypass group (8.1 %) and one of the 24 patients converted from VBG to gastric bypass (4.2 %) needed reoperations due to internal hernias during the ten-year follow-up period. Long-term data from earlier studies over a larger number of patients shows a frequency of up to 12 % for internal hernia after laparoscopic gastric bypass surgery. (126, 127) The complication rate after conversion surgery in the present study was low in comparison to results from other studies. (81, 121-125) The short-term complication rate was 12.5 %, including three minor bleedings treated conservatively. The long-term complication rate was 16.7 % including one gastrogastric fistula, one stenosis of the gastroentero-anastomosis and two incisional hernias.

In a sub-group analysis, the total daily energy intake did not differ significantly between groups six years after surgery (gastric bypass n=15 and VBG n=15), as reported using a three- month dietary recall questionnaire. (117) The gastric bypass group had a daily intake of in mean 2346 kcal and the VBG group had an intake of 2833 kcal (p=0.165). Energy density was however lower in the gastric bypass group in comparison to the VBG group, 0.88 kcal/g and 1.11 kcal/g respectively (p=0.047). The proportion of energy intake as fat was lower in gastric bypass patients compared to the VBG patients, 33.6 % and 40.9 % respectively (p=0.013) whereas the proportion of energy from carbohydrates was higher in the gastric bypass group; 48.4 % vs. 42 % in the VBG group (p=0.043). No significant difference was seen between daily energy intakes from protein. Furthermore, the gastric bypass group ate significantly fewer desserts (p=0.007) and significantly more fruit and vegetables (p=0.003) than the VBG group.

Conclusion 1

ITT analysis supports a clinical strategy with the gastric bypass being the method of choice for treatment of morbid obesity, rather than VBG. The high demand for remedial surgery following VBG suggests that this technique should not be used in modern bariatric surgery. (I)

5.2 Effect of gastric bypass surgery on body composition (I)

Body composition was analysed in a sub-group of 17 gastric bypass and 14 VBG operated patients using Dual Energy X-ray Absorptiometry (DEXA). Adipose tissue loss was significantly greater in the gastric bypass group compared to the VBG group. (Table 3)

The gastric bypass patients lost significantly less muscle mass in comparison to the VBG patients, resulting in a significantly higher increase in the proportion of lean tissue mass in the gastric bypass group. (Table 3) In general, these results confirm the previously published body composition results from the same study population. One year after surgery, and compared to the VBG group, results showed a higher fat mass loss in the gastric bypass group and a better preservation of lean tissue mass in males. (92)

The gastric bypass patients exhibited a lower bone mineral content (BMC) compared to the VBG patients; in mean (CI) 2.69 kg (2.5 to 2.88) and 3.05 (2.85 to 3.24) (p=0.016). Bone mineral density (BMD) was also lower in the gastric bypass cohort; 1.15 g/cm3 (1.12 to 1.19) compared to the VBG group; 1.27 g/cm3 (1.23 to 1.31) ($p<0.001$). T-scores also differed significantly between groups; gastric bypass 0.18 (-0.21 to 0.56) and VBG 1.41 (0.9 to 1.92) ($p<0.001$). One patient in the gastric bypass group had osteopenia with a T-score of -1.1. No patient had osteoporosis. Hence, the present six- year assessment did not deviate from the short-term results recorded one year after surgery. (92) When considering these results, it should be noted that none of the patients were prescribed supplementation therapy.

Conclusion 2

Gastric bypass surgery results in a better preservation of muscle mass and a larger loss of fat mass than after VBG surgery. (I)

Table 3: Changes in body composition 6 years after gastric bypass and VBG surgery comparing preoperatively. Included are only patients without any remedial surgery and with available baseline and 6 years data.

	Δ; Gastric bypass	Δ; VBG	p value
n (F/M)	17(13/4)	14(9/5)	
Total tissue (kg)			
All subjects	-29.1 -(31.3-27)	-20.6 -(22.8-18.5)	0.071
Female	-30.1 -(32.8-27.4)	-21.4 -(24-18.1)	0.144
Male	-26 -(28.8-23.2)	-19.9 -(23.4-16.4)	0.409
Lean tissue mass (kg)			
All subjects	-6,4 -(6.8-5.9)	-7.4 -(8.1-6.6)	0.412
Female	-6.1 -(6.5-5.6)	-6.3 -(7.1-5.6)	0.836
Male	-7.3 -(8.4-6.3)	-9.2 -(10.7-7.7)	0.532
% Lean tissue/Total tissue			
All subjects	9.5 (8.5-10.6)	3.8 (3.1-4.6)	0.009
Female	9.1 (7.8-10.4)	4.2 (3.1-5.2)	0.081
Male	10.9 (9.2-12.7)	3.2 (2.1-4.3)	0.033
Adipose tissue mass (kg)			
All subjects	-22.5 -(20.5-24.4)	-13.2 -(11.4-15)	0.026
Female	-23.7 -(21.3-26.1)	-14.6 -(12.1-17.1)	0.101
Male	-18.5 -(16.3-20.6)	-10.7 -(8.5-13)	0.142
% Adipose tissue/Total tissue			
All subjects	-10.1 -(11.2-9)	-4.4 -(5.2-3.5)	0.012
Female	-9.6 -(11-8.2)	-4.6 -(5.8-3.5)	0.092
Male	-11.6 -(13.5-9.8)	-3.8 -(5.1-2.6)	0.043
Bone mineral content (kg)			
All subjects	-0.31 -(0.35-0.27)	-0.08 -(0.12-0.04)	0.011
Female	-0.33 -(0.38-0.28)	-0.13 -(0.18-0.09)	0.072
Male	-0.23 -(0.29-0.17)	0.02 (-0.05-+0.09)	0.12
Bone mineral density (g/cm$^{2)}$			
All subjects	-0.08 -(0.08-0.07)	0.01 (-0.01-+0.02)	0.0002
Female	-0.08 -(0.09-0.07)	0.003 (-0.02-+0.02)	0.004
Male	-0.06 -(0.08-0.05)	0.01 (-0.002-+0.02)	0.038
Bone mineral density Z-score			
All subjects	-0.08 (-0.2-+0.05)	0.54 (0.38-0.71)	0.049
Female	-0.12 (-0.26-+0.03)	0.61 (0.37-0.85)	0.073
Male	0.05 (-0.29-+0.39)	0.42 (0.24-0.6)	0.506

Values are mean (confidence interval)

5.3 Meal-induced changes in appetite-regulating hormones after gastric bypass (I, II, IV)

Changes in gastrointestinal hormonal signalling with respect to ghrelin (thought to mediate hunger), GLP-1 and PYY (both hormones thought to mediate satiation/satiety) were analysed in 16 patients (11 females). Tests were carried out before gastric bypass surgery and two four, six and 42 days afterwards. Age and BMI at surgery were in mean 47.8 years and 49 kg/m^2, respectively. Blood samples were collected during fasting, 15 minutes after intake of a 400 kcal meal, and every 30 minutes thereafter for 180 minutes. Plasma levels of ghrelin, GLP-1 and PYY were analysed as AUC during the three hours after food intake. There were no significant differences in ghrelin levels on any of the days tests were made, compared to preoperative levels. However, postprandial levels of GLP-1 and PYY were significantly increased from the second day after surgery, and were maintained at higher than preoperative levels. Hunger and satiety were assessed using a visual analogue scale (VAS) while fasting, and at 60, 120 and 180 minutes after the test meal. Results were analysed as AUC after food intake. Both hunger and satiety changed significantly from day 2 after surgery. Satiety levels doubled and hunger diminished to more than half of the preoperative level.

GLP-1 and PYY responses to the 400 kcal standard meal were then stratified according to whether the patient had a good (lowest BMI tertil) or poor (highest BMI tertil) weight loss after gastric bypass surgery. This analysis was performed in mean 25.3 months after surgery. Patients with good weight loss (n=13) had a preoperative BMI of 44.1 kg/m^2 and a postoperative BMI of 25.1 kg/m^2. The BMI levels in the group with poorer weight loss (n=7) decreased from 46.6 kg/m^2 to 37.8 kg/m^2 postoperatively. Samples were collected while fasting and every 30 minutes for 180 minutes after the test meal described above. Interestingly, in the good outcome group, plasma levels of GLP-1 and PYY were 60 and 40 % higher, than in the group with poor outcome.

Energy intake, satiety and levels of GLP-1 and PYY after an ad lib meal were compared in groups with patients who had had gastric banding (n=6) and those who had a gastric bypass (n=7). The patients were offered an ad lib meal on two occasions. The hormone somatostatin was injected 30 minutes before eating on one visit, and saline on the other visit. The levels of GLP-1 and PYY, analysed as AUC over 90 minutes after food intake, decreased significantly after the somatostatin injection in both the banding and gastric bypass groups. However, the reductions in AUC for GLP-1 and PYY were greater in bypass patients. Energy intake increased and satiety was reduced after the somatostatin injection in the gastric bypass group (both $p<0.05$). There were no changes in energy intake or satiety after somatostatin injections in banding patients.

The long-term postprandial responses of GLP-1 and PYY were assessed at six and 9.4 years after surgery. At the six years follow up ghrelin levels was also assessed. Patients were included from the study randomizing patients to either gastric bypass or VBG surgery (I) and the same protocol with a 400 kcal mixed meal was used as mentioned above. The hormonal levels were assessed in fasting and after food intake as AUC, AUC above fasting level and as maximal postprandial response. Both at the six and 9.4 years follow up the postprandial levels of GLP-1 and PYY were significantly higher in the gastric bypass group compared to the VBG group. There were no significant differences in ghrelin levels between groups.

Conclusion 3

Gastric bypass surgery is strongly associated with exaggerated short and long-term postprandial responses of the gastrointestinal hormones GLP-1 and PYY. We could not define any surgery-specific changes in ghrelin concentrations. (I, II, IV)

5.4 Do preoperative levels of GLP-1 and PYY predict gastric bypass induced weight loss? (III)

Forty-three patients (F=25, M=18) scheduled for gastric bypass surgery were included in a prospective cohort study. Plasma concentrations of GLP-1 and PYY were analysed preoperatively when fasting and after food intake (a 400kcal standard meal, study protocol as described above). Patients had a mean preoperative BMI of 44 kg/m^2 which decreased to 30.3 kg/m^2 ($p<0.001$) at a weight stability point 16.2 months after surgery.

No significant correlations were found between postoperative BMI or weight change, and GLP-1 or PYY concentrations, either in fasting or in response to food intake (III). The plasma levels of GLP-1 and PYY have previously been shown to correlate to BMI in normal weight and overweight subjects. (32, 35, 128-131) However, no such correlations were found in the group of morbidly obese subjects in the present study.

Conclusion 4

A preoperative assessment of GLP-1 and PYY does not appear to be useful as a predictive tool for weight loss after gastric bypass surgery. (III)

5.5 The effect of gastric bypass surgery on energy expenditure (IV)

The recruitment of patients to this study was limited as only seven VBG female patients were available and willing to participate. These patients were matched with gastric bypass patients as discussed in the Methods section above. Despite the matching procedure it turned out that the gastric bypass group were older, 59.7 years (54.9 to 64.4) compared to 50.2 years (44.9 to 55.4) in the VBG-group (p=0.03). However, there were no significant differences regarding body composition. Following the 400kcal standard meal, levels of GLP-1 and PYY (expressed as AUC over 150 minutes) were significantly higher in the gastric bypass patients (p=0.0001 and p=0.0002, respectively). Moreover, the gastric bypass patients had a significantly higher HDL level in comparison to the VBG patients ($p<0.001$), otherwise there were no differences regarding biochemical variables.

As described in Methods, energy expenditure was assessed over 24 hours in a specially constructed “energy chamber”. Over the full 24-hour period the analyses showed a significantly higher energy expenditure in gastric bypass patients, in mean 16.98 cal/min/kg as compared to the VBG patients with 14.92 cal/min/kg (p=0.048). There was no significant difference between groups regarding energy expenditure during sleep.

Interestingly, after intake of a 600 kcal standard meal, energy expenditure became more elevated in the gastric bypass group (in mean +2.56 cal/min/kg) compared to the VBG group (+1.15 cal/min/kg) (p=0.028). (Figure 9)

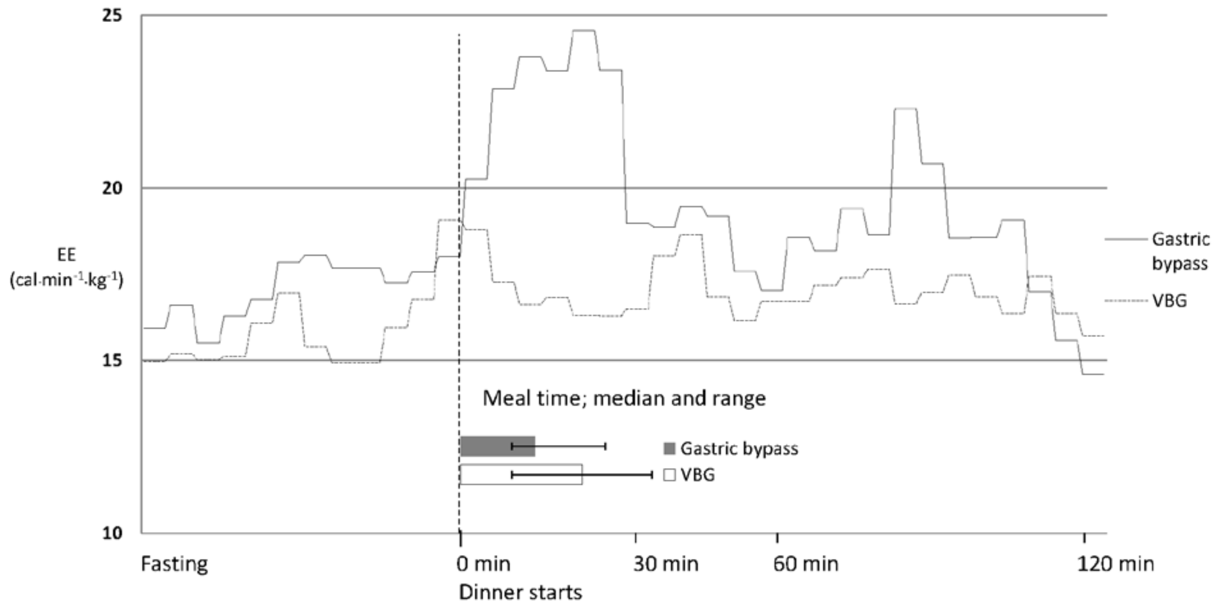

Figure 9. Energy expenditure before and after a 600 kcal standard meal for gastric bypass and VBG patients 9 years after surgery, analysed by indirect calorimetry in an energy chamber.

This data suggests that a gastric bypass operation exaggerates meal-induced thermogenesis and confirms previous observations in animal models of bariatric surgery (109, 110). To my knowledge, this is the first study regarding energy expenditure that, using the "gold standard" chamber technique, compares patients many years after their gastric bypasses or restrictive bariatric surgery. Studies made in rodents or in humans shortly after gastric bypass surgery indicate increased energy expenditure and the present study confirms that this is an effect that is maintained over time. Diet-induced thermogenesis is a well-known physiological phenomenon, but the reason(s) why the gastric bypass technique markedly influences this part of the energy homeostasis is obscure. In this study, VBG patients had been subjected to surgery and had lost a substantial amount of body weight but in contrast to gastric bypass patients the VBG patients had their gastrointestinal continuity intact.

In our study, in the gastric bypass group, there were no correlations between energy expenditure and total weight, or between lean tissue and fat tissue mass as other studies had showed a short time after surgery (96, 108). However, in the VBG group we could see the expected correlation between total tissue and energy expenditure. Energy expenditure decreases with age and the difference in age between the study groups should, if anything, have resulted in lower energy expenditure in the gastric bypass group compared to the VBG group. The physiological mechanisms mediating the findings are unknown and remain to be explained.

Conclusion 5

Gastric bypass surgery is associated with a higher meal-induced thermogenesis than VBG surgery. (IV)

6. CONCLUSIONS

1. The ITT analysis supports a clinical strategy with gastric bypass being the method of choice for treatment of morbid obesity, as compared to using VBG. The high demand for remedial surgery following VBG suggests that this technique should not be used in modern bariatric surgery. (I)

2. Gastric bypass surgery results in a better preservation of muscle mass and larger loss of fat mass compared to VBG surgery. (I)

3. Gastric bypass surgery is strongly associated with exaggerated postprandial responses of the gastrointestinal hormones GLP-1 and PYY, both in the short and long terms. (I, II, IV)

4. Preoperative assessment of GLP-1 and PYY does not appear to be useful as a predictive tool for weight loss after gastric bypass surgery. (III)

5. Gastric bypass surgery is associated with a higher meal-induced thermogenesis than VBG surgery. (IV)

7. GENERAL DISCUSSION

Summary of the research

The two main purposes of this thesis were to describe the long- term clinical outcome of gastric bypass surgery and to explore the mechanisms of action behind these effects. The investigations were in most cases compared with restrictive surgical techniques VBG and gastric banding, both in a prospective randomized setting and as cohort studies. The results can be summarised as follows:

First, the long-term follow-up of a randomized clinical study shows the superiority of the gastric bypass technique over the VBG technique as regards weight loss, eating patterns and the need for revisional surgery. This data confirms what has earlier been proposed, that the VBG technique should be abandoned in modern bariatric surgery.

Secondly, in a subsample of patients from the same randomized study it could be demonstrated that the gastric bypass technique conserves muscle mass in favour of fat mass, compared to the restrictive technique VBG. In other words, as expected, the ratio of muscle to fat mass increased after gastric bypass. However, a new finding is that this is maintained over a long time, at least six years according to the present investigation.

Thirdly, by analysing cohorts of patients who had had gastric bypass, VBG or gastric banding procedures, it was shown that the gastric bypass created markedly elevated GLP-1 and PYY responses to food intake. This occurred as early as two days after surgery, and this response remained elevated nine years after surgery. It was also discovered that the increased postprandial liberation of peptide hormones was most pronounced in patients with large weight loss.

Fourthly, a prospective cohort study showed that preoperative levels of GLP-1 and PYY when fasting, and in response to food intake, had no association with weight loss outcomes after gastric bypass surgery. It follows that such preoperative hormone measurements cannot predict weight loss on an individual basis.

Fifthly, energy expenditure was assessed nine years after surgery in two small but matched cohorts of gastric bypass and VBG patients. The gastric bypass group demonstrated higher energy expenditure after food intake, and also over the full 24-hour study period, than did the patients who had undergone a VBG procedure.

BMI and revisional surgery

In general, long-term data concerning surgically-induced weight loss supports previous reports with shorter follow-up time, as well as a few longer-term follow-up studies. (69, 71, 74) The follow up rate in this study was not complete, but in comparison to other studies it was prominent. Most studies in the literature are cohort studies or controlled case series, whereas data presented in this thesis is based on a prospective randomized setting, thus giving a high level of support to evidence that a gastric bypass is a more favourable first-hand treatment option than VBG.

Studies evaluating the clinical benefits and complications of VBG surgery have, to a large degree, been focused on unsatisfactory weight loss or weight regain. It is also well recognised that VBG patients, having been converted to gastric bypass experience substantial weight loss after the reoperation. This effect was confirmed in the present investigation as weight loss after conversion to gastric bypass was similar to that seen after primary gastric bypass surgery. (81, 121-125) However, the reason for conversion in the present study was not weight regain, but rather intolerance to the VBG technique as such. This was manifested as postprandial discomfort, to which patients reacted with unfavourable eating habits, having a negative impact on weight development. The present project highlights the negative side effects of VBG and provides evidence that weight loss is poor, thus strengthening the recommendation for discarding this surgical technique. (81, 121-125)

Eating habits and body composition

Six years after their operations, the gastric bypass patients consumed slightly above the recommended proportion of fat for total daily energy needs, whereas the VBG patients had a 30% higher intake than recommended. Neither the total energy intake nor the protein intake differed between groups so the lower energy-intake from fat in the gastric bypass group was apparently balanced by an increased consumption of carbohydrates. The long-term data in the present investigation (II) into BMI and food choices is in general similar to the short-term follow-up results recorded one year after surgery in the same study population. (92) It is interesting to note that despite energy intake not differing between the groups six years after surgery, the BMI was lower in the gastric bypass group. Based on these results it is not reduced energy intake as such, rather food composition that contributes to weight loss and a healthier clinical outcome after gastric bypass. If a low fat diet with isocaloric content can directly induce weight loss, energy expenditure must be influenced. Such a macronutrient-dependent phenomenon remains to be elucidated. The altered composition of the body can also contribute to weight loss. Already one year after surgery it was noted that the proportion of musculature to fat mass had increased more after gastric bypass than after VBG. (92) The present follow-up indicated that this effect was even more pronounced after six years. Because skeletal muscles have a higher energy turn-over (also in the resting state) than adipose tissue, such a change can account for, at least partly, a better weight loss after gastric bypass. If so, that should be reflected by increased 24-hour energy expenditure, also during sleep, in the gastric bypass patients. Although 24-hour energy expenditure was higher in the gastric bypass group, sleep energy expenditure did not differ compared to VBG patients matched for body composition. (IV) This speaks against changed body composition as determinant for higher 24h energy expenditure in gastric bypass patients. Instead, the gastric bypass patients exhibited a more pronounced meal-induced thermogenesis probably contributing to the higher energy expenditure also seen over a 24h period (as further discussed below).

GLP-1, PYY and ghrelin

It has been convincingly demonstrated that endogenous and exogenous GLP-1 and PYY are associated with a perception of satiety and eventually influence food intake behaviour. (20, 23, 128, 129, 131, 132) The present finding that the magnitude of postprandial GLP-1 and PYY responses directly relate to good or poor outcome in terms of weight loss after bariatric surgery, strengthens a role for these gut hormones in appetite physiology.

Compared to slim subjects, individuals with morbid obesity have weak GLP-1 and PYY responses to food intake. However, it is not known if such low gut hormone responses are present already before the individual gains weight, or if it is the result of the manifest morbid obesity. This is a typical chicken-or-egg problem and part of the answer may be found in the present investigation. In paper II it was reported that a significant rise of satiety with a simultaneous decreased sensation of hunger, correlated over time to increased GLP-1 and PYY liberation, occurring only two days after gastric bypass surgery. At this postoperative time point, body weight had not been markedly influenced, thus strongly indicating that it is the gastric bypass operation in itself that causes the change in hormonal response to food intake. It can be seen that in these circumstances the postprandial GLP-1 and PYY responses are not weight-dependent.

The present studies regarding hormonal response six and nine years after surgery are unique as they demonstrate unanimously that increased satiety signalling, as represented by enhanced postprandial GLP-1 and PYY, are maintained over the long term in gastric bypass patients. (20, 23, 27, 98, 133) Considering their appetite-supressing effects, it is not surprising that GLP-1 and PYY have been subjects for attempts to design obesity medication, although with almost no success. On the other hand, because GLP-1 has an incretin effect, it has been used as a target in the development of medication for type-2 diabetes. Today both GLP-1 analogues and GLP-1 degradation inhibitors are used successfully in diabetes care in an increasing group of patients. Weight loss initiated by the new GLP-1 based medications are nevertheless small; many studies report under five 5 kilos. (134)

Energy expenditure

Previous studies concerning energy expenditure in bariatric patients have mainly focused on assessment over approximately one hour, and only a short time after surgery. In general, studies comparing different surgical techniques are absent. BMR **(**Basal Metabolic Rate **-** BMR**)** was assessed before surgery in the current study group (IV) for one hour, using indirect calorimetry. Hood methodology was used, with no significant differences between groups in raw values or in BMR adjusted for total body weight (unpublished data).

Several observations of interest were made in the present investigation using the energy chamber technique. In the VBG group there was a positive correlation between DIT and the proportion of lean tissue to total tissue as well as a negative correlation between DIT and the proportion of adipose tissue to total tissue. (unpublished data) This means that the subjects with the highest share of muscles in relation to their body weight also had the greatest elevation in energy expenditure after food intake. This relationship was expected, based as it was on earlier data presented in normal-weight and obese subjects (47, 56, 58) but similar assessments had not to our knowledge been performed in bariatric patients. No correlations between energy expenditure, and lean or adipose tissue, were found in the gastric bypass group. This indicated that other mechanisms were operating after this type of surgery (unpublished data). Interestingly, the greatest difference between groups regarding energy expenditure was found after food intake, suggesting that the mechanism behind the patients' diverse metabolisms is related to altered gastrointestinal anatomy rather than to body composition. Mechanisms behind the rapid meal-induced thermogenesis after gastric bypass surgery remain obscure and have to be further investigated in the future.

Weight loss strategies – some general considerations

There have been thorough discussions aiming to define limits of good and poor outcomes after weight loss strategies. After interventions including different dietary regimes, physical activity and cognitive behavioural therapy, a weight loss of 5 to10 % is in most cases regarded as a positive outcome as it has been shown to correlate with amelioration in co-morbidities. (59-62, 66) However, long-term outcomes after non-surgical treatment options are disappointing, both in regard to weight and long-term resolution in co-morbidities. Acceptable weight loss result after surgical treatment varies, but two definitions have had the most impact; BMI less than 35 kg/m^2 for morbidly obese patients (BMI >35 and <50 kg/m^2) and less than 40 kg/m^2 for super obese patients (BMI > 50 kg/m^2) (135) and/or excess weight loss more than 50 %. (136) It may be time to concentrate the discussion on resolution in co-morbidities and the quality of life, rather than concentrating entirely on weight loss. (137, 138) As there are clear signs that bariatric surgery in many cases is economically advantageous for society, this aspect might also have an important part to play in evaluating the effectiveness of different treatment methods. (113)

Bariatric surgery results in significant weight loss a short time after the operation, regardless of the surgical technique used, and in most cases results are superior to non-surgical weight-loss methods. Nevertheless, long-term effects vary substantially between surgical methods and as the intervention is meant to achieve life-long effects on weight control, as well as health, it is of great interest to explore the effects and mechanisms of action of the surgical techniques. Better knowledge of the mechanisms of action can be helpful in improving existing methods and developing new techniques, surgical as well as non-surgical.

There have been many attempts made to find both pure physiological and psycho-social predictors for successful outcomes after bariatric surgery, although without conclusive results. Medical literature indicates that a combination of interventions, including close personal support, gives the best result. (60, 66, 67, 70) Earlier attempts in finding prognostic tools have mostly focused on weight outcome, just as the one presented in paper III in this thesis. Nevertheless, orientation towards forecasting amelioration of co-morbidities and improving quality of life might actually be of greater interest than predicting weight results. Most patients live without negative symptomatology and with improved eating habits after gastric bypass surgery. However, there is a small group of individuals who suffer from abdominal pains and postprandial negative symptoms. Being able to identify these individuals before treatment decisions are made would be of the utmost value for the patients as well as for the care providers. The treatment decision might not be affected, but it would give the care- provider a better chance to offer an extended assessment, the proper support and the follow-ups that might be necessary.

Factors contributing to choice of surgical technique differ between countries and clinical settings. There are no generally accepted algorithms used by clinicians to find the optimal surgical technique for a particular individual in need of bariatric surgery. Patients' concern for short-term complications, financial circumstances (i.e. individual, insurance companies), popularity/advertising and the skills and experience of the surgeons, can all markedly influence decision-making. Some care providers offer a less-invasive surgical technique, such as gastric banding, as the primary choice, although long-term results as to weight loss and resolution of co-morbidities appear less effective than in gastric bypass. The current bariatric practice in Scandinavian countries is entirely dominated by gastric bypass surgery due mainly to comparative studies demonstrating superior long-term outcomes after gastric bypass. Standardized assessment procedures and follow-up protocols, preferably in national registers, would be of the utmost value especially when introducing new surgical techniques. Both new techniques and variations of established ones are frequently developed and it is important to evaluate them properly, preferably in randomized clinical studies, before use on a large scale.

8. FUTURE PERSPECTIVES

As long as the prevalence of obesity is high there will be a need for different treatment options. However, it is evident that health care resources are limited and in the future the prevention of obesity should gain more focus. In addition to new preventive strategies, existing therapeutic treatments must be optimised and new techniques developed. Consequently, there will be a great need for high quality, long-term, clinical studies into weight loss, co-morbidities, quality of life and cost-effectiveness.

The indications for bariatric surgery are similar internationally. More efforts ought to be devoted to investigating whether these indications adequately select patients, or if criteria should be changed. The decision whether an individual is eligible for bariatric surgery should preferably be based on more facts then are available today. This suggests that more clinical studies have to be conducted, both with regard to clinical outcome and to developing predictive tools, in order to offer successful postoperative treatment.

Although bariatric surgery currently has relatively few complications, there will always be patients suffering from perioperative and long-term complications after surgery. The more bariatric operations are performed, the more often different health care services will come into contact with this group of patients. This is an area in urgent need of structured information about how to identify and handle patients with treatment-related problems.

It is not yet clear how the altered gut anatomy after gastric bypass interferes with the uptake of macro and micronutrients. There are currently no on-going long-term prospective or randomized studies based on this question. Most clinics follow general international guidelines concerning micronutrient surveillance and nutritional substitution after bariatric surgery, but in general these are not evidence-based. Both from the patient’s perspective and from the bariatric surgery provider’s perspective, it would be of great interest to expand knowledge in this area. To obtain such knowledge there is a need for a large clinical trial randomizing between different substitutions regimes over a long period (preferably more than 10 years to catch uncommon deficiency diseases). This should involve not only hospital-based care, but also primary care centres.

Data presented in this thesis does not support the use of GLP-1 and PYY as predictive tools for weight loss after gastric bypass surgery. Nevertheless, there might be other hormones or biomarkers worth exploring in this context. As mentioned before, further studies are needed to find predictive tools concentrating on other outcome parameters such as co-morbidities, quality of life and cost-effectiveness.

Energy expenditure is closely involved in the concept of weight loss and the results from paper IV are very interesting, which leaves the author of this paper with a great desire to continue research in this area. More studies are of course needed to confirm that gastric bypass enhances daily energy expenditure when compared with other surgical techniques. A description of the mechanism(s) behind enhanced energy expenditure would of course be very valuable, and might provide new targets in the development of non-surgical treatments. For example, changed stomach anatomy after a gastric bypass when bile acids from the liver pass through part of the small intestine, without food, creates an obvious locus of interest for a study of the relation between meal-related energy expenditure after gastric bypass and bile acid levels. As gastric bypass markedly enhances levels of GLP-1 and PYY after food intake it would also be interesting to look further into the relationship between hormonal release and energy expenditure. Unfortunately paper IV in this thesis had too few patients to allow the study necessary for such an analysis. In addition, blood sampling had to be performed before the patients entered the chamber. A future study must utilise an energy chamber that allows energy expenditure and biomarkers like GLP-1, PYY and bile acids to be assessed simultaneously with food intake.

To conclude, obesity and its associated negative impact on health are tremendous future challenges. Research into this issue is needed at all levels, from the part played by social factors to the role of molecules.

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